

Single Technology Appraisal

**Niraparib for maintenance treatment of
advanced ovarian, fallopian tube and
peritoneal cancer after response to first-
line platinum-based chemotherapy (review
of TA673) [ID6403]**

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Niraparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy (review of TA673) [ID6403]

Contents:

The following documents are made available to stakeholders:

Access the [final scope and final stakeholder list](#) on the NICE website.

- 1. Company submission** from GlaxoSmithKline:
 - a. Full submission
 - b. Summary of Information for Patients (SIP)
- 2. Clarification questions and company responses**
- 3. Patient group, professional group, and NHS organisation submission** from:
 - a. Ovarian Cancer Action
 - b. Ovacome
 - c. Target Ovarian Cancer
- 4. Expert personal perspectives** from:
 - a. Prof. Jonathan Ledermann – clinical expert, nominated by UCL Cancer Institute
 - b. Gillian Nunn – patient expert, nominated by Ovarian Cancer Action
 - c. Rachel Downing – patient expert, nominated by Target Ovarian Cancer
- 5. External Assessment Report** prepared by BMJ Technology Assessment Group
- 6. External Assessment Group response to factual accuracy check of EAR**

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

Single technology appraisal

Niraparib for first-line maintenance treatment of advanced ovarian cancer

[ID6403]

Company evidence submission

July 2025

File name	Version	Contains confidential information	Date
ID6403 Niraparib in 1L aOC resubmission 15 July 2025	Version 1	Yes	15 July 2025

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Contents

Contents	2
Tables and figures	4
Executive summary	12
1 Decision problem, description of the technology and clinical care pathway	14
1.1 Decision problem summary	14
1.2 Decision problem	15
1.3 Description of the technology being evaluated	19
1.4 Health condition and position of the technology in the treatment pathway	21
1.5 Equality considerations	35
2 Clinical effectiveness	36
2.1 Clinical effectiveness summary	36
2.2 Identification and selection of relevant studies	38
2.3 List of relevant clinical effectiveness evidence	39
2.4 PRIMA	50
2.5 PRIME	75
2.6 Meta-analysis	90
2.7 Indirect and mixed treatment comparisons	90
2.8 Effectiveness from real-world evidence (RWE)	103
2.9 Ongoing studies	115
2.10 Strengths of the clinical evidence	116
2.11 Interpretation of clinical effectiveness and safety evidence	117
3 Cost-effectiveness	121
3.1 Cost-effectiveness summary	121
3.2 Published cost effectiveness studies	122
3.3 Economic analysis	126
3.4 Clinical parameters and variables	134
3.5 Measurement and valuation of health effects	155
3.6 Cost and healthcare resource use identification, measurement and valuation	159
3.7 Severity	172
3.8 Uncertainty	172
3.9 Summary of base-case analysis inputs and assumptions	173
3.9.1 Summary of base-case analysis inputs	173
3.10 Base-case results	173
3.11 Exploring uncertainty	176
3.12 Subgroup analysis	187
3.13 Benefits not captured in the QALY calculation	187
3.14 Validation	187
3.15 Interpretation and conclusions of economic evidence	189
4 References	192
5 Appendices	208
Appendix A: Summary of product characteristics (SmPC) and UK public assessment report	208
A1.1 SmPC	208
A1.2 UK public assessment report	208
Appendix B: Identification, selection and synthesis of clinical evidence	209
B1.1 Identification and selection of relevant studies	209
B1.2 Participant flow in the relevant randomised controlled trials	317
B1.3 Critical appraisal for each study	319
B1.4 RWE studies identified in the SLR	349

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Appendix C:	Subgroup analysis	362
C1.1	Primary efficacy outcomes (PFS)	362
C1.2	Secondary efficacy outcomes (OS).....	367
C1.3	Subsequent treatments.....	373
C1.4	Impact of niraparib dosing on efficacy.....	375
Appendix D:	Adverse reactions.....	377
Appendix E:	Published cost-effectiveness studies	379
E1.1	Identification and selection of relevant studies	379
Appendix F:	Health-related quality-of-life studies.....	427
F1.1	Identification and selection of relevant studies	427
Appendix G:	Cost and healthcare resource identification, measurement and	
valuation	437	
G1.1	Identification and selection of relevant studies	437
Appendix H:	Clinical outcomes and disaggregated results from the model	453
H1.1	Clinical outcomes from the model	453
H1.2	Disaggregated results of the base-case incremental cost-effectiveness	
analysis	454	
H1.3	Detailed results of the Scenario Analysis	456
Appendix I:	Price details of treatments included in the submission	460
I1.1	Price of intervention, comparators and subsequent treatments.....	460
Appendix J: Clinical Inputs: Survival Analysis		461
J1.1	Survival in the BRCAm population	465
J1.2	Survival in the BRCAwt population	504
Appendix K: Detailed niraparib dosing approach used in scenario analyses		539
K1.1	BRCAm Population.....	539
K1.2	BRCAwt Population	542
Appendix L: Base case inputs and assumptions		546
L1.1 Assumptions.....		555

Tables and figures

List of tables

Table 1. The decision problem	16
Table 2. Technology being evaluated.....	19
Table 3. Summary of FIGO staging classification for cancer of the ovary, fallopian tube, and peritoneum.....	23
Table 4. Clinical effectiveness evidence (PRIMA and PRIME)	39
Table 5. Summary of trial methodology (PRIME and PRIMA trials)	42
Table 6. Summary of Statistical Analyses for the PRIMA and PRIME studies for the primary hypothesis ^{12,76-79}	47
Table 7. Baseline characteristics of participants enrolled in the PRIMA trial	53
Table 8. Quality assessment of PRIMA.....	56
Table 9. Summary of primary and updated PFS analyses in ITT and HRd populations	58
Table 10. Secondary efficacy outcomes for the ITT population (final analysis, cut-off 8 April 2024)	61
Table 11. Subsequent treatments in the PRIMA study in the ITT population ⁸⁷	66
Table 12. Summary of ad-hoc investigator-assessed PFS by HRD and BRCaM status (final analysis, cut-off 8 April 2024)	68
Table 13. Summary of dose intensity, exposure and the need for dose reductions and dose interruptions in the PRIMA trial.....	71
Table 14. Summary of TEAEs in the safety population.....	73
Table 15. TEAEs occurring in ≥20% of patients in either treatment arm (safety population) 73	
Table 16. TEAEs in patients receiving a fixed versus individualised starting dose of niraparib	74
Table 17. Dose modification scheme for niraparib.....	76
Table 18. Baseline characteristics of participants enrolled in the PRIME trial	78
Table 19. Quality assessment of PRIME	81
Table 20. Summary of dose intensity, exposure and the need for dose reductions and dose interruptions in the PRIME trial.....	88
Table 21. Summary of TEAEs in the safety population.....	89
Table 22. TEAEs occurring in ≥20% of patients in either treatment arm (safety population) 89	
Table 23. Summary of ITCs	93
Table 24. Results of Bucher ITCs Comparing PFS: Niraparib (PRIME) vs Rucaparib (ATHENA-MONO).....	94
Table 25. Results of Bucher ITCs Comparing OS: Niraparib (PRIME) vs rucaparib (ATHENA-MONO).....	96
Table 26. Results of Bucher ITCs Comparing PFS: niraparib (PRIMA) vs olaparib (SOLO-1)	102
Table 27. RWE of niraparib identified in the SLR	103
Table 28. Real-world PFS and TTNT in the overall population and HRd subgroup of CHAR1ZMA	105
Table 29. Summary of characteristics significantly associated with TTNT in multivariable analysis in the PREDICT study	106
Table 30. Patient characteristics treated with niraparib through the CDF (SACT dataset) ¹⁹	109
Table 31. Treatment duration with niraparib through the CDF (SACT dataset) ¹⁹	112
Table 32. Summary of overall survival results for patients treated with niraparib through the CDF (SACT dataset) ¹⁹	114
Table 33. Summary of relevant NICE technology appraisal submissions	123

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Table 34. Key Modelling Considerations for the relevant NICE technology appraisal submissions	125
Table 35. Features of the economic analysis	128
Table 36. Baseline characteristics by key Population in PRIMA trial	135
Table 37. Base case and scenario parametric modelling of the niraparib PFS from PRIMA	140
Table 38. Base case and scenario parametric modelling of niraparib from PRIMA.....	143
Table 39. Comparison of OS SACT Data Milestones for BRCaM Patients: Niraparib vs Olaparib	145
Table 40. Comparator Survival Estimate HR	147
Table 41. Summary of Survival Parameters Used in the Model.....	151
Table 42. Grade 3+ Adverse Event Incidence	154
Table 43. AE QALY Losses.....	157
Table 44. Overall One-off QALY Loss per Comparator	157
Table 45. Base-case utilities (PRIMA).....	158
Table 46. Dosing, route of administration and regimen of drugs used in 1L aOC maintenance	160
Table 47. Niraparib starting dose distribution and Relative dose intensity parameters	162
Table 48. Unit Costs per package	163
Table 49. Acquisition costs per model cycle	164
Table 50. Monthly frequency of resource use.....	165
Table 51. Cost of Resources.....	166
Table 52. Summary: Monthly resource use cost.....	166
Table 53. Adverse Event Unit Costs.....	167
Table 54. Summary of AE Costs	167
Table 55. Distribution of subsequent treatments applied in the economic model – base case (PRIMA)	169
Table 56. Dosing and duration of subsequent treatments applied in the economic model.....	170
Table 57. Unit costs for the administration of subsequent treatments.....	170
Table 58. Summary of subsequent treatment costs	171
Table 59. Terminal care costs.	171
Table 60 Summary features of QALY shortfall analysis.....	172
Table 61. Summary of QALY shortfall analysis	172
Table 62. Base-case results with niraparib PAS discount - BRCaM.....	175
Table 63. Base-case results with niraparib PAS discount - BRCaWt	175
Table 64. Probabilistic base-case results with niraparib PAS discount – BRCaM	177
Table 65. Probabilistic base-case results with niraparib PAS discount – BRCaWt.....	177
Table 66. Results of scenario analyses – niraparib versus olaparib (BRCaM)	181
Table 67. Results of scenario analyses – niraparib versus rucaparib (BRCaWt).....	184
Table 68. Ovid Embase search strategy (last search date: 06 February 2025).....	211
Table 69. Ovid Medline search strategy (last search date: 06 February 2025)	214
Table 70. OVID Cochrane Central Register of Controlled Trials search strategy (last search date: February 6, 2025).....	218
Table 71. National Health Service Economic Evaluations Database (via CRD; last search date: 06 February 2025).....	220
Table 72. INAHTA search strategy (last search date: 06 February 2025).....	221
Table 73. European Association for Cancer Research congress.....	221
Table 74. The Professional Society for Health Economics and Outcomes Research Asia congress (search date: 25 March 2024).....	222
Table 75. ESMO Gynaecological Cancer Congress (abstracts only; search date: 25 March 2024)	222
Table 76. National Cancer Research Institute congress (search date: 25 March 2024).....	222
Table 77. British Gynaecological Cancer Society (search date: 10 February 2025)	222
Table 78. NICE search strategy (search date: 25 March 2024)	223
Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer	

Table 79. CDA search strategy (search date: 25 March 2024)	223
Table 80. Scottish Medicines Consortium search strategy (search date: 25 March 2024)	223
Table 81. National Centre for Pharmacoeconomics search strategy (search date: 25 March 2024)	223
Table 82. PICO selection criteria	224
Table 83. Included clinical trials – Primary/secondary publications and trial characteristics	229
Table 84. Included RWE studies - Publications and study characteristics	231
Table 85. List of included clinical studies	236
Table 86. List of excluded clinical studies	262
Table 87. Summary of study designs	299
Table 88. Comparison of HRD Testing	301
Table 89. Comparison of Subsequent Treatment Distributions	302
Table 90. Treatment Characteristics	303
Table 91. High and low-Risk Definitions	305
Table 92. Baseline Characteristics: Overall Population	306
Table 93. Baseline Characteristics: BRCaM and High-risk Subgroup	308
Table 94. PFS Definitions Across Studies	310
Table 95. Comparison of Assessment Schedules Across Trials	311
Table 96. Steps for Implementation of Anchored STC for TTE Outcomes	313
Table 97. Summary of Covariates Included in STCs	315
Table 98. Summary of Areas of Concern	316
Table 99. Quality Assessment for the identified RCTs using the Cochrane Risk of Bias Assessment Tool 2.0	321
Table 100. Quality Assessment for the identified RWE studies using the ROBINS-I tool	330
Table 101. Summary of study and patient characteristics in the identified RWEs for niraparib	349
Table 102. Summary of effectiveness results of niraparib in RWEs	356
Table 103. Summary of safety results of niraparib in RWEs	359
Table 104. OS by HRD and BRCA status (final analysis, cut-off 8 April 2024)	368
Table 105. Overall survival in the HRd population	372
Table 106. Subsequent treatments in the PRIMA study in the BRCaM population ⁸⁷	373
Table 107. Subsequent treatments in the PRIMA study in the HRD/BRCaM population ⁸⁷	374
Table 108. TEAEs leading to dose reductions in the ITT population ^a	378
Table 109. Search strategies for Embase and MEDLINE (original & previous SLR updates)	381
Table 110. Embase (via Ovid) search strategy (last search date: 10 February 2025)	383
Table 111. Cochrane Central Register of Controlled Trials (via Ovid; last search date: 10 February 2025)	385
Table 112. INAHTA search strategy (last search date: 10 February 2025)	386
Table 113. EconLit (last search date: 10 February 2025)	386
Table 114. EACR Congress	387
Table 115. ISPOR Asia congress (indexed in Embase from 2023)	387
Table 116. ESMO Gynaecological Cancer Congress (abstracts only)	387
Table 117. NCRI congress (up to 2023 as it ceased to operate in July 2023)	388
Table 118. BGSC congress	388
Table 119. NICE searches (technology appraisal guidance only)	388
Table 120. CDA-AMC searches (reimbursement review reports only)	389
Table 121. SMC searches (medicine advices only)	389
Table 122. NCPE searches	389
Table 123. PICOS selection criteria for economic evaluations	390
Table 124. List of included economic evaluations and cost-effectiveness studies	394
Table 125. Overview of included economic evaluations and cost-effectiveness studies (original SLR and subsequent updates)	401
Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer	

Table 126. Quality assessment of economic evaluations and cost-effectiveness studies ..	423
Table 127. PICOS selection criteria for HSUVs	428
Table 128. Overview of included RCTs reporting HRQoL outcomes	430
Table 129. HRQoL data reported in the overall population of the included studies	432
Table 130. Utility data reported in the included studies	435
Table 131. PICOS selection criteria for costs/HCRU	437
Table 132. List of included costs/HCRU studies	439
Table 133. Costs outcomes reported in the included studies	443
Table 134. HCRU outcomes reported in the included studies	448
Table 135. Observed survival and model estimated survival for niraparib (BRCAm)	453
Table 136. Observed survival and model estimated survival for niraparib (BRCAwt)	453
Table 137. Disaggregated Health Outcomes (BRCAm)	454
Table 138. Disaggregated Cost Outcomes (BRCAm)	454
Table 139. Disaggregated Health Outcomes (BRCAwt)	454
Table 140. Disaggregated Cost Outcomes (BRCAwt)	455
Table 141. Detailed results of the Scenario Analysis (BRCAm)	456
Table 142. Detailed results of the Scenario Analysis (BRCAwt)	458
Table 143. Unit Costs per package for 1L maintenance and subsequent treatments	460
Table 144. AIC-BIC rules of thumb	463
Table 145. AIC and BIC Estimates for niraparib PFS distributions (BRCAm)	469
Table 146. AIC and BIC Goodness-of-Fit relative to the distribution with the lowest AIC and BIC for niraparib PFS (BRCAm)	470
Table 147. PFS observed survival estimates for niraparib (BRCAm)	477
Table 148. Expected PFS per parametric distribution for niraparib (BRCAm)	478
Table 149. AIC and BIC Estimates for niraparib OS distributions (BRCAm)	483
Table 150. AIC and BIC Goodness-of-Fit relative to the distribution with the lowest AIC and BIC for niraparib OS (BRCAm)	484
Table 151. OS survival estimates	491
Table 152. Expected OS per parametric distribution for niraparib curves (BRCAm)	492
Table 153. AIC and BIC Estimates for TTDD distribution fits for the BRCAm population - PRIMA	495
Table 154. AIC and BIC Goodness-of-Fit per standard parametric distribution relative to the distribution with the lowest AIC and BIC for niraparib TTDD (BRCAm) – PRIMA	496
Table 155. AIC and BIC estimates for TTDD distribution fits for the BRCAm population for niraparib and olaparib - SACT	499
Table 156. AIC and BIC estimates for niraparib PFS distribution fits (BRCAwt)	506
Table 157. AIC and BIC Goodness-of-Fit relative to the distribution with the lowest AIC and BIC for niraparib PFS (BRCAwt)	507
Table 158. PFS observed survival estimates for niraparib (BRCAwt)	513
Table 159. Expected PFS per parametric distribution for niraparib (BRCAwt)	514
Table 160. AIC and BIC Estimates for niraparib OS distribution fits (BRCAwt)	519
Table 161. AIC and BIC Goodness-of-Fit relative to the distribution with the lowest AIC and BIC for niraparib OS distribution fits (BRCAwt)	520
Table 162. OS survival estimates	527
Table 163. Expected OS per parametric distribution for niraparib (BRCAwt)	528
Table 164. AIC and BIC Estimates for niraparib TTDD distribution fits for the BRCAwt population	531
Table 165. AIC and BIC Goodness-of-Fit per standard parametric distribution relative to the distribution with the lowest AIC and BIC for niraparib TTDD (BRCAwt) - PRIMA	532
Table 166. AIC and BIC Estimates for TTDD distribution fits for the BRCAwt population for niraparib - SACT	535
Table 167. Detailed niraparib dosing distribution for BRCAm population	539
Table 168. Detailed niraparib dosing distribution for BRCAwt population	542
Table 169 Summary of variables applied in the economic model	546
Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer	

Table 170. Summary of key assumptions used in the economic model.....	555

List of figures

Figure 1. Frequency of HRD and BRCA mutations in patients with OC	22
Figure 2. Diminishing effect of chemotherapy across subsequent chemotherapy lines	25
Figure 3. 3-year net survival in patients with ovarian cancer in the UK.....	26
Figure 4. Algorithm of initial management of advanced eOC (ESMO 2023)	30
Figure 5. UK treatment pathway for PARPi maintenance therapy	33
Figure 6. Positioning of niraparib in the treatment pathway	35
Figure 7. PRIMA study design.....	51
Figure 8. PRIMA patient enrolment by biomarker status	52
.....	
.....	Error! Bookmark not defined.
.....	Error! Bookmark not defined.
.....	Error! Bookmark not defined.
.....	Error! Bookmark not defined.
.....	Error! Bookmark not defined.
.....	Error! Bookmark not defined.
.....	Error! Bookmark not defined.
Figure 15. PRIME study design.....	77
.....	Error! Bookmark not defined.
.....	Error! Bookmark not defined.
.....	Error! Bookmark not defined.
.....	Error! Bookmark not defined.
Figure 20. Network of Evidence for ITC FA.....	91
.....	96
.....	98
.....	100
.....	101
Figure 27. Kaplan-Meier treatment duration for patients treated with niraparib through CDF (SACT dataset) ¹⁹	113
Figure 28. Kaplan-Meier survival plot for patients treated with niraparib through the CDF (SACT dataset) ¹⁹	115
Figure 29. Three-State Partitioned Survival Model.	132
Figure 30. Distribution of Patients in Three-State Partitioned Survival Model: Progression-free and On-treatment, Progression-free and Off-treatment, Progressed, and Death Health States	132
.....	138
.....	139

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

.....	141
.....	142
Figure 35. Comparison of OS SACT Data for BRCAm Patients: Niraparib vs Olaparib	145
.....	150
.....	150
.....	159
.....	178
.....	178
.....	179
.....	180
Figure 43. PRISMA flow diagram	228
Figure 44. Participant flow in the PRIMA trial ¹⁶	318
Figure 45. Participant flow in the PRIME trial ¹³	319
.....	362
.....	363
.....	364
.....	364
.....	365
.....	366
.....	367
.....	369
.....	370
.....	371
.....	372
.....	376
.....	377
Figure 59. PRISMA flow diagram	393
Figure 60. NICE DSU TSD14 guidance for parametric survival model selection	462
Figure 61. KM plots for PFS (INV) for the BRCAm population in PRIMA	466
Figure 62. Smoothed PFS hazard for BRCAm population in PRIMA	467
Figure 63. Average PFS hazard for BRCAm population in PRIMA	468
.....	473
.....	474
.....	476

.....	477
Figure 68. KM plots for OS for the BRCAm population in PRIMA.....	481
Figure 69. Smoothed OS hazard for BRCAm population in PRIMA.....	482
Figure 70. Average OS hazard for BRCAm population in PRIMA.....	483
.....	487
.....	488
.....	490
.....	491
.....	495
.....	498
.....	500
.....	501
.....	502
Figure 80. SACT TTDD KM data to the approximate end of available follow-up (42 months for NIRA and 38 months for OLA), then assume all patients discontinue.....	502
.....	503
.....	503
Figure 84. KM plots for PFS (INV) for the BRCAwt population in PRIMA	504
Figure 85. Smoothed PFS hazard for BRCAwt population in PRIMA	505
Figure 86. Average PFS hazard for BRCAwt population in PRIMA	506
.....	509
.....	510
.....	512
.....	513
Figure 91. KM plots for OS for the BRCAwt population in PRIMA	517
Figure 92. Smoothed OS hazard for BRCAwt population in PRIMA	518
Figure 93. Average OS hazard for BRCAwt population in PRIMA.....	519
.....	522
.....	523
.....	526
.....	527
.....	531
.....	534

.....	536
.....	537
Figure 102. Niraparib SACT TTDD curve until 42 months, then assume all patients discontinue.....	537
.....	538
.....	538
.....	539
.....	542

Executive summary

Women diagnosed with ovarian, fallopian tube, or peritoneal cancers—collectively referred to as ovarian cancer (OC)—are frequently diagnosed at an advanced stage,^{1,2} where the probability of achieving a cure is low.³ Standard initial treatment for advanced ovarian cancer typically includes cytoreductive surgery followed by platinum-based chemotherapy, with or without antiangiogenic therapies such as bevacizumab.^{1,4-6} However, despite these interventions, approximately 80% of patients experience disease recurrence and progression after first-line (1L) treatment.^{4,7} The prognosis for patients who relapse is particularly poor, as the effectiveness of platinum-based chemotherapy diminishes with successive lines of therapy.⁸ The risk of recurrence is highest within the first five years following 1L therapy and decreases thereafter.³ Patients who remain disease-free for 7 to 10 years are often considered to be in long-term remission or “cured”.^{9,10} These challenges underscore the need for treatments that can delay the first recurrence and improve the likelihood of achieving long-term remission or a cure in the 1L setting.¹¹⁻¹⁵

Poly-ADP ribose polymerase inhibitor (PARPi) monotherapy has become the established standard of care for maintenance treatment in women with advanced OC who have responded to 1L platinum-based chemotherapy, particularly for those who did not receive or were unable to tolerate bevacizumab during induction chemotherapy.¹¹⁻¹⁵

Niraparib has established itself as a standard-of-care maintenance therapy option in the treatment of advanced OC, demonstrating efficacy in prolonging progression-free survival (PFS) across the 1L maintenance setting regardless of biomarker status (BRCAm, BRCAwt, HRd, HRp).^{12,16} It is also the only PARPi to have demonstrated efficacy and safety in two robust phase III randomised controlled trials (RCTs) - PRIMA^{12,16} and PRIME¹³. Despite fundamental differences in study designs and patient populations across trials for other approved PARPi monotherapies (olaparib¹⁷ and rucaparib¹⁸), evidence from SACT data¹⁹ and real-world studies²⁰ suggests that PARPi therapies deliver comparable outcomes in the first-line maintenance setting. Similar PFS and overall survival (OS) outcomes were also observed across the PARPi therapies in the second-line setting, where trial designs are more consistent.²¹⁻²³

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Among the approved PARPi therapies, niraparib is the only treatment available in a single tablet strength (100mg), allowing for straightforward dose reductions by simply reducing the number of tablets required per dose.²⁴

Niraparib is well-tolerated, with an acceptable safety profile effectively managed through individualised starting doses, and dose interruptions or modifications when required.²⁵ Its availability in the NHS since 2018, initially in the relapsed setting and later reimbursed for first-line induction via the Cancer Drugs Fund (CDF) in 2022, has resulted in a well-established safety profile.¹⁹

With an efficacy profile consistent with the PARPi class and an established, manageable safety profile, niraparib has the potential to be a cost-effective treatment option in this setting, regardless of biomarker status.

1 Decision problem, description of the technology and clinical care pathway

1.1 Decision problem summary

Disease overview and burden

- Ovarian cancer (OC) is an umbrella term for ovarian, fallopian tube, and peritoneal cancer,² with epithelial OC (eOC) accounting for 90% of cases (70% of which are classified as high-grade serous OC),^{1,2} and is often linked to genetic mutations such as BRCA, which contribute to homologous recombination deficiency (HRD) and increased risk of OC.^{1,2}
 - Approximately 60% of patients are diagnosed at an advanced stage (III-IV, as classified by FIGO) where potential for cure is low
 - OC is the fifth leading cause of cancer-related mortality among women in the UK, with 4,159 deaths in 2022. Five-year survival rates are 39% for stage III and 22% for stage IV disease
- The risk of recurrence for advanced eOC is highest within the first 5 years after first-line (1L) therapy³ and decreases thereafter, with those disease-free for 7 to 10 years considered likely to be in long-term remission (or considered “cured”).^{9,10}
- The majority of patients (~80%) experience disease recurrence and progression following standard 1L treatment
 - Patients with advanced-stage disease, normal BRCA gene expression (BRCAwt), suboptimal debulking, and high residual disease volume are considered high-risk for relapse and have a worse prognosis compared to those with stage III disease who achieve complete resection following primary debulking surgery (PDS)
 - Moreover, the presence of multiple high-risk factors is associated with significantly poorer survival outcomes compared to patients with fewer or no high-risk factors
- Prognosis is poor for patients who relapse. Although retreatment with platinum-based chemotherapy (PBC) is indicated for many, its effectiveness tends to decrease when used in second and subsequent lines of treatment
 - Therefore, there is a need for treatments that can delay the first recurrence and maximise the opportunity to achieve long-term remission or a “cure” in the 1L setting

Treatment pathway

- Standard of care treatment in the NHS involves surgical intervention followed by 1L treatment with PBC, with or without bevacizumab^{1,4-6}
- PARPi are widely recognised as the standard of care for 1L maintenance, recommended for patients with a complete or partial response to PBC in order to reduce the rate of relapse and improve the likelihood of achieving long-term remission
 - PARPi monotherapy is typically considered for patients who did not receive or were unable to tolerate bevacizumab during induction chemotherapy
 - Niraparib,²⁶ olaparib,²⁷ and rucaparib²⁸ are PARPi therapies indicated for 1L maintenance treatment. However, niraparib is the only treatment licensed and reimbursed regardless of biomarker status.²⁶
 - Olaparib is only available for the treatment of BRCAm patients in this setting,²⁷ while rucaparib is used in patients who are BRCAwt.²⁸
 - Olaparib is licensed and reimbursed in England as an add-on to bevacizumab for HRd patients who have responded to 1L treatment with PBC plus bevacizumab

1.2 Decision problem

The submission covers the technology's full marketing authorisation for this indication as summarised in Table 1.

Table 1. The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with advanced epithelial (Federation of Gynaecology and Obstetrics [FIGO] stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of 1L platinum-based chemotherapy	Adults with advanced epithelial (Federation of Gynaecology and Obstetrics [FIGO] stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of 1L platinum-based chemotherapy	NA
Intervention	Niraparib (Zejula)	Niraparib (Zejula)	NA
Comparator(s)	• Olaparib plus bevacizumab (if HRD-positive and after complete or partial response to 1L platinum-based chemotherapy with bevacizumab) • Olaparib (if BRCA mutation-positive) • Rucaparib (if HRd BRCAwt or non-HRD [HRp and HRunknown]) • Bevacizumab monotherapy at a dose of 7.5 mg/kg (after response to 1L platinum-based chemotherapy plus bevacizumab) • Routine surveillance	• Olaparib (if BRCA mutation-positive) • Rucaparib (if BRCA mutation-negative, also referred to as BRCA wild-type ([BRCAwt])	Clinical experts confirmed that due to the approval of one or more PARPi across various biomarkers (e.g., HRd, HRp, BRCAm and BRCAwt), routine surveillance is not considered for patients who are eligible for PARPi in clinical practice.^{27,28} As such, GSK does not consider routine surveillance to be a relevant comparator for evaluating niraparib. Bevacizumab monotherapy is not considered a relevant comparator as availability of niraparib will not displace its usage from the treatment pathway. Bevacizumab is initiated alongside 1L platinum-based chemotherapy and continued until disease progression or for a maximum of 15 months or until unacceptable toxicity, whichever occurs

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			earlier. In contrast, PARPi monotherapies such as niraparib are utilised as maintenance therapies following a response to 1L PBC alone or if bevacizumab could not be tolerated alongside PBC. Therefore, as stated by clinical advice, PARPi monotherapies do not displace bevacizumab from the treatment pathway. Similarly, the olaparib plus bevacizumab regimen is also not displaced with niraparib availability and therefore is not considered a suitable comparator. This regimen is indicated as an add-on of olaparib to a pre-existing bevacizumab component which is initiated alongside PBC. Clinical experts have confirmed that PARPi monotherapies, such as niraparib are used in patients who have not initiated bevacizumab alongside 1L platinum-based chemotherapy or had to discontinue due to intolerance.¹⁰

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Outcomes	• Overall survival • Progression-free survival • Progression-free survival 2, that is progression-free survival on the next line of therapy • Response rate • Time to first subsequent therapy • Adverse effects of treatment • Health-related quality of life	• Overall survival • Progression-free survival • Progression-free survival 2, that is progression-free survival on the next line of therapy • Response rate • Time to first subsequent therapy • Adverse effects of treatment • Health-related quality of life	NA

Abbreviations: BRCAm = BRCA mutation-positive, BRCAwt = BRCA wild-type, FIGO = Federation of Gynaecology and Obstetrics, GSK = GlaxoSmithKline, HRD = homologous recombination deficiency, HRd = homologous recombination deficient; HRp = homologous recombination proficient, HRunknown = homologous recombination status unknown, NICE = National Institute for Health and Care Excellence, PARPi = Poly (ADP-Ribose) Polymerase Inhibitor

1.3 Description of the technology being evaluated

A description of niraparib, the technology being appraised, has been summarised in Table 2. The summary of product characteristics is included in Appendix A.

Table 2. Technology being evaluated

UK approved name and brand name	Niraparib (Zejula)
Mechanism of action	Niraparib is an inhibitor of poly(ADP-ribose) polymerase (PARP) enzymes, PARP-1 and PARP-2, which play a role in DNA repair. <i>In vitro</i> studies have shown that niraparib-induced cytotoxicity may involve inhibition of PARP enzymatic activity and increased formation of PARP-DNA complexes, resulting in DNA damage, apoptosis and cell death. ²⁴
Marketing authorisation/CE mark status	Niraparib (Zejula) was first approved in Europe (EMA, European Medicines Agency) by the European Commission on 16 July 2017, ²⁹ as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy. The approval for the requested indication, i.e., as monotherapy for the maintenance treatment of adult patients with advanced epithelial (FIGO stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of 1L platinum-based chemotherapy, was granted in Europe (EMA) on 27 October 2020. ³⁰ The dates of authorisation of Zejula 100 mg film-coated tablets by the MHRA was 6 December 2022 (marketing authorisation number PLGB 19494/0304). ²⁴
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Niraparib is indicated for two specific uses in the maintenance treatment of ovarian cancer: -as monotherapy for the maintenance treatment of adult patients with advanced epithelial (FIGO stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy. - as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy. The indication of interest for this appraisal is Zejula as monotherapy for the maintenance treatment of adult patients with advanced epithelial (FIGO stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy. ²⁴

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

UK approved name and brand name	Niraparib (Zejula)
Method of administration and dosage	Niraparib is administered orally (film-coated tablets). The recommended starting dose of niraparib is 200 mg (two 100 mg tablets), taken once daily. For patients who weigh ≥ 77 kg and have a baseline platelet count $\geq 150,00/\mu\text{L}$, the recommended starting dose is 300 mg (three 100 mg tablets), taken once daily. The medication may be interrupted or its dose reduced according to the Summary of Product Characteristics (SmPC) in case of adverse reactions.²⁴ The treatment should be continued until disease progression or unacceptable toxicity.²⁴
Additional tests or investigations	The recommended tests during treatment are: 1) weekly complete blood counts for the first month, followed by monthly monitoring for the next 10 months, and periodically thereafter 2) blood pressure monitoring at least weekly for the first two months, then monthly for the first year, and periodically thereafter. Home blood pressure monitoring may be considered for suitable patients, with instructions to contact their healthcare provider if blood pressure rises.²⁴
List price and average cost of a course of treatment	The list price of niraparib is £4,500 for 1 pack of 56 x 100 mg tablets, and £6,750 for 1 pack of 84 x 100 mg tablets.³¹ At the list price and recommended starting dose of 200 mg daily, a 30-day cycle costs £4,821 per patient. For a starting dose of 300 mg daily, the cost increases to £7,232 per 30-day cycle.
Patient access scheme (if applicable)	The proposed patient access scheme is [REDACTED] for 1 pack of 56 x 100 mg tablets (discount [REDACTED]), and [REDACTED] for 1 pack of 84 x 100 mg tablets (discount [REDACTED]).

1.4 Health condition and position of the technology in the treatment pathway

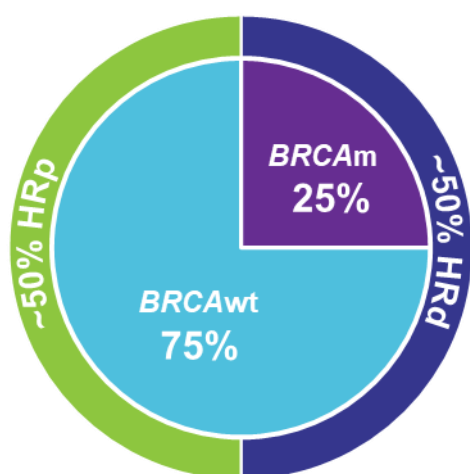
1.4.1 Disease overview

1.4.1.1 Definition and aetiology

Ovarian cancer (OC) encompasses a diverse group of neoplasms with varying clinical, pathological, and molecular characteristics¹ and is used as an umbrella term to refer to ovarian, fallopian tube and peritoneal cancer.² Epithelial OC (eOC), which originates in the surface layer covering the ovary, fallopian tube, or peritoneum, accounts for the majority of OC tumours (90%) and includes various histological subtypes such as high-grade serous (70%), endometrioid (10%), clear cell (6% to 10%), low-grade serous (5%) and mucinous (3% to 4%).^{1,2}

The exact causes of eOC are not fully understood, but several risk factors for developing the disease have been identified, including genetic mutations and hereditary predispositions (i.e., family history of OC).⁴ A key risk factor for the development of OC is mutations in the BRCA genes (BRCAm), which are crucial for DNA repair.⁴ There is an association between deleterious germline BRCA mutations (gBRCAm) and a 16% to 65% increased risk of eOC, typically of high-grade serous histology.¹ BRCA mutations, as well as other gene defects, contribute to a condition known as homologous recombination deficiency (HRD), where cells lose their ability to effectively repair double-strand breaks in DNA through the homologous recombination repair pathway. HRD increases genetic instability and the risk of OC.³² Current tests detect up to 50% of high-grade serous eOC as being HRD-positive (HRd),^{1,33} with half of these cases attributed to BRCA1/2 mutations (Figure 1).³⁴

Figure 1. Frequency of HRD and BRCA mutations in patients with OC



Abbreviations: BRCA = breast cancer gene; BRCAm = breast cancer gene mutation; BRCAwt = breast cancer wild type; HRD = homologous recombination deficiency; HRd = homologous recombination deficient; HRp = homologous recombination proficient; OC = ovarian cancer.

Adapted from Cancer Genome Atlas Research Network;³³ Pennington 2014.³⁴

1.4.1.2 *Diagnosis and staging*

The diagnosis of eOC involves several steps, starting with a thorough physical examination and a detailed medical history in patients with suspected eOC based on clinical symptoms.¹ Laboratory tests include measurements of serum biomarkers such as cancer antigen 125 (CA-125), carcinoembryonic antigen (CEA), and carbohydrate antigen 19-9 (CA19-9), levels of which are often abnormal in eOC.¹ Imaging tests, such as transvaginal or transabdominal ultrasound, assess changes in the ovaries, while CT scans of the thorax, abdomen, and pelvis help to determine the extent of the disease and assist in planning surgery.¹ Definitive confirmation of eOC requires pathological examination of tumour samples from either a diagnostic biopsy or surgical specimen. It is recommended that all patients with high-grade eOC be tested for germline and somatic BRCAm and HRD.¹

The FIGO (International Federation of Gynaecology and Obstetrics) system classifies eOC into different stages (Table 3).⁴ Advanced stages of eOC are characterised by the spread of cancer into the abdominal cavity or to lymph nodes (stage III) or the presence of distant metastases, such as to the bones, liver, or lungs (stage IV).³⁵ At least two-thirds of eOC cases are diagnosed at an advanced stage with poor prognosis (Section 1.4.2), which negatively impacts patients' psychological well-being (Section

1.4.2) due to limited hope for recovery.^{4,36} The focus of this appraisal is on patients with stage III-IV OC.

Table 3. Summary of FIGO staging classification for cancer of the ovary, fallopian tube, and peritoneum

Stage	Description
I	Tumour confined to the ovaries or fallopian tube(s)
II	Tumour involves one or both ovaries or fallopian tubes with pelvic extension (below pelvic brim) or primary peritoneal cancer
III	Tumour involves one or both ovaries or fallopian tubes, or primary peritoneal cancer, with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes
IV	Distant metastasis excluding peritoneal metastases

Abbreviations: FIGO = International Federation of Gynaecology and Obstetrics

Highlighted boxes represent the focus of this appraisal.

Source: Berek 2021⁴

1.4.1.3 Clinical presentation

The symptoms of OC are usually non-specific and can resemble those of less serious conditions, which can delay diagnosis in the early stages of the disease; symptoms include pelvic or abdominal pain, a swollen abdomen, loss of appetite, urinary and bowel changes, fatigue, weight loss, nausea/vomiting, constipation, indigestion and vaginal bleeding.^{1,37,38} Based on data from 574 patients with newly diagnosed ovarian cancer in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS), the most common symptoms of ovarian cancer are abdominal issues (65%), including abdominal or pelvic pain (39.5%), increased abdominal size or bloating (39.2%), and changes in bowel habits (20%).³⁹ The median interval from symptom onset to diagnosis is 80 days and having more than one symptom is associated with an increased risk of death (20% increase with each additional symptom).³⁹ Approximately 2% of patients are asymptomatic at the time of diagnosis.³⁹

1.4.1.4 Epidemiology (incidence, prevalence)

OC is the sixth most common cancer among women in the UK, with 7,078 patients diagnosed with OC in 2022 based on the National Disease Registration Service (NDRS).⁴⁰

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

An analysis of incidence trends among all eOC cases in the UK indicates the number of new cases has remained relatively stable over time, with an age-standardised rate (ASR) of 13.7 per 100,000 in 1995–1999 compared to 13.2 per 100,000 in 2010–2014. However, the proportion of the serous subtype has increased over time, from 4.4 per 100,000 in 1995–1999 to 7.1 per 100,000 in 2010–2014.⁴¹ Cancer Research UK projects that OC incidence will rise between 2023–2025 and 2038–2040, with approximately 9,400 new OC cases diagnosed every year by 2038–2040.⁴²

Furthermore, it is estimated that 61.8% of OC cases are diagnosed with advanced disease, i.e., stage III or IV.^{42,43}

1.4.2 Disease burden

1.4.2.1 Prognosis (mortality, survival)

OC is the fifth most common cause of cancer-related mortality among women in the UK, with 4,159 deaths in 2022 and an ASR of 4.8 per 100,000, based on GLOBOCAN 2022 data.⁴⁴

The introduction of poly-ADP ribose polymerase inhibitors (PARPi) has significantly improved the prognosis for patients with advanced OC.^{1,45} Historically, five-year survival rates for all eOC in the UK were relatively low, reported at 38.9% in 2010–2014.⁴¹ Furthermore, approximately 80% of patients experienced disease recurrence and progression after standard first-line (1L) platinum-based chemotherapy (PBC) treatment.^{4,7}

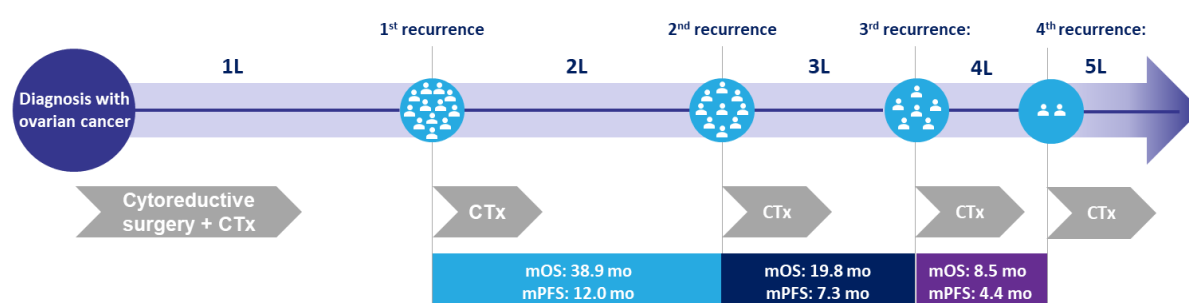
The risk of recurrence is greatest within the first five years following 1L therapy, and decreases from five to ten years post-treatment.³ Those who remain disease-free for at least seven to ten years after initial treatment are likely to be in long-term remission and considered “cured”.^{9,10} Studies have shown that their mortality rate is comparable to that of an age-matched population.⁹

Unfortunately, for patients who relapse and are indicated for retreatment with PBC, its effectiveness tends to decrease when used in second and later lines of treatment. This decline is reflected in lower response rates, shorter progression-free survival (PFS), and poorer overall survival (OS), as observed in real-world UK clinical practice prior to the introduction of PARPis (Figure 2).⁸

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Therefore, the potential to achieve long-term remission or “cure” is greatest with 1L treatment. Given that resistance to PBC increases with additional lines, there is a need for treatments that can delay the first recurrence and maximise the potential for “cure”. PARPi maintenance therapy, following 1L PBC, has been clinically proven to extend PFS and platinum-free interval by delaying disease recurrence, and reducing the need for repeated courses of PBC, thereby addressing this critical unmet need in aOC.¹¹⁻¹⁵

Figure 2. Diminishing effect of chemotherapy across subsequent chemotherapy lines



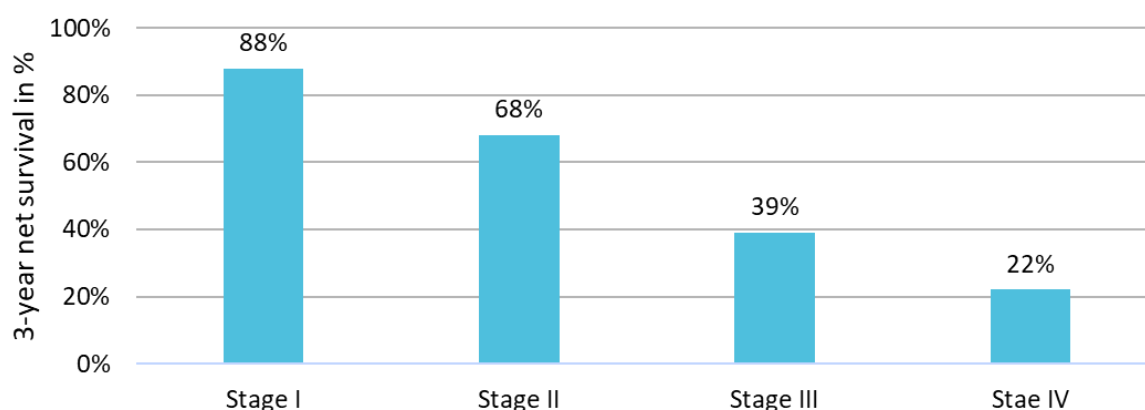
Abbreviations: CTx = chemotherapy
Adapted from Lord 2020⁸

1.4.2.2 Prognostic factors impacting outcomes in ovarian cancer

Key prognostic factors for eOC include the stage of disease at diagnosis, BRCAm/HRD status, type of debulking surgery, use of perioperative chemotherapy and residual disease (RD) volume post-cytoreductive surgery.⁴⁶ Numerous studies have shown that advanced stages of OC are associated with very poor survival outcomes, which are worse than earlier stages. Data from the UK (2010–2014) indicate that 1-year and 3-year survival rates for stage I OC were 95% and 88%, respectively, dropping to 70% and 39%, respectively, for stage III; at stage IV rates were even lower, at 52% and as low as 22%, respectively (Figure 3).⁴⁷ Similarly, data from the UKCTOCS study showed that patients with advanced (stages III and IV) and high-grade OC tumours had a 1-year survival rate of 75% and a 5-year survival rate of only 25%.³⁹ The UK Million Women Study further supports these findings, showing that survival rates for stage III OC were 76% at 1 year, 26% at 5 years and 12% at 10 years, and 61%, 14% and 7%, respectively, for patients with stage IV disease. Women diagnosed at stage III had a seven-fold higher overall risk of death compared to those Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

diagnosed at stage I (risk ratio – RR=7.23; 95% confidence interval – CI: 6.33, 8.27), whereas those diagnosed at stage IV had a ten-fold higher risk (RR=10.54; 95% CI: 9.16, 12.13).⁴⁸

Figure 3. 3-year net survival in patients with ovarian cancer in the UK



Adapted from Cabasag 2020.⁴⁷

BRCA wild-type (BRCAwt) disease and HRp disease are also considered prognostic factors in eOC.^{46,49} Among patients receiving 1L therapy, BRCAwt patients have an 83% higher risk of death compared to patients with BRCAm (HR: 1.83; 90% CI: 1.51, 2.23; $p < 0.0001$).⁴⁶ Patients with BRCAwt/HRp disease have been shown to have shorter PFS (14.9 months) and OS (42.3 months) than germline BRCAm (23.5 months and 68.8 months, respectively) and somatic BRCAm/HRd patients (20.2 months and 69.2 months, respectively).⁴⁹ Time to next treatment is also significantly shorter for BRCAwt patients compared to BRCAm patients, with a 74% increased rate of progression to subsequent treatment in the former group (HR: 1.74; 95% CI: 1.51, 2.02).⁴⁶ BRCA1 and BRCA2 play an important role in DNA damage repair through homologous recombination, and thus deficiency in these proteins leads to a diminished capacity to repair DNA, making tumours more sensitive to PBC and PARP inhibitors.⁵⁰ However, the presence of BRCA mutations increases the risk of developing a second primary cancer.⁵¹

Neoadjuvant chemotherapy (NACT) and interval debulking surgery (IDS) are associated with poorer prognostic outcomes, as patients more likely to achieve successful debulking with no visible residual disease (VRD) are typically selected for upfront primary debulking surgery (PDS).⁵² PDS is often not feasible in women with Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

more extensive disease due to the complexity of procedures,⁵² such as bowel resection which may result in significant blood loss and high morbidity risk. In such cases, NACT is administered to reduce tumour burden prior to IDS.⁵² Therefore, PDS is associated with better outcomes compared to IDS or no surgical intervention in advanced stages of eOC.^{39,46} The risk of death is three times higher for patients without surgery (HR: 3.34; 90% CI: 2.91–3.84) and 40% higher for those with IDS plus neoadjuvant chemotherapy (HR: 1.40; 90% CI: 1.24–1.58) compared to PDS plus adjuvant chemotherapy.⁴⁶ The time to the next line of treatment is also significantly shorter for patients undergoing IDS with NACT (44% increased risk; HR: 1.44; 90% CI: 1.31–1.58) and for those who do not undergo surgery (twofold increased risk; HR: 2.25; 90% CI: 2.00–2.54) compared to patients receiving PDS with adjuvant chemotherapy.⁴⁶

VRD also significantly impacts prognosis. Patients with VRD have over a two-fold higher risk of death compared to those with no visible residual disease (NVRD) (HR: 2.26; 90% CI: 2.01, 2.54).⁴⁶ Low RD volume after surgical debulking is linked to significantly longer disease-specific survival (DSS), with patients having <2 cm of RD showing a median DSS of 7.33 years compared to 1.46 years for patients with ≥2 cm of RD.⁵³ Additionally, median PFS is significantly better for those with <2 cm of RD (3.35 years) compared to those with higher RD volumes (0.89 years).⁵³

In summary, patients with advanced stage eOC, BRCAwt status, suboptimal debulking and high residual disease volume are considered high-risk and have a worse prognosis. Moreover, the presence of multiple high-risk factors is associated with significantly shorter OS compared to fewer or no high-risk factors.⁴⁶

1.4.2.3 Humanistic burden (Quality of life [QoL])

OC imposes a substantial humanistic burden, affecting patients' physical, emotional, social, and psychological well-being. In the UK, over 80% of healthcare professionals (HCPs) believe advanced eOC severely impacts patients' emotional health and their ability to plan for the future. More than 65% report significant effects on personal identity, over 60% observe negative impacts on romantic relationships, and approximately 50% note disruptions to sleep and family or social life. Additionally, HCPs frequently observe emotional challenges such as anxiety (50%), fear (39%),

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

anger (28%), and feelings of helplessness and depression (23%) resulting from an eOC diagnosis.⁵⁴

Patient-reported data align with these observations, indicating that eOC has a profound emotional impact. Over half of patients reported severe impacts on emotional well-being (58%), future planning (66%), personal identity (49%), relationships with their spouse or partner (45%), sleep (51%), and family/social life (40%).⁵⁴ Additionally, more than 70% experienced moderate or greater anxiety, with 64% reporting fear, anger, or resentment, 57% feeling helpless, and 56% feeling numb or empty. Among those affected, 20–33% experienced these emotions to a great extent.⁵⁴

Up to 80% of women experience fear and anxiety due to the high risk of cancer recurrence.⁵⁵⁻⁵⁷ This persistent fear imposes a heavy psychological burden, exacerbated by the awareness of their prognosis during the maintenance phase.⁵⁴ Prior to the widespread availability of PARPi treatments as maintenance therapies, patients being managed with active surveillance following response to 1L PBC had reported greater psychological distress compared to those receiving 1L maintenance therapy, including higher levels of anger and resentment (83% vs 49%), anxiety (81% vs 63%), and fear (77% vs 55%).⁵⁴ Prior to PARPi availability, the watch-and-wait strategy, coupled with the anticipation of relapse within the first few years post-treatment, contributes to significant emotional distress, as patients may feel they are no longer actively fighting the disease or under the protection of treatment. Limited healthcare engagement following chemotherapy for those not receiving active treatment further exacerbates this anxiety.^{58,59}

These findings highlight the critical role of maintenance therapy in improving quality of life, particularly in mitigating the deterioration associated with cancer recurrence.⁶⁰

1.4.2.4 *Economic burden*

The economic burden among patients with OC is largely driven by ambulatory care visits, with a median of approximately 6 monthly visits during active treatment following their initial OC diagnosis.⁶¹ As eOC recurs, the costs of subsequent lines of treatment increase; mean total monthly health care costs for patients with at least two treatment lines have been shown to increase by nearly 80% from before the second line of

treatment to during or after the second line.⁶¹ Similarly, the mean cost of treatment among patients with recurrent stage III/IV OC has been shown to increase by 38% for two relapses and by 86% for three or more relapses, compared to the first relapse.⁶² Additional costs can also arise from multiple hospitalisations and invasive procedures such as stenting due to bowel obstruction, which is a hallmark of disease progression.⁶³ Patients with relapsed eOC can present with multiple episodes of malignant bowel obstruction (median of 3 episodes per patient), requiring hospitalisation with a median duration of 8 days.⁶³

Given the escalating costs and diminishing efficacy⁸ of repeated chemotherapy, maintenance therapy becomes essential for patients with eOC.¹ Maintenance therapy in eOC can extend the intervals between relapses,^{12,15,64} potentially reducing the need for costly treatments and improving patients' quality of life.

1.4.3 Treatment pathway

1.4.3.1 Initial management of advanced eOC

Initial management of advanced eOC involves a multidisciplinary approach that includes surgery, chemotherapy and sometimes antiangiogenic therapies (e.g., bevacizumab).^{1,4-6} PARPis are used as maintenance therapy after 1L treatment (Section 1.4.3.2).

Based on individual patient characteristics (age, comorbidities, performance status and fitness) and the likelihood of achieving complete cytoreduction, the possible treatment options for initial eOC management according to ESMO guidelines are 1) PDS followed by a chemotherapy-based regimen, 2) neoadjuvant treatment followed by IDS and a chemotherapy-based regimen or 3) a chemotherapy-based regimen alone.^{1,4} NICE guidelines are generally consistent with this, recommending primary surgery (before chemotherapy or after neoadjuvant chemotherapy) and 1L systemic anti-cancer therapy.^{5,6}

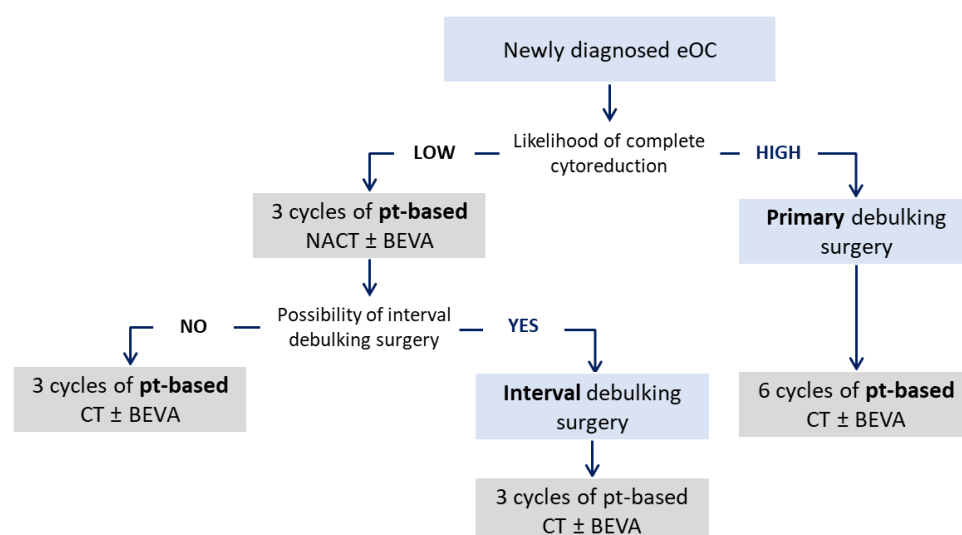
The goal of surgical treatment is to achieve complete or optimal cytoreduction, with NVRD, as the volume of residual disease after surgery is the most important prognostic indicator for PFS and OS.^{1,4-6} PDS is considered the gold standard for

patients with stage III-IV eOC who can undergo surgery and for whom complete resection seems achievable.^{1,4,52}

Systemic PBC is recommended for all advanced eOC as 1L therapy.^{5,6} The standard of care typically involves a platinum agent (carboplatin or cisplatin) in combination with a taxane (paclitaxelⁱ) with or without bevacizumab, a monoclonal antibody targeting vascular endothelial growth factor (VEGF).^{1,4-6} While NICE technology appraisal guidance does not recommend the addition of bevacizumab to a paclitaxel and carboplatin regimen for the 1L treatment of advanced OC,^{6,65} the drug became available for routine use in the UK via a commissioning policy.⁶⁶ It is typically reserved for patients with poor prognosis and those with ascites or bulky disease, consistent with the patient population that benefited most from the addition of bevacizumab in ICON-7.^{10,67}

The steps shown in the pathway for management of advanced ovarian cancer, as outlined by ESMO recommendations, are in Figure 4.^{5,6}

Figure 4. Algorithm of initial management of advanced eOC (ESMO 2023)



Abbreviations: BEVA = bevacizumab; CT = chemotherapy; NACT = neoadjuvant chemotherapy; pt = platinum
Adapted from ESMO guidelines¹

ⁱ Docetaxel is an alternative to paclitaxel for patients who have contraindications to paclitaxel and/or cannot tolerate it.

1.4.3.2 Maintenance treatment after first-line therapy

PARPi monotherapy phase III clinical trials such as SOLO-1, PRIMA, PRIME and ATHENA-MONO have demonstrated significant improvements in PFS, establishing the efficacy of maintenance therapy in extending the time patients remain free from relapse following initial treatment with PBC.¹¹⁻¹⁵ In addition, olaparib has demonstrated improvements in PFS when added to bevacizumab following response to 1L treatment with carboplatin-paclitaxel-bevacizumab.⁶⁴

Recent real-world clinical data further support the efficacy of PARPis as maintenance therapies in advanced eOC. Richardson et al. demonstrated significant improvements in real-world PFS for both BRCAm and HRd patients receiving maintenance PARPis compared to no maintenance (BRCAm: HR 0.48 [95% CI: 0.26, 0.87]; HRd: HR 0.36 [95% CI: 0.24, 0.55]).⁶⁸ Additionally, real-world evidence shows that median PFS is nearly three times longer in patients receiving maintenance therapy (26.9 months) versus those on active surveillance (11.3 months; $p < 0.0001$).⁶⁸ PARPis are generally well-tolerated, with most adverse effects being low-grade and manageable through dose reductions and interruptions. Common side effects include nausea, fatigue, and myelosuppression.¹

Therefore, PARPi are considered the standard of care for 1L maintenance and are recommended by various clinical guidelines.^{1,4-6} European (ESMO) guidelines recommend maintenance treatment with a PARPi monotherapy for patients who have achieved a complete or partial response (CR or PR) to 1L platinum-paclitaxel chemotherapy.^{1,5,6}

The following PARPi monotherapy maintenance therapies are available for use in the NHS following response to 1L PBC:

- **Olaparib:** recommended as a maintenance therapy following response to platinum-based chemotherapy for patients who are BRCA mutation-positive (**TA962**)²⁷
- **Niraparib:** recommended for use within the Cancer Drugs Fund as a maintenance therapy following response to platinum-based chemotherapy for patients, irrespective of biomarker status (**TA673**)²⁶

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

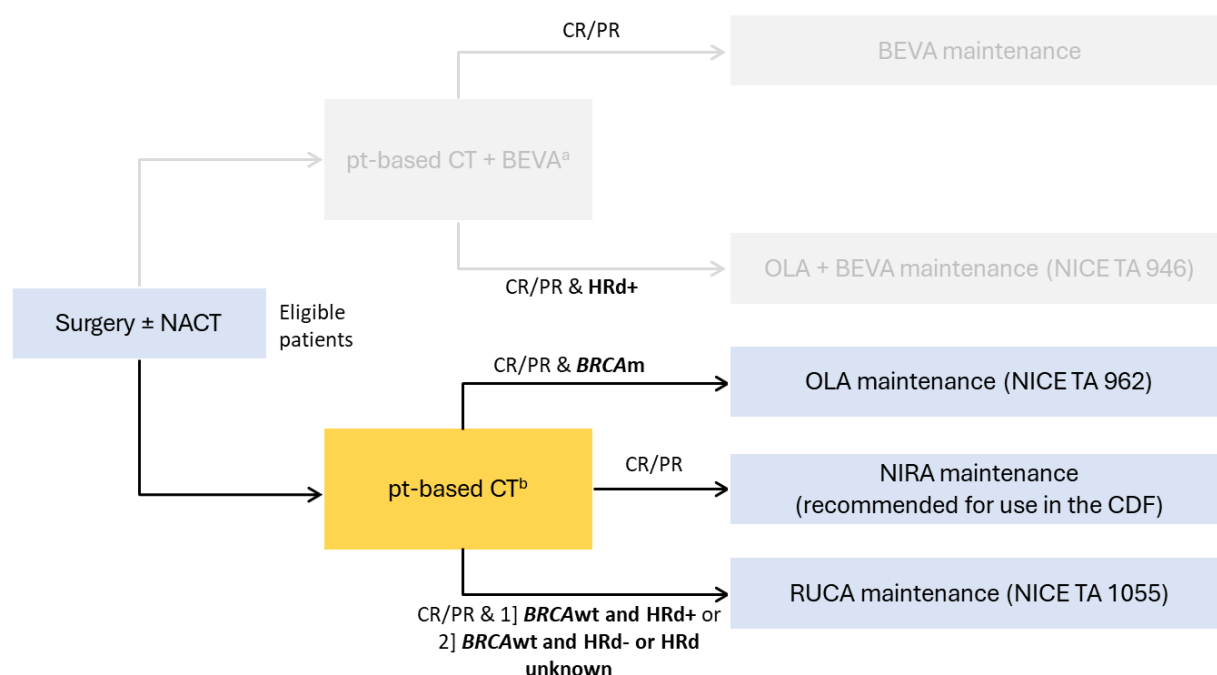
- **Rucaparib:** recommended as a maintenance therapy following response to platinum-based chemotherapy for patients who are BRCA mutation-negative and:
 - homologous recombination deficiency (HRD)-positive or
 - homologous recombination deficiency (HRD)-negative or unknown (i.e. non-HRD-positive), and bevacizumab is not a treatment option because of NHS England's BEV3 and BEV10 commissioning approval criteria for having it are not met, or it is contraindicated or not tolerated (**TA1055**)²⁸

The positive NICE recommendation for rucaparib was issued in separate drafts: one in July 2024 for HRD-positive patients and another in March 2025 for non-HRD-positive patients. For non-HRD-positive patients, the recommendation includes an additional restriction, stipulating that it applies only to patients who are ineligible for bevacizumab maintenance. However, UK clinicians¹⁰ have confirmed that PARPi monotherapies are not considered for patients who would otherwise be treated with bevacizumab in the maintenance phase as illustrated in Figure 5, and therefore this restriction does not constitute a tangible access barrier for patients with non-HRD-positive disease. Therefore, the NICE appraisal outcome results in rucaparib being available in the NHS for all BRCA mutation-negative ovarian cancer patients following a response to 1L PBC.

In addition to the PARPi monotherapies, bevacizumab is available as a maintenance treatment for patients who have completed 1L treatment with carboplatin-paclitaxel-bevacizumab.^{66,69} Similarly, olaparib is licensed and reimbursed in England as an add-on to bevacizumab for HRd patients who have responded to 1L treatment with PBC plus bevacizumab.^{1,5,6}

PARPi monotherapy as maintenance therapy is usually considered for patients who did not receive or could not tolerate bevacizumab during induction chemotherapy (Figure 5).¹⁰ As such, bevacizumab and olaparib plus bevacizumab are not considered as part of the same maintenance treatment pathway as PARPi monotherapy, as illustrated in Figure 5.¹⁰

Figure 5. UK treatment pathway for PARPi maintenance therapy



Abbreviations: BEVA = bevacizumab; BRCAm = breast cancer gene mutant; BRCAwt = breast cancer gene wildtype; CDF = cancer drug fund; CR/PR = complete response/partial response; CT = chemotherapy; HRd = homologous recombination deficient; NACT = neoadjuvant chemotherapy; NICE = National Institute for Health and Care Excellence; NIRA = Niraparib; OLA = olaparib; PARPi = poly(ADP-ribose) polymerase inhibitor; pt = platinum; RUCA = rucaparib; TA = Technology Appraisal

^a Patients who receive BEVA during induction chemotherapy can then receive BEVA or OLA + BEVA as maintenance therapy. Since PARPi monotherapy as maintenance therapy is recommended only for patients who did not receive or could not tolerate BEVA during induction chemotherapy, the bevacizumab treatment path is greyed out in the figure above.

^b PARPi monotherapy is usually given to patients who do not receive BEVA during induction.

Adapted from NICE TA946; NICE TA962; NICE TA1055.^{27,28,70}

Before entering baseline commissioning, olaparib, like niraparib, was available through the Cancer Drugs Fund. Information on patients treated with these drugs was collected within the Systemic Anti-Cancer Therapy (SACT) dataset. Available data for niraparib are presented in Section 2.8.

1.4.3.3 Place of niraparib in the treatment pathway

Niraparib is currently available in England, in line with its licensed indication for maintenance treatment in adults with advanced epithelial (FIGO stages III and IV) high-grade ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) following completion of 1L PBC. Niraparib is reimbursed via the Cancer Drugs Fund for all patients in this setting, regardless of biomarker status, previous surgical outcomes or other prognostic factors (Figure 6).

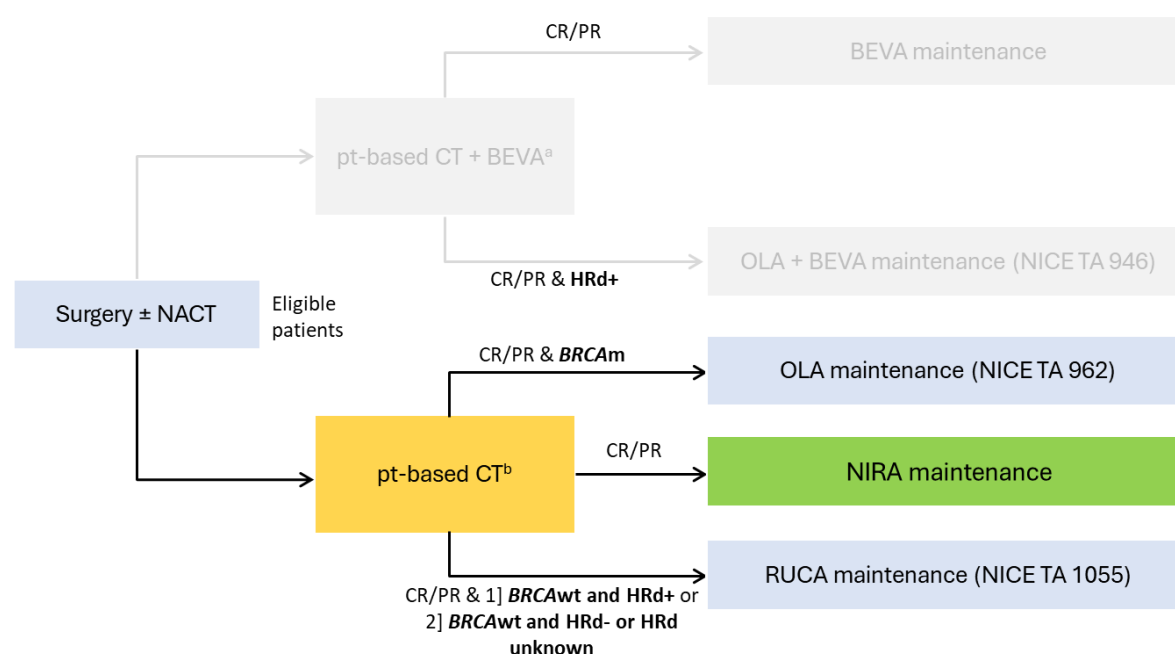
Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Niraparib has established its position as a maintenance therapy after 1L PBC in the treatment pathway for OC,¹² particularly due to its efficacy in prolonging PFS regardless of biomarker (BRCAm, BRCAwt, HRd, HRp).^{24,71} The introduction of niraparib into clinical practice has provided a crucial option for maintenance therapy,¹ addressing the unmet need delaying relapse following response to chemotherapy.

The availability of niraparib through the Cancer Drugs Fund facilitated data collection as part of the managed access agreement, providing valuable insights into real-world usage and outcomes in the UK. Evidence from SACT and real-world studies suggest that available PARPi therapies provide similar outcomes for patients in the 1L maintenance setting. This class effect has also been observed, and is more established in the second-line setting, as supported by findings from meta-analyses reporting that single-agent PARPis (niraparib, olaparib, rucaparib) did not show any statistically significant or clinically meaningful differences in terms of efficacy (PFS) in patients with platinum-sensitive advanced eOC.⁷²

The transition of niraparib from the Cancer Drugs Fund to routine commissioning would ensure sustained access for a broad patient population and enable physicians and patients to choose the most appropriate PARPi treatment based on individual preferences and tolerability profiles.

Figure 6. Positioning of niraparib in the treatment pathway



Abbreviations: BEVA = bevacizumab; BRCAm, breast cancer gene mutant; BRCAwt, breast cancer gene wildtype; CR/PR = complete response/partial response; CT = chemotherapy; HRd = homologous recombination deficient; NACT = neoadjuvant chemotherapy; NICE = National Institute for Health and Care Excellence; NIRA = Niraparib; OLA = olaparib; PARPi = poly(ADP-ribose) polymerase inhibitor; pt = platinum; RUCA = rucaparib; TA = Technology Appraisal

^a Patients who receive BEVA during induction chemotherapy can then receive BEVA or OLA + BEVA as maintenance therapy. Since PARPi monotherapy as maintenance therapy is recommended only for patients who did not receive or could not tolerate BEVA during induction chemotherapy, the bevacizumab treatment path is greyed out in the figure above.

^b PARPi monotherapy is usually given to patients who do not receive BEVA during induction.

1.5 Equality considerations

There are no known equality issues relating to the use of niraparib in patients with advanced ovarian cancer following response to 1L PBC.

2 Clinical effectiveness

2.1 Clinical effectiveness summary

Clinical Effectiveness and Safety of Niraparib:

- Among the PARPis approved for maintenance treatment after 1L PBC in advanced OC, niraparib is the only one that has confirmed efficacy and safety in two phase III RCTs, PRIMA¹² and PRIME¹³
 - PRIMA (NCT02655016):¹² an international, phase III, multicentre, randomised, placebo-controlled trial that enrolled patients irrespective of their BRCA or HRD status. The trial is notable among PARPi studies for its inclusion of patients with the highest risk of progression and the greatest unmet need
 - PRIME (NCT03709316):¹³ a phase III, multicentre, randomised, placebo-controlled trial that complements the findings of the PRIMA trial. Notably, PRIME included patients not assessed in the PRIMA study, specifically those with stage III disease and no residual disease following PDS (factors associated with low-risk of relapse), further establishing niraparib's efficacy in both low-risk and high-risk groups
- Both PRIMA^{12,16} and PRIME¹³ are positive trials that successfully achieved their primary endpoint of PFS:
 - In the PRIMA study, the primary endpoint of PFS assessed by blinded independent committee review (BICR) was met at the primary analysis (17 May 2019), with niraparib significantly reducing the risk of disease progression or death in both ITT (HR: 0.62) and HRd (HR: 0.43) populations compared to placebo ($p < 0.001$).¹² A descriptive final analysis (data cut-off 8 April 2024) confirmed sustained PFS benefit, with niraparib reducing the risk of progression or death by 34% versus placebo in the ITT population (HR: 0.66; median PFS: 13.8 vs 8.2 months).¹⁶ In the HRd population, median PFS was over twice as long with niraparib (24.5 vs 11.2 months; HR: 0.51)¹⁶
 - In the PRIME study, at the primary cut-off (30 September 2021), niraparib maintenance treatment significantly reduced the risk of disease progression by 55% relative to placebo in the ITT population (HR: 0.45; 95% CI: 0.34, 0.60; $p < 0.001$), with a median PFS of 24.8 months for niraparib compared to 8.3 months for placebo¹³ This study demonstrated a longer mPFS compared to PRIMA, likely due to its inclusion of patients with both low- and high-risk profiles.¹³
- No statistically significant difference differences in OS were observed between niraparib and placebo in the ITT population in the final analysis of the PRIMA trial, with median OS of 46.6 months for niraparib and 48.8 months for placebo (HR: 1.01; 95% CI: 0.84, 1.23; $p = 0.8834$).¹⁶
 - The lack of OS benefit is a common observation in aOC trials,^{14,17,64} where extended post-progression survival can obscure treatment effects and make

- it difficult to demonstrate statistically significant differences between treatment arms
- As PRIMA¹² was designed with PFS as the primary endpoint, differences in post-progression treatments, and potential for unblinding after progression may have impacted OS outcomes
 - Despite not achieving statistical significance for OS, the median OS observed in PRIMA was numerically high (~4 years in the ITT and 6 years in the HRd), which is particularly noteworthy given the high-risk patient population.¹⁶ Moreover, survival in the PRIMA trial is consistent with that observed for a similarly high-risk population of the PAOLA-1 PARPi trial investigating olaparib as an add-on to bevacizumab⁷³
 - In the PRIME study, at the primary analysis cut-off (30 September 2021), median OS was not reached in either arm. Niraparib showed a numerical OS benefit (HR: 0.63; 95% CI: 0.38, 1.03), with a 24-month OS rate of 87.3% versus 82.7% for placebo.¹³
 - No direct head-to-head comparisons exist between niraparib and relevant comparators (olaparib and rucaparib) in 1L aOC maintenance trials. Differences in trial populations and paucity of necessary published information for comparator therapies precluded the undertaking of a robust, adjusted indirect treatment comparison (ITC). Nevertheless, exploratory ITCs were conducted to support decision making:
 - ITCs revealed no statistically significant differences in PFS between niraparib (PRIMA^{12,16}) and olaparib (SOLO-1¹⁷). Real-world evidence further supports comparable outcomes between olaparib and niraparib in BRCAm patients, with no statistically significant differences in PFS or OS. Additionally, SACT data showed overlapping OS Kaplan-Meier curves for niraparib and olaparib in the first 27 months, with similar survival rates at key milestones (6–24 months), supporting treatment equivalence and a potential PARPi class effect
 - Exploratory ITCs comparing niraparib (PRIME¹³) to rucaparib (ATHENA-MONO¹⁸) found no statistically significant differences in PFS or OS outcomes
 - Niraparib was well tolerated in PRIMA^{12,16} and PRIME,¹³ with an acceptable and established safety profile and no new safety signals identified.
 - Notably, AE frequency was higher in PRIMA^{12,16}, where patients initially started on a fixed starting dose (FSD) before transitioning to the individualised starting dose (ISD) following a protocol amendment, compared to PRIME¹³ and recent UK-specific real-world data,²⁵ where patients received individualised starting doses aligned with the dosing label from the outset, consistent with UK clinical practice.
 - A post-hoc analysis of PRIMA data examined the efficacy and safety of the ISD versus the FSD and found no significant differences in efficacy between the two dosing strategies across the overall population or the HRd/HRp subgroups⁷⁴
 - ISD was associated with a lower incidence of AEs, demonstrating improved tolerability without compromising efficacy⁷⁵

2.2 Identification and selection of relevant studies

An SLR was conducted on 25 March 2024 to identify evidence on the clinical efficacy or effectiveness, safety and HRQoL of niraparib and relevant comparators in first-line maintenance treatment of advanced OC.²⁰ Given the publication of additional and updated data across comparators of interest, an update of the SLR was conducted on 6 February 2025 to capture new and relevant published evidence.²⁰ The same methodology was followed for the original 2024 SLR and the SLR 2025 update.²⁰

The population scope for the SLR included patients with advanced (stage III) or metastatic (stage IV) OC (tumours of the ovary, peritoneum, and fallopian tube) who had a response (complete response or partial response) to first-line therapy. Subgroups of interest included but were not limited to:²⁰

- Bevacizumab use in first-line setting,
- High-risk,
- BRCAm or BRCAwt,
- Homologous recombination deficient (HRd),
- Homologous recombination proficient (HRp),
- Homologous recombination unknown (HRunknown),
- High-risk subgroups: high-risk + BRCAm, high-risk + HRd, high-risk + HRd + BRCAwt, high-risk + HRp,
- HRd subgroups: HRd + BRCAwt, HRd + BRCAm,
- Receipt of neoadjuvant chemotherapy,
- Depth of response to first-line therapy e.g., complete response or partial response subgroups.

The SLR included clinical trials (RCTs, non-RCTs, single-arm trials) and RWE studies (e.g. observational studies or patient registries) to provide a comprehensive overview of relevant evidence in the first-line maintenance setting.²⁰

The 2024 SLR resulted in the inclusion of 117 publications reporting on 31 unique studies.²⁰ The 2025 SLR update identified 653 publications (146 duplicates) through

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

database searches, of which 507 records were screened at the title and abstract level.²⁰ From these records, 34 publications were included in the review, reporting on 14 new unique studies.²⁰ As such, the combined 2024 SLR and 2025 SLR update included a total of 151 publications, reporting on 45 unique studies.²⁰ Of the 45 studies, 26 investigated niraparib, two of which were phase III trials (PRIMA and PRIME) and are presented in the following sections.²⁰ Key RWE studies identified from the SLR are presented in Section 2.8.1.

Full details of the methodology and results of the SLR are detailed in Appendix B1.1

2.3 List of relevant clinical effectiveness evidence

The SLR identified two phase III RCTs investigating the use of niraparib as a maintenance therapy for advanced OC (Table 4):

- **PRIMA (NCT02655016)**, comparing niraparib versus placebo in patients with newly diagnosed, histologically confirmed advanced ovarian cancer (cancer of the ovary, peritoneum or fallopian tube) with high-grade serous or endometrioid tumours classified as FIGO stage III or IV (including patients with stage III disease with visible residual tumour after primary debulking surgery, inoperable stage III disease, or any stage IV disease, as well as those who had received neoadjuvant chemotherapy) and had a complete or partial response to 6 to 9 cycles of first-line platinum-based chemotherapy
- **PRIME (NCT03709316)**, comparing niraparib versus placebo in patients with newly diagnosed, histologically confirmed, high-grade (dominantly) serous or endometrioid ovarian cancer (epithelial ovarian cancer, fallopian tube carcinoma, or primary peritoneal carcinoma) classified as FIGO stage III or IV, who received primary or interval cytoreductive surgery, irrespective of postoperative residual disease status, and had a complete or partial response to 6 to 9 cycles of platinum-based chemotherapy.

A summary of PRIMA and PRIME is provided in Table 4.

Table 4. Clinical effectiveness evidence (PRIMA and PRIME)

Study	PRIMA (NCT02655016) ¹²	PRIME (NCT03709316) ¹³
Study design	Multicentre, randomised, double-blind, placebo-controlled phase III trial	Multicentre, randomised, double-blind, placebo-controlled, phase III trial

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Study	PRIMA (NCT02655016) ¹²	PRIME (NCT03709316) ¹³
Population	Patients (≥18 years of age) with newly diagnosed, histologically confirmed advanced ovarian cancer (cancer of the ovary, peritoneum or fallopian tube) with high-grade serous or endometrioid tumours classified as stage III or IV (including patients with stage III disease with visible residual tumour after primary debulking surgery, inoperable stage III disease, or any stage IV disease, as well as those who had received neoadjuvant chemotherapy) and had a complete or partial response to 6 to 9 cycles of first-line platinum-based chemotherapy	Patients (≥18 years of age) with newly diagnosed, histologically confirmed, high-grade (dominantly) serous or endometrioid ovarian cancer (epithelial ovarian cancer, fallopian tube carcinoma, or primary peritoneal carcinoma) classified as FIGO stage III or IV, who received primary or interval cytoreductive surgery, irrespective of postoperative residual disease status, and had a complete or partial response to 6 to 9 cycles of platinum-based chemotherapy
Intervention(s)	<u>Initial protocol:</u> - Niraparib 300 mg once daily <u>Amended protocol:^a</u> - Niraparib 300 mg once daily for patients with baseline body weight ≥77 kg and a platelet count ≥150,000 per cubic millimetre, - Niraparib 200 mg once daily for patients with baseline body weight <77 kg or platelet count <150,000 per cubic millimetre or both	- Niraparib 300 mg once daily for patients with baseline body weight ≥77 kg and a platelet count ≥150,000 per cubic millimetre, - Niraparib 200 mg once daily for patients with baseline body weight <77 kg or platelet count <150,000 per cubic millimetre or both
Comparator(s)	Matched placebo once daily	Matched placebo once daily
Indicate if study supports application for marketing authorisation	Yes	Yes (Chinese marketing authorisation)
Indicate if study used in the economic model	Yes	Yes
Rationale if study not used in model	N/A	N/A

Study	PRIMA (NCT02655016) ¹²	PRIME (NCT03709316) ¹³
Reported outcomes specified in the decision problem	• Progression-free survival • Overall survival • Time to first subsequent therapy • Progression-free survival 2 • Patient reported outcomes (FOSI, EQ-5D-5L, EORTC-QLQ-C30, EORTC-QLQ-OV28) • Adverse events	• Progression-free survival • Overall survival • Time to first subsequent anticancer therapy • Adverse events
All other reported outcomes	N/A	N/A

Abbreviations: AUC = area under the curve; EORTC-QLQ-(C30/OV28) = European Organisation for Research and Treatment of Cancer - Quality of Life Questionnaire-(Core 30/Ovarian Cancer Module 28); EQ-5D-5L = EuroQol 5-Dimension 5-Level; FOSI = Functional Assessment of Cancer Therapy-Ovarian Symptom Index; HRD = homologous recombination deficiency

^a The PRIMA trial was amended on 27 November 2017 to incorporate an individualised starting dose.

^b The marketing authorisation for niraparib is for the maintenance treatment of adult patients with advanced epithelial (FIGO stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy.⁷¹

^c The NICE recommendation for niraparib is for maintenance treatment for advanced (FIGO stages III and IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer after response to first-line platinum-based chemotherapy in adults.²⁶

A summary of the study designs and methodology of the PRIMA (NCT02655016) and PRIME (NCT03709316) studies are presented in Table 5, and a summary of the statistical analysis for their primary hypothesis is presented in Table 6. The PRIMA and PRIME trials are discussed in further detail in Section 2.4 and Section 2.5, respectively.

Table 5. Summary of trial methodology (PRIME and PRIMA trials)

	PRIMA (NCT02655016)¹²	PRIME (NCT03709316)¹³
Location	North America and Europe	China
Trial design	Multicentre, randomised, double-blind, placebo-controlled, phase III trial	Multicentre, randomised, double-blind, placebo-controlled, phase III trial
Eligibility criteria for participants	Key inclusion criteria: • Female patients, ≥18 years of age • Newly diagnosed, histologically confirmed advanced cancer of the ovary, peritoneum, or fallopian tube (collectively defined as ovarian cancer) classified as stage III or IV according to FIGO: ○ FIGO stage III with residual disease after primary debulking surgery ○ FIGO stage III with neoadjuvant chemotherapy and interval debulking surgery ○ FIGO stage III with inoperable disease ○ Any FIGO stage IV • Chemotherapy criteria: ○ Prior ≥6 and ≤9 cycles of first-line platinum-based chemotherapy; patients must have had ≥2 post-operative cycles of platinum-based therapy following interval debulking surgery ○ Physician assessed CR or PR after ≥3 cycles of therapy ○ CA-125 in the normal range or CA-125 decrease by >90% their front-line therapy that is stable for at least 7 days • Participants must undergo central tumour HRD testing • ECOG performance status 0 or 1	Key inclusion criteria: • Female patients, ≥18 years of age • Histologically confirmed high-grade serous/endometrioid epithelial ovarian cancer, fallopian tube carcinoma or primary peritoneal carcinoma classified as stage III or IV according to FIGO • Chemotherapy criteria: ○ Prior ≥6 and ≤9 cycles of first-line platinum-based chemotherapy ○ Assessed CR or PR after ≥3 cycles of therapy ○ CA-125 in the normal range or CA-125 decrease by >90% their front-line therapy that is stable for at least 7 days • Patients agree to the collection of blood samples for the detection of germline BRCAm (status must be known prior to randomisation) • ECOG performance status 0 or 1 Key exclusion criteria: • Diagnosed with mucinous, clear cell subtypes of epithelial ovarian cancer (except for those carrying germline BRCA)

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

	PRIMA (NCT02655016)¹²	PRIME (NCT03709316)¹³
	Key exclusion criteria: • Mucinous or clear cell subtypes of epithelial ovarian cancer, carcinosarcoma or undifferentiated ovarian cancer • Stage III disease with complete cytoreduction (i.e., no visible residual disease) after primary debulking surgery • >2 debulking surgeries • Bevacizumab as maintenance treatment** • Simultaneously enrolled in any clinical trial of niraparib or any other investigational therapy • Prior treatment with a known PARP inhibitor or have participated in a study where any treatment arm included administration of a known PARP inhibitor • Known $\geq$Grade 3 anaemia, neutropenia or thrombocytopenia due to prior chemotherapy that persisted for >4 weeks • History or current diagnosis of MDS or AML • Undergone major surgery (per Investigator judgment) within three weeks of starting the study or patient has not recovered from any effects of any major surgery • Drainage of ascites within 4 weeks prior to enrolment • Undergone palliative radiotherapy encompassing >20% of the bone marrow within one week of the first dose of study treatment	mutation), carcinosarcoma, or undifferentiated ovarian cancer • Undergone more than two debulking surgeries • Received or planned to receive bevacizumab as maintenance treatment** • Previously been treated with PARP inhibitors (including niraparib) • Any known $\geq$ Grade 3 anaemia, neutropenia or thrombocytopenia due to prior chemotherapy that persisted for >4 weeks • Patients who experienced transfusion-dependent anaemia or thrombocytopenia • Drainage of ascites within 4 weeks prior to enrolment • Undergone major surgery (per investigator judgement) within 3 weeks of starting the study, or patients have not recovered from any effects of any major surgery • Undergone palliative radiotherapy encompassing >20% of the bone marrow within 3 weeks of enrolment • Diagnosed and/or treated for invasive cancer less than 5 years prior to study enrolment[†] • History or current diagnosis of MDS or AML
Settings and locations where the data were collected	181 clinical sites in 20 countries: US, Canada, Spain, Belgium, Italy, France, Denmark, Germany, UK, Israel, Finland, Switzerland, Ireland, Sweden, Norway, Russia, Ukraine, Czechia, Poland, Hungary	29 hospitals in 1 country: China

	PRIMA (NCT02655016)¹²	PRIME (NCT03709316)¹³
Trial drugs	Subjects were randomly assigned (2:1) to receive: • Oral niraparib capsules 300 mg once daily or, individualised starting dose of 200 mg for patients with baseline body weight <77 kg or platelet count <150,000 per cubic millimetre or both* • Placebo oral once daily	Subjects were randomly assigned (2:1) to receive: • Oral niraparib capsules 300 mg once daily or, starting dose of 200 mg for patients with baseline body weight <77 kg or platelet count <150,000 per cubic millimetre or both • Matched placebo oral once daily
Primary outcomes	Hierarchical testing for PFS (defined as the time from the date of treatment randomisation to the date of first documentation of progression [by blinded central review] or death by any cause in the absence of documented progression, whichever occurs first): • PFS in HRd population • PFS in the overall population	PFS (defined as the time from randomisation to the date of first documentation of disease progression [as assessed by blinded, independent, central imaging assessment] that meets the RECIST 1.1 criteria for disease progression or death due to any cause) in the ITT population
Other outcomes used in the economic model/specified in the scope	• Hierarchical testing for OS (defined as the time from the date of randomisation to the date of death by any cause) ○ OS in the overall population ○ OS in the HRd population • Time to first subsequent therapy • Progression-free survival 2 (time from randomisation to progression while the patient was receiving a subsequent anticancer therapy) • PROs (FOSI, EQ-5D-5L, EORTC-QLQ-C30, EORTC-QLQ-OV28) • AEs	• Overall survival • Time to first subsequent anticancer therapy • AEs

	PRIMA (NCT02655016)¹²	PRIME (NCT03709316)¹³
Stratification factors	• Clinical response after first-line platinum-based chemotherapy (complete or partial response) • Receipt of neoadjuvant chemotherapy (yes or no) • Homologous recombination status determined by Myriad myChoice HRD test (deficient vs. proficient or not determined)	• Germline BRCA status • Clinical response after first-line platinum-based chemotherapy (complete or partial response) • Receipt of neoadjuvant chemotherapy (yes or no) • Homologous recombination status determined by BGI HRD test (deficient vs. proficient or not determined)
Pre-planned subgroups	• Age categories (<65 years or ≥65 years) • Region (North America or rest of world) • ECOG performance status (0 or 1) • Stage of disease at initial diagnosis (III or IV) • Primary tumour site (ovarian, primary peritoneal, fallopian tube) • Neoadjuvant chemotherapy (yes or no), according to randomisation • Neoadjuvant chemotherapy (yes or no), according to eCRF • Best response to platinum regimen (CR or PR), according to randomisation • Best response to first platinum regimen (CR or PR), according to eCRF • Baseline CA-125 level (≤ULN or >ULN) • Starting dose subgroup (fixed starting dose or individualised starting dose) • tBRCA status (tBRCAm, tBRCAwt), ITT population • HRD status (tBRCAm, [non-tBRCAm and HRd], HRp, HRunknown[†]), ITT population	• Age (18-64 years or ≥65 years) • History of intraperitoneal chemotherapy (yes or no) • Satisfactory surgical cytoreduction for ovarian cancer (yes or no) • Tumour staging (III or IV) • HRD status (positive or negative) • Administration of neoadjuvant chemotherapy from CRF (yes or no) • Best overall response following the first-line platinum-based chemotherapy from CRF (CR or PR) • gBRCA mutation status from central laboratory (yes or no)

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Abbreviations: AE = adverse events; AML = acute myeloid leukaemia; BGI = Beijing Genomics Institute; BRCA = breast cancer gene; CR = complete response; CRF = case report form; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; EORTC-QLQ-(C30/OV28) = European Organisation for Research and Treatment of Cancer - Quality of Life Questionnaire-(Core 30/Ovarian Cancer Module 28); EQ-5D-5L = EuroQol 5-Dimension 5-Level; FIGO = International Federation of Gynaecology and Obstetrics; FOSI = Functional Assessment of Cancer Therapy-Ovarian Symptom Index; HRD = homologous recombination deficiency; HRd = homologous recombination deficient; HRp = homologous recombination proficient; HRQoL = health-related quality of life; ITT = intent-to-treat; MDS = myelodysplastic syndrome; PARP = poly (ADP-ribose) polymerase; PFS = progression free survival; PR = partial response; PRO = patient reported outcomes; tBRCAm = tumour breast cancer gene mutation; tBRCAwt; tumour breast cancer gene wild type; UK = United Kingdom; ULN = upper limit of normal; US = United States

* PRIMA trial was amended on 27 November 2017 to incorporate an individualised starting dose

** Patients who received bevacizumab with first-line platinum-based therapy but are unable to receive bevacizumab as maintenance therapy due to adverse events or for any other reason were not excluded from the trial, however, the last dose of bevacizumab had to be received ≥ 28 days prior to signing the main informed consent form

† Patients with definitively treated uterine cervical or urinary tract carcinoma in situ, non-melanomatous skin cancer or ductal carcinoma in situ of the breast were not excluded

‡ The trial refers to this population as HR not determined

Table 6. Summary of Statistical Analyses for the PRIMA and PRIME studies for the primary hypothesis^{12,76-79}

Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
PRIMA (NCT02655016)	The primary objective was to evaluate the efficacy of niraparib versus placebo as maintenance treatment, as measured by PFS in patients with stage III or IV OC (including fallopian and peritoneal cancers) with CR or PR after front-line platinum-based chemotherapy (superiority hypothesis).	A hierarchical testing approach was used to control the overall type I error rate for the PFS endpoint. First, the analysis of PFS was conducted in HRd patients at the one-sided alpha level of 0.025. If the result was positive, a PFS analysis was conducted in the intent-to-treat (ITT) population with a one-sided alpha level of 0.025; otherwise, the PFS analysis was to become exploratory in the ITT population. PFS was compared between treatment groups using a stratified log-rank test, using the randomisation stratification factors (i.e., administration of neoadjuvant therapy, best response to platinum therapy, and HRD test status). The HR and two-sided 95% CI were derived from a stratified Cox proportional hazards model to estimate the treatment effect. Graphical displays using the Kaplan-Meier (KM) method were employed. Sensitivity analyses were performed on PFS to assess the robustness of the primary analysis outcome. Analyses of PFS were conducted across demographic and baseline characteristics, including but not limited to age, race, region, and ECOG performance status.	It was calculated that at least 620 patients (including 310 patients with HRd) would provide a power of more than 90% to detect a significant difference in PFS survival between niraparib and placebo at a one-sided type I error of 0.025. These criteria corresponded to a HR for PFS of 0.50 in the group with HRd and 0.65 in the overall population of all the patients who had undergone randomisation.	Censoring for the primary endpoint was determined as follows: 1) No evaluable baseline or no evaluable post-baseline radiological assessments; PFS was censored at the date of randomisation unless death or progression occurred within two visits of randomisation. 2) Patients who progressed or died and had not started subsequent anti-cancer therapy were censored at the date of the latest evaluable radiological assessment. 3) Patients who started subsequent anti-cancer therapy were censored at the date of the latest evaluable radiological assessment prior to the start of subsequent anti-cancer therapy. 4) Patients who progressed or died after two or more missed radiological assessments were censored at the date

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
				of the latest evaluable radiological assessment prior to the missed interval.
PRIME (NCT03709316)	The primary objective was to evaluate the efficacy of niraparib versus placebo as maintenance treatment, as measured by PFS, in patients with stage III or IV OC (including fallopian and peritoneal cancers) with CR or PR following first-line platinum-based chemotherapy.	The overall type I error level was controlled at a two-sided 0.05 significance level for the PFS endpoint. PFS was compared between treatment groups using the stratified log-rank test. In addition, the HR with 95% CI was estimated using a stratified Cox proportional hazards model that included treatment group and stratification variables. PFS was also descriptively summarised using the Kaplan-Meier methodology. The sensitivity analyses for the primary endpoint included 1) PFS assessed by the investigator; 2) PFS with censoring, which considered study withdrawal as progression; 3) PFS analysis where the assessments of stratification variables germline BRCA and HRD come from the central laboratory; and 4) analysis deriving progression date using the midpoint between the time of progression and the previous radiographic assessment if scans were performed outside the protocol-scheduled visit window. Subgroup analyses included HRD and germline BRCA status, neoadjuvant chemotherapy, best overall response after platinum-based chemotherapy, age, history of intraperitoneal	It was calculated that 246 PFS events would provide a power of 90% to detect a significant difference in PFS between the niraparib and placebo groups at a two-sided significance level of 0.05, assuming a 0.65 HR for PFS in the ITT population. A sample size of 381 patients (254 receiving niraparib and 127 receiving placebo) was determined to be appropriate.	Censoring for the primary endpoint was determined as follows: 1) No baseline radiological assessment or no post-baseline radiographic assessment: PFS was censored at the date of randomisation. 2) Patients who progressed or died before data cut-off: PFS was censored at the date of last evaluable radiological assessment. 3) Patients who progressed or died after two or more missed consecutive radiological assessments: PFS was censored at the date of last evaluable radiological assessment prior to the missed visit. 4) Patients who received subsequent anti-cancer therapy before progressive disease or death: PFS was censored at the date of the last evaluable radiological

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
		chemotherapy, satisfactory surgical cytoreduction, and tumour staging. Additionally, post-hoc subgroup analyses were performed for indeterminate HRD and suboptimal debulking. No multiple testing adjustment was conducted for subgroup analyses.		assessment before the start of subsequent anti-cancer therapy

Abbreviations: BRCA = breast cancer gene; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; HRD = homologous recombination deficiency; HRd = homologous recombination deficient; ITT = intent to treat; CR = complete response; OC = ovarian cancer; PFS = progression-free survival; PR = partial response

2.4 PRIMA

2.4.1 Summary of methodology of the relevant clinical effectiveness evidence

PRIMA included patients with newly diagnosed, histologically confirmed advanced OC (cancer of the ovary, peritoneum, or fallopian tube).¹² Patients had high-grade serous or endometrioid tumours, FIGO stage III (excluding stage III with no residual disease after primary debulking surgery) or IV and had received 6-9 cycles of 1L PBC, which had resulted in complete or partial response.¹² Notably, the PRIMA trial is unique amongst pivotal trials of PARPis due to its exclusion of stage III patients with a favourable prognosis as a result of being optimally debulked following upfront primary debulking surgery; while surgery modality is not a prognostic factor on its own, it is common practice to select patients with better prognosis for PDS (Section 1.4.2.1). As a result, patients enrolled in PRIMA reflect a population at high risk of relapse.¹²

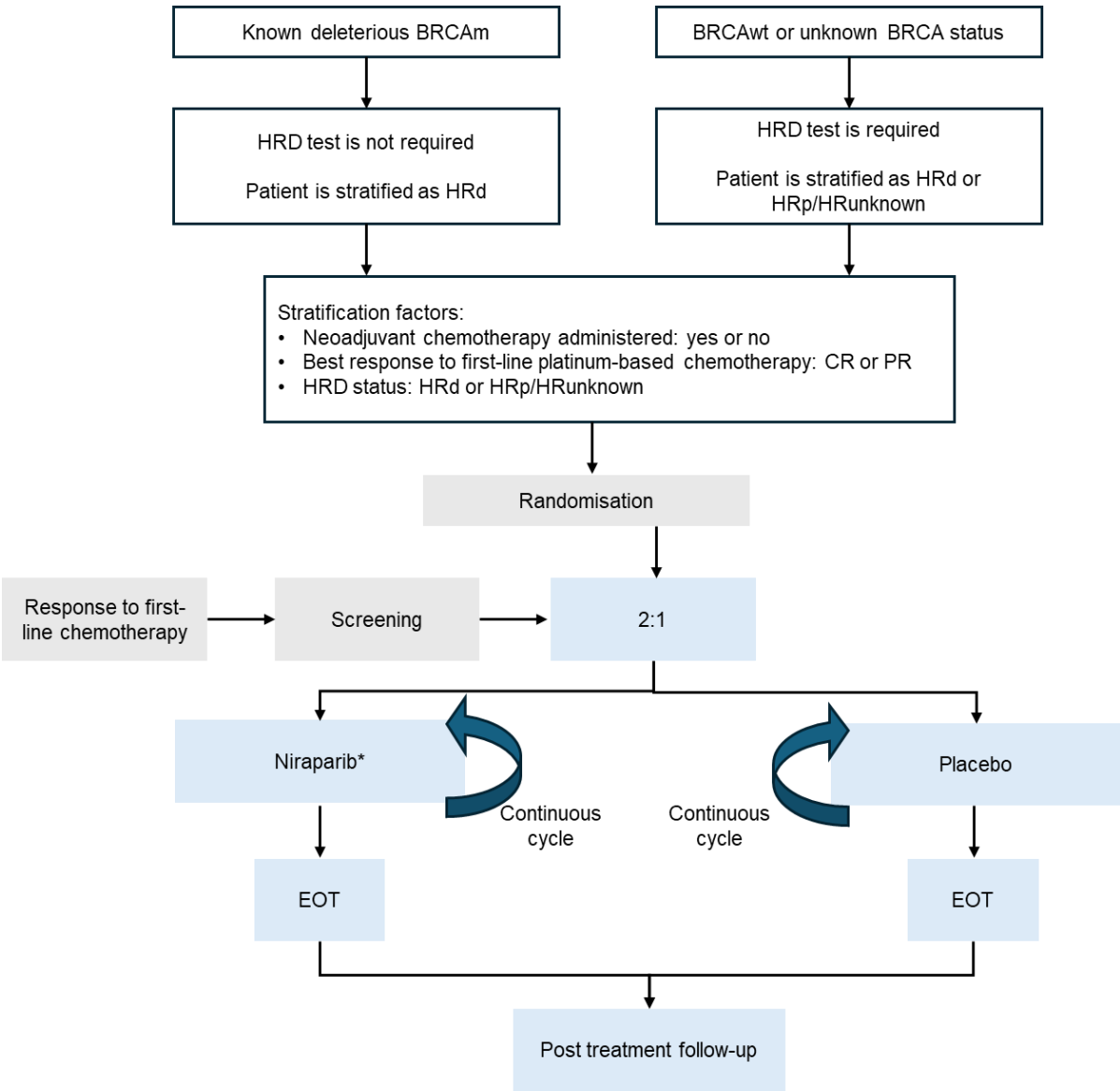
Patients were randomised 2:1 to receive either:¹²

- Niraparib once daily in 28-day cycles for 36 months or until disease progression,
- Placebo once daily in 28-day cycles for 36 months or until disease progression.

In the initial protocol, all patients received a fixed starting dose of niraparib of 300 mg once daily.¹² However, the PRIMA trial was amended on 27 November 2017 to incorporate an individualised starting dose of 200 mg once daily for patients with a baseline body weight of <77 kg or a platelet count of <150,000 per cubic millimetre or both (based on analysis of NOVA data⁸⁰).¹² As a result, 475 patients received the fixed starting dose of 300 mg, while 258 (approximately one third) received the individualised starting dose of 200 mg. In addition, dose modifications were permitted and prespecified as part of the trial protocol to manage the incidence of adverse effects, regardless of starting dose.¹²

PRIMA was designed for hierarchical testing of the primary endpoint, progression-free survival, in the HRd population first and then in the overall population.¹² Progression-free survival was defined as the time from treatment randomisation to the earlier date of assessment of progression or death by any cause in the absence of progression. Secondary endpoints of the PRIMA study are presented in Table 5, while the study design is illustrated in Figure 7.

Figure 7. PRIMA study design



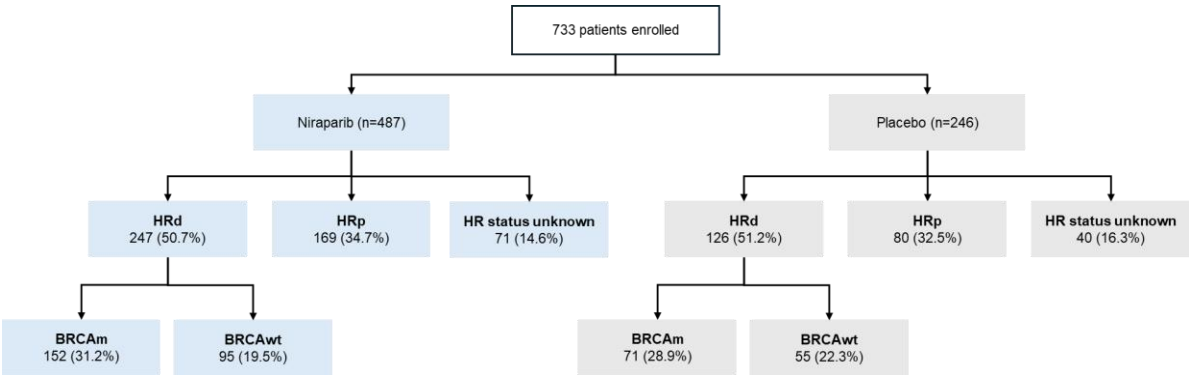
Abbreviations: BRCA = breast cancer gene; CR = complete response; BRCAm = breast cancer gene mutation; BRCAwt = breast cancer gene wild type; EOT = end-of-treatment; HRd = homologous recombination deficient; HRp = homologous recombination proficient; HRunknown = homologous recombination unknown; PFS = progression-free survival; PR = partial response

* The starting dose of study treatment will be based upon the patient’s baseline body weight and baseline platelet count. Patients with a baseline body weight ≥ 77 kg and a baseline platelet count $\geq 150,000$ μL will receive 300 mg, and those with a baseline body weight < 77 kg and/or a baseline platelet count $< 150,000$ μL will receive 200 mg.

Source: Adapted from González-Martín 2019¹²

Of the patients who underwent randomisation, 50.9% (n=373) had tumours with HRd, and 30.4% (n=223) had tumours with BRCA mutations (HRd BRCAm)¹². The patient enrolment by biomarker status is presented in Figure 8.

Figure 8. PRIMA patient enrolment by biomarker status



Abbreviations: BRCA = breast cancer gene; BRCAm = breast cancer gene mutation; BRCAwt = breast cancer gene wild type; HRd = homologous recombination deficient; HRp = homologous recombination proficient; HRunknown = homologous recombination unknown

Source: Adapted from González-Martín 2019¹²

Patient baseline characteristics were well balanced between the niraparib and placebo arms.¹² Similar proportions of patients in the niraparib and placebo arms had high-risk characteristics such as ECOG PS 1 (30.8% vs 29.3%), FIGO stage IV disease (34.7% vs 35.8%), receipt of neoadjuvant chemotherapy (66.1% vs 67.9%) and partial response to PBC (30.8% vs 30.0%).¹²

The baseline characteristics for PRIMA are presented in Table 7.

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Table 7. Baseline characteristics of participants enrolled in the PRIMA trial

	Niraparib		Placebo	
	HRd population (n=247)	Overall population (N=487)	HRd population (n=126)	Overall population (N=246)
Median age (range), years	58 (32, 83)	62 (32, 85)	58 (33, 82)	62 (33, 88)
ECOG PS, n (%)				
0	182 (73.7)	337 (69.2)	97 (77.0)	174 (70.7)
1	65 (26.3)	150 (30.8)	29 (23.0)	72 (29.3)
FIGO stage, n (%)				
III	161 (65.2)	318 (65.3)	78 (61.9)	158 (64.2)
A	4 (1.6)	7 (1.4)	1 (0.8)	4 (1.6)
B	10 (4.0)	16 (3.3)	9 (7.1)	12 (4.9)
C	140 (56.7)	285 (58.5)	67 (53.2)	138 (56.1)
Not specified	7 (2.8)	10 (2.1)	1 (0.8)	4 (1.6)
IV	86 (34.8)	169 (34.7)	48 (38.1)	88 (35.8)
Primary tumour location, n (%)				
Ovary	201 (81.4)	388 (79.7)	105 (83.3)	201 (81.7)
Fallopian tube	32 (13.0)	65 (13.3)	13 (10.3)	32 (13.0)
Peritoneum	14 (5.7)	34 (7.0)	8 (6.3)	13 (5.3)
Histologic type, n (%)*				
Serous	234 (94.7)	465 (95.5)	116 (92.1)	230 (93.5)
Endometrioid	5 (2.0)	11 (2.3)	6 (4.8)	9 (3.7)
Other	8 (3.2)	11 (2.3)	4 (3.2)	6 (2.4)
Receipt of neoadjuvant chemotherapy, n (%)				
Yes	156 (63.2)	322 (66.1)	80 (63.5)	167 (67.9)
No	91 (36.8)	165 (33.9)	46 (36.5)	79 (32.1)
Clinical response after platinum-based chemotherapy, n (%)				
CR	185 (74.9)	337 (69.2)	93 (73.8)	172 (70.0)
PR	62 (25.1)	150 (30.8)	33 (26.2)	74 (30.0)
Cancer antigen 125 level, n (%)				
<ULN	236 (95.5)	450 (92.4)	120 (95.2)	226 (91.9)
>ULN	9 (3.6)	34 (7.0)	5 (4.0)	18 (7.3)
Missing data	2 (0.8)	3 (0.6)	1 (0.8)	2 (0.8)
No. of cycles of platinum-based chemotherapy, n (%)				
6	165 (66.8)	333 (68.4)	84 (66.7)	170 (69.1)
7-9	52 (21.1)	124 (25.5)	28 (22.2)	62 (25.2)

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

	Niraparib		Placebo	
	HRd population (n=247)	Overall population (N=487)	HRd population (n=126)	Overall population (N=246)
Missing data	30 (12.1)	30 (6.2)	14 (11.1)	14 (5.7)

Abbreviations: CR = complete response; ECOG = Eastern Cooperative Oncology Group; FIGO = International Federation of Gynaecology and Obstetrics; HRd = homologous recombination deficient; PR = partial response; ULN = upper limit of normal

* Histologic data for one patient were missing, but cytologic analysis identified a serous tumour

Source: González-Martín 2019¹²

2.4.2 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

PRIMA efficacy and safety analyses were performed in accordance with a comprehensive Statistical Analysis Plan,^{76,77} which was discussed in the previous niraparib in aOC NICE submission (ID1680).⁸¹ A summary of the key information regarding the statistical analysis is provided below.

2.4.2.1 Primary efficacy analysis

The primary endpoint in the PRIMA study was PFS, defined as the time from the date of treatment randomisation to the date of first documentation of progression (by blinded central review) or death by any cause in the absence of documented progression, whichever occurs first. A hierarchical testing approach was used to control the overall type I error rate for the PFS endpoint. First, the analysis of PFS was conducted in HRD patients at the one-sided alpha level of 0.025. If the result was positive, a PFS analysis was conducted in the intent-to-treat² (ITT) population with a one-sided alpha level of 0.025.^{76,77} The assumptions for the statistical analysis of PFS are presented in Table 6.

2.4.2.2 Secondary efficacy analysis

Secondary endpoints included OS (the time from randomisation to the date of death by any cause), PFS2 (the time from randomisation to the earliest date of assessment of

² Defined as all patients randomised into the study. For this analysis, patients were analysed as randomised. Patients who were incorrectly stratified during randomisation were analysed and presented under the stratum assigned during randomisation

progression on the next anticancer therapy after study treatment or death by any cause), TFST (the time from randomisation to the date of the first subsequent anticancer therapy or death by any cause) and PROs.^{76,77}

Time-to-event endpoints (OS, PFS2, and TFST) were evaluated using a stratified log-rank test with randomisation stratification factors and summarised using the Kaplan–Meier methodology. A stratified Cox proportional hazards model was used to calculate the HRs and 95% CIs for the ITT and HRd populations, and additional prespecified exploratory subgroups, with no formal statistical testing conducted for exploratory subgroups (based on, e.g., previous neoadjuvant chemotherapy, age, dose, geographical region, response to PBC, FIGO stage).^{76,77}

The final OS analysis was planned after approximately 440 deaths in the overall population (60% maturity). A hierarchical testing strategy was used to control the overall type I error at the two-sided 0.05 level. First, testing was conducted in the ITT population, followed by the HRd population, using a Lan-DeMets alpha spending function with O'Brien stopping boundaries. If significance was not achieved in the ITT population, testing was stopped. The trial had 80% power to identify a statistically significant difference in OS if the true HR in the ITT population was 0.75.¹⁶

PROs (FOSI, EQ-5D-5L, EORTC-QLQ-C30, EORTC-QLQ-OV28) were analysed descriptively to examine changes from baseline in overall scores, sub-scores, and individual items.^{76,77}

Secondary endpoint analyses were conducted using data from the final clinical cut-off date of April 8, 2024.¹⁶

2.4.2.3 Safety analysis

Safety analyses were summarised descriptively for the SAF population. The severity of the toxicities was graded by the Investigator according to the National Cancer Institute (NCI) Common Terminology for Adverse Events (CTCAE) v4.03. Any AEs leading to

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

death or discontinuation of study treatment, events classified as NCI CTCAE v4.03 Grade 3 or higher, study treatment-related events, and SAEs were presented.^{76,77}

2.4.3 Critical appraisal of the relevant clinical effectiveness evidence

The PRIMA trial is a randomised, double-blinded, placebo-controlled trial. The quality assessment of this trial is noted in Table 8. The complete quality assessment for PRIMA is presented in Appendix B of the previous niraparib in aOC NICE submission (ID1680).

Table 8. Quality assessment of PRIMA

Quality assessment	PRIMA	Notes
Was randomisation carried out appropriately?	Yes	Randomisation was performed in a double-blinded manner with the use of an interactive Web-response system, with stratification according to clinical response to platinum-based chemotherapy, receipt of neo-adjuvant chemotherapy, and status of HRD status.
Was the concealment of treatment allocation adequate?	Yes	The identity of the treatments was concealed using study treatments that were identical in appearance, packaging, labelling, and schedule of administration. Patients and investigators were only unblinded to homologous recombination deficiency testing results or study treatment in cases associated with important medical reasons, as determined by the investigator, and for specific non-urgent medical events. The process for unblinding the identity of the assigned treatment was outlined in the Pharmacy Manual. Patients who required unblinding were discontinued from study treatment but were to remain on study until progression or death, withdrawal of consent, or loss to follow-up.
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Baseline characteristics were well balanced in each cohort. Stratification at randomisation was used in the PRIMA study to mitigate any potential imbalance in baseline characteristics or prognostic factors that could impact the treatment effect.
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	The objective assessment of progressive disease was determined by central radiologic and clinical review in a blinded manner, according to RECIST. Study patients,

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Quality assessment	PRIMA	Notes
		Investigators, study staff, and the Sponsor's study team and its representatives were blinded to the patient's central homologous recombination deficiency testing status and identity of the assigned treatment from the time of randomisation until final database lock. Patients and investigators were not unblinded to homologous recombination deficiency testing results or study treatment except in cases associated with important medical reasons as determined by the Investigator and for specific non-urgent medical events. Patients who required unblinding were discontinued from study treatment but were to remain on study until progression or death, withdrawal of consent, or loss to follow-up.
Were there any unexpected imbalances in dropouts between groups?	No	Among all enrolled patients, 90 (18.6%) patients randomised to niraparib and 55 (22.5%) patients randomised to placebo had discontinued from the study by the time of data cut-off. The reasons for discontinuation from study were death (9.9% for niraparib and 12.3% for placebo), withdrawal of consent (7.4% for niraparib and placebo), lost to follow-up (0.2% for niraparib and 0.4% for placebo), and other (0.8% in niraparib and 2.5% in placebo).
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	All primary and secondary endpoint analyses are reported in the published PRIMA manuscript.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes, the ITT population is the primary population for efficacy analyses which is referred to as the "overall" population in the PRIMA publication.
Did the authors of the study publication declare any conflicts of interest?	No	None reported

Abbreviations: HRD = homologous recombination deficiency; ITT = intention to treat

2.4.4 Clinical effectiveness results of the relevant studies

2.4.4.1 Primary efficacy outcome: PFS

The primary PRIMA endpoint of PFS assessed by BICR was met at the primary analysis clinical cut-off (17 May 2019). Maintenance treatment with niraparib led to a statistically significant reduction in the risk of disease progression or death, as assessed by BICR, in both ITT (HR: 0.62; 95% CI 0.50, 0.76; $p < 0.001$) and HRd (HR: 0.43; 0.31, 0.59; $p < 0.001$) populations.¹² Median PFS was longer in the niraparib group compared to the placebo group in both populations (ITT: 13.8 months vs 8.2 months; HRd: 21.9 months vs 10.4 months).¹² Comparable results were also observed for investigator-assessed PFS in the updated (clinical cut-off: 17 November 2021)⁸² PFS analyses (Table 9).

Table 9. Summary of primary and updated PFS analyses in ITT and HRd populations

Analysis (cut-off)	BICR/IA	Median PFS (95% CI), months		HR (95% CI)	p-value
		Niraparib	Placebo		
ITT population (niraparib: 487 patients vs placebo: 246 patients)					
Primary (17 May 2019)	BICR	13.8 ██████████	8.2 ██████████	0.62 (0.50, 0.76)	<0.001
	IA	13.8 (11.3, 14.2)	8.2 (7.6, 9.8)	0.63 (0.51, 0.76)	<0.001
Updated (17 November 2021)	IA	13.8 (NA)	8.2 (NA)	0.66 (0.56, 0.79)	<0.001
HRd population (niraparib: 247 patients vs placebo: 126 patients)					
Primary (17 May 2019)	BICR	21.9 ██████████	10.4 ██████████	0.43 (0.31, 0.59)	<0.001
	IA	21.9 ██████████	11.2 ██████████	0.46 (0.34, 0.63)	<0.001
Updated (17 November 2021)	IA	24.5 (NA)	11.2 (NA)	0.52 (0.40, 0.68)	<0.001

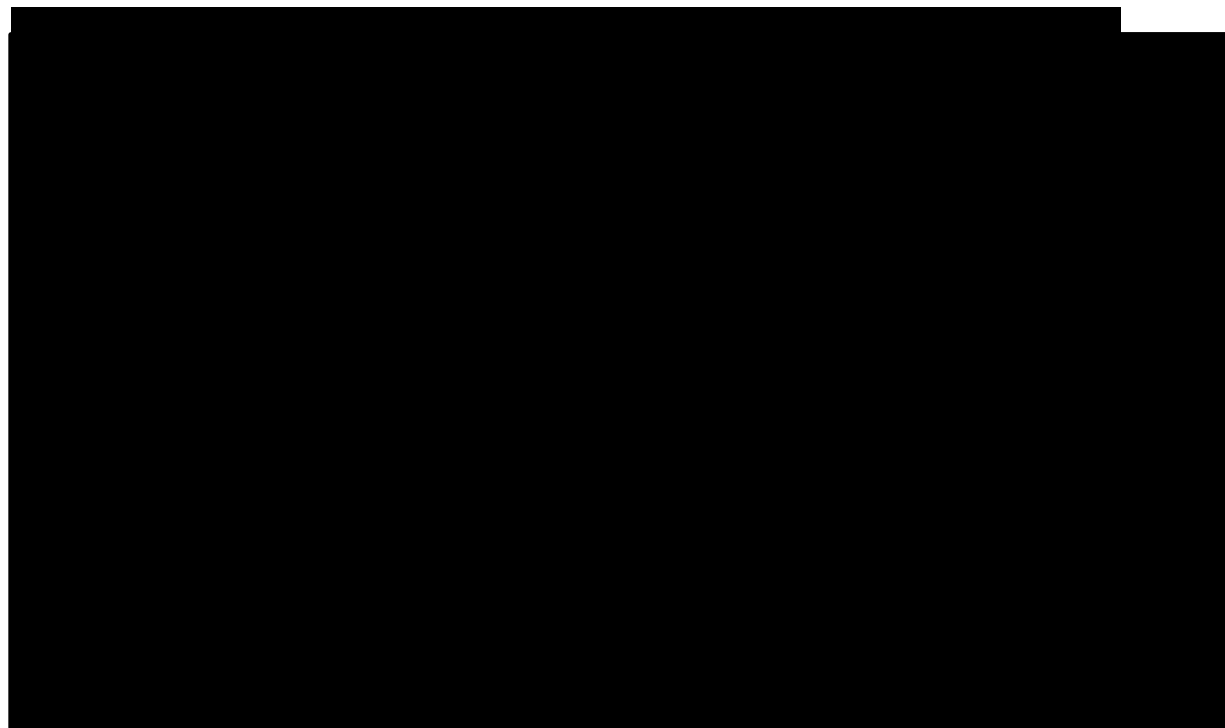
Abbreviations: BICR = blinded independent central review; CI = confidence interval; HR = hazard ratio; HRd = homologous recombination deficient; IA = investigator assessment; ITT = intent-to-treat; NA = not available; NE = not estimable; PFS = progression-free survival

Source: Gonzalez-Martin 2019¹², Gonzalez-Martin 2023⁸² and CSR⁸³

At the final analysis (data cut-off 8 April 2024), an ad hoc descriptive analysis of investigator-assessed PFS showed sustained benefits with niraparib maintenance treatment after a median follow-up of 73.9 months in the niraparib arm and 73.8 months

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

in the placebo arm.¹⁶ Maintenance treatment with niraparib led to a reduction in the risk of disease progression or death by 34% versus placebo in the ITT population (HR: 0.66; 95% CI: 0.55, 0.78).¹⁶ In the HRd population, median PFS for patients treated with niraparib was more than double that of those receiving placebo (24.5 months vs 11.2 months), with sustained PFS benefit versus placebo (HR: 0.51; 95% CI: 0.40, 0.66).¹⁶ The Kaplan-Meier plots for PFS with niraparib and placebo in the ITT and HRd populations are presented in **Error! Reference source not found.** and **Error! Reference source not found.**



Abbreviations: CI = confidence interval; ITT = intention-to-treat; PFS = progression-free survival
Source: Monk 2024¹⁶

Abbreviations: CI = confidence interval; HRd = homologous deficient population; PFS = progression-free survival
Source: Monk 2024¹⁶

2.4.4.2 Secondary efficacy outcomes

A summary of the key secondary efficacy endpoints at the final analysis for niraparib versus placebo in the PRIMA trial can be found in Table 10 and are described in further detail below.

Table 10. Secondary efficacy outcomes for the ITT population (final analysis, cut-off 8 April 2024)

	Niraparib (N=487)	Placebo (N=246)
TFST ^a		
Median (95% CI), months	17.0 ██████████	12.0 (██████████)
Event rate overall, n (%)	██████████	██████████
Hazard ratio (95% CI)	0.74 (0.62, 0.89)	
PFS2		
Median (95% CI), months	30.1 ██████████	27.6 ██████████
Event rate overall, n (%)	██████████	██████████
Hazard ratio (95% CI)	0.96 (0.79, 1.17)	
Overall Survival		
Median (95% CI), months	46.6 ██████████	48.8 ██████████
Event rate overall, n (%)	██████████	██████████
p-value	p=0.8834	
Hazard ratio (95% CI)	1.01 (0.84, 1.23)	

Abbreviations: CI = confidence interval; ITT = intention-to-treat; PFS2 = progression-free survival; TFST = time to first subsequent therapy

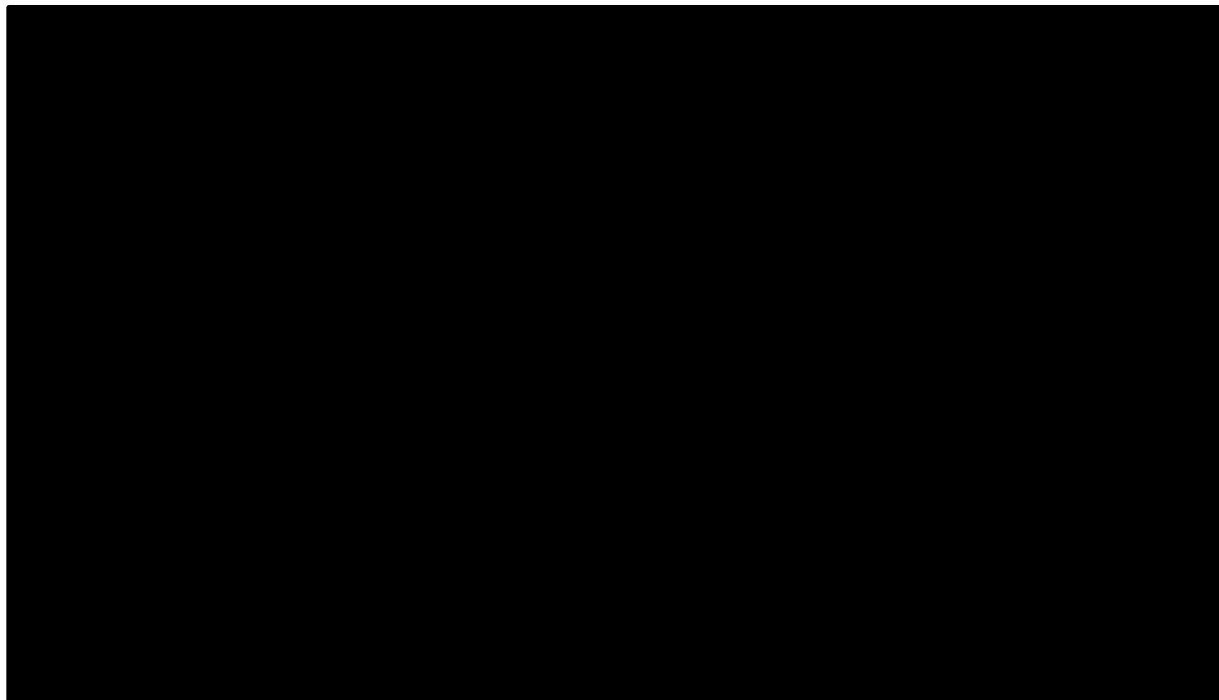
^a p-values for time to first subsequent therapy and progression were not reported

Source: Monk 2024¹⁶ and CSR 2024⁸⁴

As of the final data cut, data maturity for TFST was [REDACTED]% ([REDACTED] events in 733 participants).⁸⁴ In line with the results for PFS, median TFST was longer in the niraparib arm (17.0 months) compared with the placebo arm (12.0 months; HR: 0.74; 95% CI: 0.62, 0.89) in the ITT population.¹⁶ The Kaplan-Meier plot for TFST with niraparib and placebo is presented in [REDACTED].

[REDACTED]

[REDACTED]



Abbreviations: CI = confidence interval; HR = hazard ratio; ITT = intention-to-treat; TFST = time to first subsequent therapy
Source: OS CSR 2024⁸⁴

As of the final data cut, maturity for the PFS2 data was [REDACTED]% ([REDACTED] events in 733 participants).⁸⁴ Median PFS2 was numerically longer in the niraparib arm (30.1 months) compared with the placebo arm (27.6 months; HR 0.96; 95% CI: 0.79, 1.17)¹⁶. The Kaplan-Meier plot for PFS2 with niraparib and placebo is presented in [REDACTED].

Abbreviations: CI = confidence interval; HR = hazard ratio; ITT = intention-to-treat; PFS2 = progression-free survival 2
Source: OS CSR 2024⁸⁴

As of the final data cut, a total of 458 deaths occurred, representing 62.5% data maturity.¹⁶ In the ITT population, median OS was 46.6 months in the niraparib arm compared with 48.8 months in the placebo arm (HR: 1.01; 95% CI: 0.84, 1.23; p=0.8834).¹⁶ The Kaplan-Meier plot for OS is presented in **Error! Reference source not found.** No statistically significant difference was observed between niraparib and placebo in this secondary endpoint.

Abbreviations: CI = confidence interval; ITT = intention-to-treat; OS = overall survival
Source: Monk 2024¹⁶

Patient-reported outcomes

PROs were evaluated over time using least square (LS) mean change from baseline, with results reported through Cycle 24.⁸⁵ After Cycle 13, the interpretation of PRO results was difficult due to the decreasing number of patients for each cycle. Similar results were reported for PRO results (EORTC QLQ-C30, EORTC QLQ-OV28, FOSI and EQ-5D-5L) from baseline to Cycle 24 and baseline to Cycle 30.^{85,86} The PRIMA trial was not powered to determine treatment differences for PRO endpoints.

All data presented in this section are from the final data cut-off (8 April 2024).⁸⁵ Patient PRO adherence rates remained consistently high (>80%) across all PRO instruments and at all timepoints throughout the trial.⁸⁶

- Symptoms and quality of life, as measured by mean FOSI scores, were equivalent between niraparib and placebo groups in the ITT population at baseline (niraparib Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

LS mean: 25.6 versus placebo: 25.4) and after 24 weeks (niraparib LS mean: 26.2 versus placebo: 25.6).⁸⁵

- Baseline EQ-5D-5L VAS mean scores were similar between niraparib and placebo patients in the ITT population (niraparib LS mean: 75.5 versus placebo LS mean: 74.8).⁸⁵ At Cycle 24, EQ-5D-5L VAS scores remained similar between the niraparib and placebo arms (niraparib LS mean: 84.6 versus placebo LS mean: 80.1).⁸⁵ No difference in overall EQ-5D-5L VAS scores between treatment arms was observed over time; however, scores trended upward, indicating better QoL over time.⁸⁵
- From baseline to Cycle 24, the LS mean changes for global health/overall QoL as measured by the EORTC QLQ-C30, were similar across treatment arms (niraparib LS mean at Cycle 24: 78.8 versus placebo LS mean at Cycle 24: 74.5).⁸⁵
- Higher LS mean change from baseline through Cycle 24 was reported in the niraparib arm compared with the placebo arm in the abdominal/gastrointestinal symptoms domain of the EORTC QLQ-C30 scale, indicating worsening of symptoms.⁸⁵ Niraparib was associated with higher symptom scores for appetite loss, nausea and vomiting, and constipation compared to placebo early in the treatment.⁸⁵ However, the differences in symptom scores between the treatment groups for appetite loss, nausea and vomiting diminished after 7–9 cycles.⁸⁵ Additionally, the increase in symptom scores for constipation in the niraparib group lessened over time.⁸⁵
- On the EORTC QLQ-OV28 scale, no difference was observed between treatment arms for attitude toward disease/treatment at 24 weeks (niraparib LS mean: 71.6 versus placebo LS mean: 62.3).⁸⁵ Scores increased over time in both arms, indicating better functioning.⁸⁵ For abdominal/GI symptoms, there was a transient, slight increase compared with baseline in the niraparib arm at cycle 3, indicating worse symptoms.⁸⁵ However, differences between treatment arms resolved over time.⁸⁵

Overall, long-term PRO data from PRIMA showed that niraparib as 1L maintenance did not negatively impact overall health-related quality of life.⁸⁵ Niraparib use was linked to an early, temporary increase in self-reported gastrointestinal symptoms; however, these symptoms resolved over time.⁸⁵ Combined with previously published efficacy and safety data, QoL findings support the use of niraparib as a well-tolerated 1L maintenance treatment option.⁸⁵

2.4.5 Subsequent treatments used in the relevant studies

The latest data on subsequent treatments in the overall ITT population in the PRIMA study are presented in Table 11 (data for BRCAm and BRCAwt are provided in the Appendix, C.1.3.1).

Table 11. Subsequent treatments in the PRIMA study in the ITT population⁸⁷

Subsequent treatment		Niraparib, n (%) (N = 487)	Placebo, n (%) (N = 246)
Any second-line therapy			
Carboplatin			
Cisplatin			
Taxane			
Doxorubicin			
Gemcitabine			
Bevacizumab			
Cyclophosphamide			
PARPi	Any		
	Niraparib		
	Olaparib		
	Rucaparib		
	Talazoparib		
Checkpoint inhibitor			

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Subsequent treatment		Niraparib, n (%) (N = 487)	Placebo, n (%) (N = 246)
Antibody drug conjugate			
Hormonal Therapy			
Other			
Any third-line therapy			
Carboplatin			
Cisplatin			
Taxane			
Doxorubicin			
Gemcitabine			
Bevacizumab			
Cyclophosphamide			
PARPi	Any		
	Niraparib		
	Olaparib		
	Rucaparib		
	Talazoparib		
Checkpoint inhibitor			
Antibody drug conjugate			
Hormonal Therapy			
Other			

Abbreviations: PARPi = poly (ADP-ribose) polymerase

2.4.6 Subgroup analysis

2.4.6.1 Primary efficacy outcome: PFS

Results for the ad-hoc subgroup analyses performed at the final analysis data cut-off (8 April 2024; Section 2.4.4.2) for investigator-assessed PFS were consistent with those for the primary subgroup analysis results.⁸⁴ Niraparib demonstrated PFS benefit compared to placebo across all analysed subgroups, including basic demographic factors (e.g., age, geographic region, race), prognostic factors in advanced OC (e.g., response to PBC, BRCA/HRD status [relevant to patient groups in the decision problem]), and niraparib dose (Table 12; **Error! Reference source not found.**; Appendix C.1.1.1).^{16,84} Interaction test results were not available.^{16,84}

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Table 12. Summary of ad-hoc investigator-assessed PFS by HRD and BRCAm status (final analysis, cut-off 8 April 2024)

Subgroup	Niraparib		Placebo		HR (95% CI)	p-value
	N	Median PFS (95% CI), months	N	Median PFS (95% CI), months		
BRCAm	152	30.1 (NA)	71	11.5 (NA)	0.43 (0.31, 0.59)	NA
BRCAwt	310	██████████	163	██████████	0.77 (0.62, 0.95)	NA
HRp	169	8.4 (NA)	80	5.4 (NA)	0.67 (0.50, 0.89)	NA

Abbreviations: BRCAm = breast cancer gene mutated; BRCAwt = breast cancer gene wild type; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; HRD = homologous recombination deficiency; HRd = homologous recombination deficient; HRp = homologous recombination proficient; NA = not available; PFS = progression-free survival
Source: Monk 2024,¹⁶ GSK Data on File⁸⁸

[Redacted]

[Redacted]

[Redacted]

[Redacted]

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

2.4.6.2 Secondary efficacy outcomes

The results for the subgroup analyses for OS from the PRIMA trial are presented in Appendix C.1.2.1.

2.4.7 Adverse reactions

2.4.7.1 Overview

Niraparib was generally well tolerated and has an acceptable and established safety profile, with no new safety signals identified.¹⁶ The safety analysis was conducted in the safety population (niraparib: n=484; placebo: n=244) for patients who received at least 1 dose of study drug.¹⁶ Safety results are presented for the final analysis (clinical cut-off 8 April 2024).¹⁶

2.4.7.2 Exposure

The median drug exposure from first to last dose for niraparib- and placebo-treated patients was [REDACTED] months and [REDACTED] months, respectively.⁸⁴ The median number of cycles (equal to one month) was [REDACTED] cycles for niraparib-treated patients and [REDACTED] cycles for placebo-treated patients; [REDACTED]% versus [REDACTED]% of patients in the niraparib and placebo arms started at least 36 cycles (respectively).⁸⁴ The mean dose intensity³ in the niraparib and placebo groups was [REDACTED] mg/day and [REDACTED] mg/day, respectively, and the mean relative dose intensity⁴ was [REDACTED]% and [REDACTED]%, respectively.⁸⁴

³ Calculated as the sum of the daily doses actually consumed divided by overall treatment exposure in days

⁴ Calculated as $100 \times [\text{dose intensity (mg/day)} / \text{intended dose intensity (mg/day)}]$, where intended dose is starting dose of 300 mg/day or 200 mg/day

2.4.7.3 Dosage

Dose reductions and interruptions were allowed in the trial for the management of adverse events (AEs; Table 13). In the niraparib group, █ patients (█%) had at least one study drug interruption due to AEs compared to █ patients (█%) in the placebo group in the ITT population.⁸⁴ Overall, █ patients (█%) in the niraparib group and █ patients (█%) in the placebo group had a dose reduction in the ITT population.⁸⁴

Table 13. Summary of dose intensity, exposure and the need for dose reductions and dose interruptions in the PRIMA trial

Parameter	Niraparib (N=484)	Placebo (N=244)
Overall Treatment Exposure (months)		
Mean (SD)	██████████	██████████
Median	██	██
Min, Max	██	██
Time on Study (months)		
Mean (SD)	██████████	██████████
Median	██	██
Min, Max	██	██
Dose Intensity (mg/day)		
Mean (SD)	██████████	██████████
Median	██	██
Min, Max	██	██
Relative Dose Intensity (%)		
Mean (SD)	██████████	██████████
Median	██	██
Min, Max	██	██
Overall Dose Interruptions due to AE, n (%)	██████████	██████████
Overall Dose Reductions due to AE, n (%)	██████████	██████████

Abbreviations: max = maximum; min = minimum; SD = standard deviation

Source: OS CSR⁸⁴

2.4.7.4 Safety profile

Incidence of adverse events

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

In the safety population, most subjects in both treatment groups experienced at least one TEAE, including 479 (99.0%) of 484 subjects who received niraparib and 229 (93.9%) of 244 subjects who received placebo.¹⁶ In the niraparib arm, 96.5% of patients experienced a treatment-related AE compared to 71.7% of patients in the placebo arm.¹⁶ The proportions of patients experiencing a Grade ≥ 3 TEAE were 73.8% and 23.8% in the niraparib and placebo arms, respectively.¹⁶ In the niraparib arm, 12 patients (2.5%) experienced an adverse event leading to death, and in the placebo arm, 4 patients (1.6%) experienced an adverse event leading to death.¹⁶ A summary of TEAEs is presented in Table 14.

In the niraparib arm, 198 patients (40.9%) experienced serious TEAEs, as did 43 patients (17.6%) in the placebo arm.¹⁶ In patients who received one or more doses of study treatment, MDS or AML events were reported in 11 patients (2.3%) in the niraparib arm and 4 patients (1.6%) in the placebo arm.¹⁶ New malignancies (excluding MDS/AML) were developed among 2.5% of patients in both the niraparib and placebo arms.¹⁶

Table 14. Summary of TEAEs in the safety population

TEAEs, n (%)	Niraparib (N=484)	Placebo (N=244)
Any TEAEs	479 (99.0)	229 (93.9)
Treatment-related	467 (96.5)	175 (71.7)
TEAEs with Grade≥3	357 (73.8)	58 (23.8)
Treatment-related	324 (66.9)	21 (8.6)
Serious TEAEs	198 (40.9)	43 (17.6)
Treatment-related	175 (36.2)	17 (6.9)
TEAEs leading to dose interruption	391 (80.8)	56 (23.0)
TEAEs leading to dose reduction	347 (71.7)	25 (10.2)
TEAEs leading to treatment discontinuation	79 (16.3)	9 (3.7)
TEAEs leading to death	12 (2.5)	4 (1.6)

Abbreviations: TEAE = treatment-emergent adverse event

Source: Monk 2024¹⁶ and OS CSR⁸⁴

Common adverse events

The most common AEs occurring in at least 20% of patients in either treatment arm are presented in Table 15. The most common Grade ≥3 AEs in the niraparib group were thrombocytopenia (39.9%), anaemia (32.0%) and neutropenia (21.5%).¹⁶

Table 15. TEAEs occurring in ≥20% of patients in either treatment arm (safety population)

TEAE, n (%)	Niraparib (n=484)		Placebo (n=244)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Thrombocytopenia^a	326 (67.4)	193 (39.9)	12 (4.9)	1 (0.4)
Anaemia^b	316 (65.3)	155 (32.0)	48 (19.7)	5 (2.0)
Nausea	282 (58.3)	6 (1.2)	73 (29.9)	2 (0.8)
Neutropenia^c	210 (43.4)	104 (21.5)	19 (7.8)	4 (1.6)
Constipation	202 (41.7)	2 (0.4)	53 (21.7)	0
Fatigue	180 (37.2)	11 (2.3)	76 (31.3)	1 (0.4)
Headache	136 (28.1)	3 (0.6)	42 (17.2)	0
Insomnia	124 (25.6)	5 (1.0)	37 (15.2)	1 (0.4)
Abdominal pain	121 (25.0)	10 (2.1)	80 (32.8)	1 (0.4)

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

TEAE, n (%)	Niraparib (n=484)		Placebo (n=244)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Vomiting	118 (24.4)	4 (0.8)	32 (13.1)	2 (0.8)
Arthralgia	105 (21.7)	3 (0.6)	63 (25.8)	0
Hypertension ^d	100 (20.7)	35 (7.2)	23 (9.4)	5 (2.0)
Dyspnoea	98 (20.2)	3 (0.6)	38 (15.6)	2 (0.8)
Diarrhoea	96 (19.8)	4 (0.8)	61 (25.0)	1 (0.4)
Decreased appetite	96 (19.8)	3 (0.6)	23 (9.4)	0

Abbreviations: TEAE = treatment-emergent adverse event

^a Included thrombocytopenia and platelet count decreased

^b Included anaemia, haemoglobin decreased, red blood cell decreased, haematocrit decreased and anaemia macrocytic

^c Includes neutropenia, neutrophil decreased, febrile neutropenia and neutropenic sepsis

^d Includes hypertension, blood pressure increased and blood pressure fluctuation

Source: Monk 2024¹⁶

Adverse events with fixed versus individualised starting dose of niraparib

An individualised dosing regimen was introduced to allow patients with platelet count below 150,000/μL and/or weighing below 77kg to start on a lower dose of 200mg per day.¹⁶ Consistent with the primary analysis, the safety profile of niraparib improved with the use of an individualised starting dose.¹⁶ Patients on an individualised starting dose had a lower incidence of Grade ≥3 TEAEs compared to patients who received a fixed starting dose of niraparib (63.9% versus 79.0%, respectively).¹⁶ The AEs experienced by patients who received fixed versus individualised starting dose of niraparib are presented in Table 16.

Table 16. TEAEs in patients receiving a fixed versus individualised starting dose of niraparib

TEAE, n (%)	Fixed starting dose (n=315)		Individualised starting dose (n=169)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Thrombocytopenia ^a	234 (74.3)	155 (49.2)	92 (54.4)	38 (22.5)
Anaemia ^b	227 (72.1)	115 (36.5)	89 (52.7)	40 (23.7)
Nausea	189 (60.0)	4 (1.3)	93 (55.0)	2 (1.2)

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

TEAE, n (%)	Fixed starting dose (n=315)		Individualised starting dose (n=169)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Neutropenia ^c	150 (47.6)	79 (25.1)	60 (35.5)	25 (14.8)
Constipation	144 (45.7)	1 (0.3)	58 (34.4)	1 (0.6)
Fatigue	121 (38.4)	7 (2.2)	59 (34.9)	4 (2.4)
Headache	96 (30.5)	2 (0.6)	40 (23.7)	1 (0.6)
Insomnia	86 (27.3)	5 (1.6)	38 (22.5)	0
Abdominal pain	83 (26.3)	5 (1.6)	38 (22.5)	5 (3.0)
Vomiting	82 (26.0)	4 (1.3)	36 (21.3)	0
Arthralgia	70 (22.2)	3 (1.0)	35 (20.7)	0
Hypertension ^d	70 (22.2)	26 (8.3)	30 (17.8)	9 (5.3)
Dyspnoea	68 (21.6)	3 (1.0)	30 (17.8)	0
Diarrhoea	69 (21.9)	1 (0.3)	27 (16.0)	3 (1.8)
Decreased appetite	63 (20.0)	2 (0.6)	33 (19.5)	1 (0.6)

Abbreviations: TEAE = treatment-emergent adverse event

^a Included thrombocytopenia and platelet count decreased

^b Included anaemia, haemoglobin decreased, red blood cell decreased, haematocrit decreased and anaemia macrocytic

^c Includes neutropenia, neutrophil decreased, febrile neutropenia and neutropenic sepsis

^d Includes hypertension, blood pressure increased and blood pressure fluctuation

Source: Monk 2024¹⁶

2.5 PRIME

2.5.1 Summary of methodology of the relevant clinical effectiveness evidence

PRIME included patients with newly diagnosed, histologically confirmed, high-grade (predominantly) serous or endometrioid ovarian cancer (epithelial ovarian cancer, fallopian tube carcinoma, or primary peritoneal carcinoma) that was classified as FIGO stage III or IV.¹³ Patients who received primary or interval debulking surgery were included in the trial, regardless of the cytoreductive outcome (optimal, residual tumour ≥1 cm or suboptimal, residual tumour >1 cm).¹³ Patients also received 6 to 9 cycles of PBC and had a complete or partial response.¹³ The trial stratified by subgroups, including HRD

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

status, germline BRCA status, receipt of neoadjuvant chemotherapy and clinical response with 1L PBC.¹³

Patients were randomised 2:1 to receive either:¹³

- Niraparib orally once daily,
 - 300 mg for patients with a body weight of ≥ 77 kg and platelet count $\geq 150,000$ per cubic millimetre or
 - 200 mg for patients with a body weight of < 77 kg and/or platelet count $< 150,000$ per cubic millimetre
- Matched placebo orally once daily.

Patients were treated until disease progression, unacceptable toxicity, or up to a maximum of 36 months.¹³ In the case of AEs caused by the study treatment, the investigator adjusted the dose according to the prespecified dose modification criteria, involving dose interruptions (no longer than 28 days) or dose reductions (Table 17).¹³

Table 17. Dose modification scheme for niraparib

Dose level	Starting dose: 300 mg QD	Starting dose: 200 mg QD
Starting dose	300 mg QD	200 mg QD ^a
First dose reduction	200 mg QD ^c	100 mg QD ^{b,c}
Second dose reduction	100 mg QD ^{b,c}	Not applicable

Abbreviations: QD = once daily

^a For patients whose starting dose is 200 mg, dose elevation to 300 mg was allowed if there was no dose interruption or reduction caused by AEs in the first two cycles of treatment.

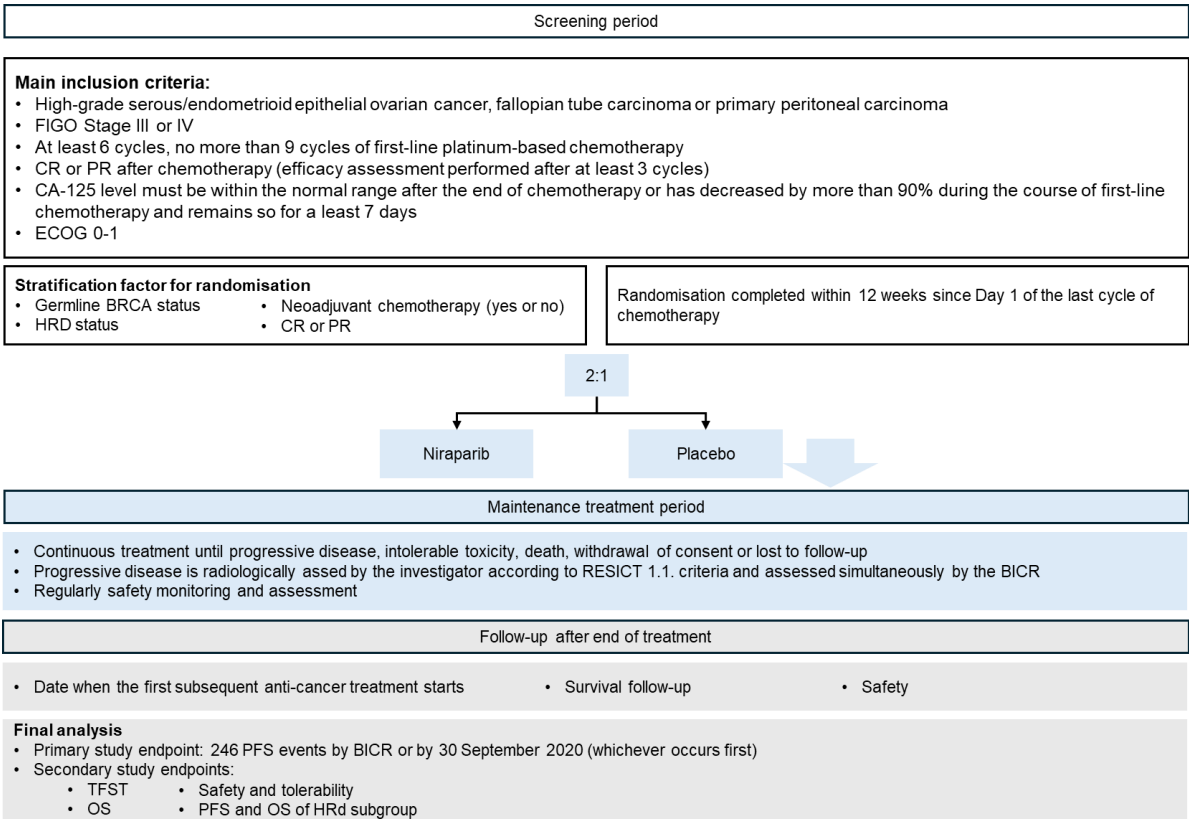
^b If AES requiring dose modification occurred at the dose level of 100 mg, treatment should be discontinued unless the investigator considered the patient would benefit from continuing medication or further dose reduction and the permission of the sponsor's medical monitor was obtained.

^c After reduction of study drugs from 200 mg QD to 100 mg QD, the dose escalation back to 200 mg QD might have been considered if it is well tolerated during at least one treatment cycle. After reduction of study drugs from the starting dose of 300 mg QD to 200 mg QD, the dose escalation back to 300 mg QD might have been considered if it was well tolerated during at least two treatment cycles.

Source: Li 2023¹³

The primary endpoint was progression-free survival by BICR in the ITT population, whereby PFS was defined as the duration from randomisation to disease progression or death of any cause, whichever occurred earlier.¹³ Secondary endpoints of the PRIME study are presented in Table 5, while the study design of PRIME is illustrated in Figure 9. Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Figure 9. PRIME study design



Abbreviations: BICR = blind independent central review; BRCA = breast cancer gene; Ca A-125 = cancer antigen 125; CR = complete response; ECOG = Eastern Cooperative Oncology Group; FIGO = FIGO = International Federation of Gynaecology and Obstetrics; HRD = homologous recombination deficiency; OS = overall survival; PFS = progression-free survival; PR = partial response; TFST = time to first subsequent therapy
Source: Li 2023¹³

In the overall trial population (n=384), the proportion of patients with stage IV disease was 28.1% (n=108), 46.9% (n=180) received neoadjuvant chemotherapy, 13.0% (n=50) achieved suboptimal debulking and 18.0% (n=69) had a partial response to PBC.¹³ Germline BRCA mutations were reported in 32.6% of patients and the proportion of patients with HRd, HRp and HRunknown disease were 66.9%, 22.1% and 10.9%, respectively.¹³

Patient baseline characteristics were well balanced between the niraparib and placebo arms.¹³ Similar proportions of patients in the niraparib and placebo arms had ECOG 1 (61.6% vs 59.7%), FIGO stage III (71.4% vs 72.9%), FIGO stage IV (28.6% vs 27.1%),
Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

and complete response after PBC (83.1% vs 79.8%).¹³ A partial response after PBC was reported in smaller proportion of patients in the niraparib arm (16.9%) compared with the placebo arm (20.2%).¹³

The baseline characteristics for PRIME are presented in Table 18.

Table 18. Baseline characteristics of participants enrolled in the PRIME trial

	Niraparib (N=255)	Placebo (N=129)
Median age (range), years	53 (32, 77)	54 (33, 77)
ECOG PS, n (%)		
0	98 (38.4)	52 (40.3)
1	157 (61.6)	77 (59.7)
FIGO stage, n (%)		
III	182 (71.4)	94 (72.9)
A	8 (3.1)	5 (3.9)
B	14 (5.5)	8 (6.2)
C	154 (60.4)	80 (62.0)
Not specified	6 (2.4)	1 (0.8)
IV	73 (28.6)	35 (27.1)
Primary tumour location, n (%)		
Ovary	229 (89.8)	117 (90.7)
Fallopian tube	19 (7.5)	9 (7.0)
Peritoneum	7 (2.7)	3 (2.3)
Histologic type, n (%)		
Serous	253 (99.2)	128 (99.2)
Endometrioid	2 (0.8)	0
Other	0	1 (0.8)
Neoadjuvant chemotherapy, n (%)		
Yes	121 (47.5)	59 (45.7)
No	134 (52.5)	70 (54.3)
Clinical response after platinum-based chemotherapy, n (%)		
CR	212 (83.1)	103 (79.8)
PR	43 (16.9)	26 (20.2)
Cancer antigen 125 level, n (%)		
≤35 U/mL	252 (98.8)	128 (99.2)
>35 U/mL	3 (1.2)	1 (0.8)

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

	Niraparib (N=255)	Placebo (N=129)
Germline BRCA variant status, n (%)^a		
Germline BRCA variant	85 (33.3)	40 (31.0)
Non-germline BRCA variant	170 (66.7)	89 (69.0)
Homologous recombination status, n (%)^b		
Deficient	170 (66.7)	87 (67.4)
Proficient	60 (23.5)	25 (19.4)
Unknown	25 (9.8)	17 (13.2)
Cytoreductive surgery outcome, n (%)^c		
Optimal debulking (R0/R1)	193 (75.7)	105 (81.4)
Suboptimal debulking (R2)	36 (14.1)	14 (10.9)
Missing	26 (10.2)	10 (7.8)

Abbreviations: BRCA = breast cancer gene; CR = complete response; ECOG = Eastern Cooperative Oncology Group; FIGO = International Federation of Gynaecology and Obstetrics; HRD = homologous recombination deficiency; PR = partial response; ULN = upper limit of normal

^a Germline BRCA variants included pathogenic and suspected pathogenic ones; the others were classified as non-germline BRCA variants.

^b The homologous recombination status was deficient if a patient had germline BRCA variants and/or the tumour HRD status was positive on the HRD assay, proficient if a patient had no germline BRCA variants and the tumour HRD status was negative on the HRD assay, and unknown if a patient had no germline BRCA mutations and the tumour HRD status was unknown on the HRD assay.

^c Optimal debulking was defined as the largest residual tumour nodule measuring ≤1 cm; suboptimal debulking was defined as the largest residual tumour nodule measuring >1 cm.

Source: Li 2023¹³

2.5.2 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

PRIME efficacy and safety analyses were performed in accordance with a comprehensive Statistical Analysis Plan.^{78,79}

2.5.2.1 Primary efficacy analysis

The primary endpoint in the PRIME study was PFS in the ITT population, defined as the time from randomisation to the date of first documentation of disease progression (as assessed by blinded, independent, central imaging assessment) that meets the RECIST 1.1 criteria for disease progression or death due to any cause.^{78,79} The assumptions for the statistical analysis of PFS are presented in Table 6.^{78,79}

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

2.5.2.2 Secondary efficacy analysis

Secondary endpoints in the PRIME study included OS (defined as duration from randomisation to death of any cause) and TFST (defined as duration from randomisation to the initiation of first subsequent anticancer therapy or death) in the ITT population, and PFS and OS in the subgroup of patients with germline BRCAm and HRD.^{78,79}

TFST was tested hierarchically after significance was shown for PFS, with controlled overall type I errors at the two-sided 0.05 level. For both OS and TFST, a stratified Cox proportional hazard model was used to estimate HRs and 95% CIs. OS was also plotted using the Kaplan-Meier method.^{78,79}

2.5.2.3 Safety analysis

Safety was explored in the safety analysis population and analyses were performed descriptively, with TEAEs summarised by treatment group. TEAE grading was conducted using the NCI CTCAE, version 4.03. TEAEs leading to death, treatment discontinuation or dose reduction, TEAEs grade 3 or higher, SAEs and TRAEs were presented in the PRIME study.^{78,79}

The relationship between TEAEs and the study drug was assessed based on, among other factors, symptom timing and its relief upon drug reduction or withdrawal and recurrence upon reintroduction, possible alternative causes, and evidence from literature. In case of insufficient information, TEAEs were considered conservatively a TRAE.^{78,79}

2.5.3 Critical appraisal of the relevant clinical effectiveness evidence

The PRIME trial is a randomised, double-blinded, placebo-controlled trial. The quality assessment of this trial is noted in Table 19.

Table 19. Quality assessment of PRIME

Quality assessment	PRIME	Notes
Was randomisation carried out appropriately?	Yes	Randomisation was performed in a double-blinded manner with the use of an interactive Web-response system, with stratification according to clinical response to platinum-based chemotherapy, receipt of neo-adjuvant chemotherapy, germline <i>BRCA</i> status and HRD status.
Was the concealment of treatment allocation adequate?	Yes	The identity of the treatments was concealed using study treatments that were identical in appearance, packaging, labelling, and schedule of administration. Patients and investigators were only unblinded to study treatment in cases associated with important medical reasons, as determined by the investigator. The process for unblinding the identity of the assigned treatment was outlined in the study protocol. Patients who required unblinding were permanently discontinued from the study.
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Baseline characteristics were well balanced in each cohort. Stratification at randomisation was used in the PRIME study to mitigate any potential imbalance in baseline characteristics or prognostic factors that could impact the treatment effect.
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	The objective assessment of progressive disease was determined by central radiologic review in a blinded manner, according to RECIST. Study patients, Investigators, study staff, and the Sponsor's study team and its representatives were blinded to the identity of the assigned treatment from the time of randomisation until final database lock. Patients and investigators were not unblinded to study treatment except in cases associated with important medical reasons, as determined by the Investigator. Patients who required unblinding were permanently discontinued from the study.
Were there any unexpected imbalances in dropouts between groups?	No	The drop out rate and the reasons for discontinuation were balanced across the treatment arms.

Quality assessment	PRIME	Notes
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	All primary and secondary endpoint analyses are reported in the Statistical Analysis Plan
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes, the ITT population is the primary population for efficacy analyses. It was not described how missing data was handled in the analysis and whether adjusted values were analysed.
Did the authors of the study publication declare any conflicts of interest?	Yes	Two of the authors were employees of and holding shares and stock options in Zai Lab during the conduct of the study. One author reported grants from Zai Lab during the conduct of the study.

Abbreviations: BRCA = breast cancer gene; HRD = homologous recombination deficiency; ITT = intention to treat

2.5.4 Clinical effectiveness results of the relevant studies

2.5.4.1 Primary efficacy outcome: PFS

At the primary analysis clinical cut off (30 September 2021), PFS results for the PRIME trial were reported for a median duration of follow-up of 27.5 months (95% CI: 25.3, 27.6) and 27.6 months (95% CI: 24.9, 30.3) for the niraparib and placebo groups, respectively, for patients in the ITT population.¹³

Maintenance treatment with niraparib led to a statistically significant reduction in the risk of disease progression or death by 55% versus placebo in the ITT population as assessed by BICR (HR: 0.45; 95% CI: 0.34, 0.60; $p < 0.001$).¹³ Median PFS was longer in the niraparib group compared to the placebo group, at 24.8 months vs 8.3 months, respectively.¹³ This provided patients treated with niraparib a median increase of 16.5 months of living without disease progression or death compared to those treated with placebo.¹³ A smaller proportion of patients in the niraparib treatment group had progressed or died compared to those in the placebo group (48.2% vs 66.7%).¹³ The Kaplan-Meier plot for PFS with niraparib and placebo is presented in [REDACTED].

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Abbreviations: BICR = blinded independent central review; CI = confidence interval; ITT = intention-to-treat; NE = not estimable; PFS = progression-free survival
Source: Li 2023¹³

Patients treated with niraparib maintained a lower risk of death or progression throughout their follow-up period compared to those treated with placebo.¹³ Furthermore, these benefits in PFS occurred early in the treatment period, with a distinct separation between the Kaplan-Meier plots for niraparib and placebo demonstrated at 3 months since randomisation.¹³

2.5.4.2 Secondary efficacy outcomes

Niraparib led to a statistically significant reduction in the risk of receiving TFST.¹³ In line with results for PFS, niraparib statistically significantly improved TSFT (HR: 0.45; 95% CI: 0.34, 0.59; $p < 0.001$) (**Error! Reference source not found.**).¹³ Median time to first subsequent treatment was longer in the niraparib arm (29.2 months) compared with the placebo arm (11.9 months).¹³

[REDACTED]

[REDACTED]

Abbreviations: CI = confidence interval; ITT = intention-to-treat; NE = not estimable; TFST = time to first subsequent anti-cancer therapy
Source: Li 2023¹³

At the primary analysis cut-off (30 September 2021), median OS was not reached in either treatment arm, with 37 and 28 events occurring in the niraparib and placebo arms, respectively, in the ITT population. OS data show a numerical benefit in favour of treatment with niraparib (HR: 0.63; 95% CI: 0.38, 1.03).¹³ The estimated 24-month OS rate was 87.3% for niraparib and 82.7% for placebo.¹³ The Kaplan-Meier plot for OS with niraparib and placebo is presented in **Error! Reference source not found..**

Abbreviations: ITT = intention-to-treat; mo = months NE = not estimable; NR = not reached; OS = overall survival
Source: Li 2023¹³

Subgroup analyses for the HRd subgroup are presented in Section 2.5.6.

2.5.5 Subsequent treatments used in the relevant studies

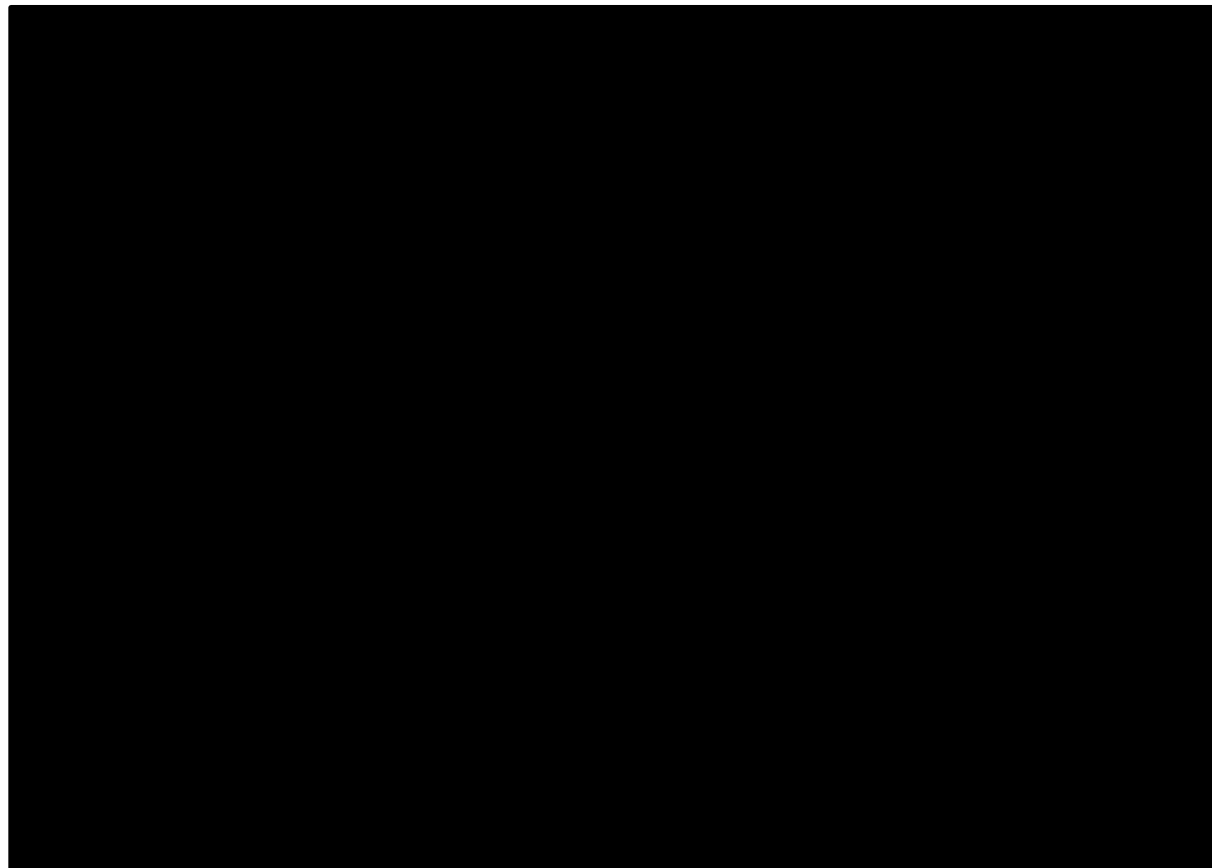
Details on subsequent treatment therapies were not provided in the PRIME study.

2.5.6 Subgroup analysis

2.5.6.1 Primary efficacy outcome

PFS results were consistent across pre-planned subgroup analyses, with niraparib performing better than placebo across the predefined subgroups (**Error! Reference source not found.**).¹³ The risk of disease progression or death was significantly lower in patients treated with niraparib compared to placebo in both the HRd (HR 0.48; 95% CI: 0.34, 0.68) and HRp (HR 0.41; 95% CI: 0.22, 0.75) subgroups, and regardless of whether they had gBRCAm (HR 0.40; 95% CI: 0.23, 0.68) or not (HR 0.48; 95% CI: 0.34, 0.67).¹³ Kaplan-Meier curves for above subgroups are presented in the Appendix (Section C.1.1.2).

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer



Abbreviations: BRCA = breast cancer gene; CI = confidence interval; ITT = intention to treat; PFS = progression-free survival

^a The germline BRCA variants include pathogenic and suspected pathogenic ones; the others were classified as non-germline BRCA variants

^b The homologous recombination status was deficient if a patient had germline BRCA variants and/or the tumour homologous recombination deficiency (HRD) status was positive on the HRD assay (BGI Genomics), proficient if a patient had no germline BRCA variants and the tumour HRD status was negative on the HRD assay, and indeterminate if a patient had no germline BRCA variants and the tumour HRD status was unknown on the HRD assay.

Source: Li 2023¹³

2.5.6.2 Secondary efficacy outcomes

The results for the subgroup analyses for OS from the PRIME trial are presented in Appendix C.1.2.2.

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

2.5.7 Adverse reactions

2.5.7.1 Overview

Niraparib was generally well tolerated and has an acceptable and established safety profile, with no new safety signals identified.¹³ The safety analysis was conducted in the safety population (niraparib: n=255; placebo: n=129) for patients who received at least 1 dose of the study drug.¹³ Safety results are presented for the primary analysis (clinical cut off 30 September 2021).¹³

2.5.7.2 Exposure

The median study drug exposure was 19.3 months (range: 0.1, 38.5) with niraparib and 10.2 months (range: 0.4, 38.2) with placebo.¹³ The median relative dose intensity (percentage of administered doses relative to initially planned doses) in the niraparib and placebo groups were 100% (range: 26.0%, 147.0%) and 100.0% (range: 36.0%, 147.0%), respectively.¹³

2.5.7.3 Dosage

Dose reductions and interruptions were allowed in the trial for the management of AEs (Table 20).¹³ In the niraparib group, 160 patients (62.7%) had at least one TEAE leading to treatment interruption compared to 25 patients (19.4%) in the placebo group.¹³ Dose reductions due to TEAEs occurred in 103 patients (40.4%) in the niraparib arm vs 8 patients (6.2%) in the placebo arm.¹³ In the niraparib group, the most common TEAEs leading to dose reductions were haematologic TEAEs, including decreased platelet count (24.3%), anaemia (10.2%), decreased neutrophil count (9.8%) and decreased white blood cell count (3.1%).¹³ Detailed results on TEAEs leading to dose reductions in both treatment arms are presented Table 108, Appendix D. Most TEAEs were well controlled, leading to low treatment discontinuation rates in both niraparib (6.7%) and placebo (5.4%) arms.¹³

Table 20. Summary of dose intensity, exposure and the need for dose reductions and dose interruptions in the PRIME trial

Parameter	Niraparib (N=255)	Placebo (N=129)
Overall treatment exposure (months)		
Median	19.3	10.2
Min, Max	0.1, 38.5	0.4, 38.2
Relative dose intensity (%)		
Median	100.0	100.0
Min, Max	26.0, 147.0	36.0, 147.0
Overall dose interruptions due to AE, n (%)	160 (62.7)	25 (19.4)
Overall dose reductions due to AE, n (%)	103 (40.4)	8 (6.2)

Abbreviations: AE = adverse event; max = maximum; min = minimum; SD = standard deviation

Source: Li 2023¹³

2.5.7.4 Safety profile

Incidence of adverse events

In the safety population, most subjects in both treatment groups experienced at least one TEAE, including 253 (99.2%) of 255 subjects who received niraparib and 121 (93.8%) of 129 subjects who received placebo.¹³ In the niraparib arm, 97.6% of patients experienced a treatment-related AE compared to 86.0% of patients in the placebo arm.¹³ The proportions of patients experiencing a Grade ≥ 3 TEAE were 54.5% and 17.8% in the niraparib and placebo arms, respectively.¹³ In the niraparib arm, 1 patient (0.4%) experienced an adverse event leading to death (while no deaths were reported in the placebo arm).¹³ A summary of TEAEs is presented in Table 21.

In the niraparib arm, 48 patients (18.8%) experienced serious TEAEs, as did 11 patients (8.5%) in the placebo arm.¹³ One case of MDS and one case of AML were reported in the niraparib arm, the latter of which led to death.¹³

Table 21. Summary of TEAEs in the safety population

TEAEs, n (%)	Niraparib (N=255)	Placebo (N=129)
Any TEAEs	253 (99.2)	121 (93.8)
Treatment-related	249 (97.6)	111 (86.0)
TEAEs with Grade^a≥3	139 (54.5)	23 (17.8)
Treatment-related	125 (49.0)	9 (7.0)
Serious TEAEs	48 (18.8)	11 (8.5)
Treatment-related	38 (14.9)	5 (3.9)
TEAEs leading to treatment interruption	160 (62.7)	25 (19.4)
TEAEs leading to dose reduction^b	103 (40.4)	8 (6.2)
TEAEs leading to treatment discontinuation	17 (6.7)	7 (5.4)
TEAEs leading to death	1 (0.4)	0

Abbreviations: TEAE = treatment-emergent adverse event

^a Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.

^b Included both direct dose reduction and dose reduction following treatment interruption.

Source: Li 2023¹³

Common adverse events

The most common AEs occurring in at least 20% of patients in either treatment arm are presented in Table 22. Among the most common Grade ≥3 AEs in the niraparib group were anaemia (18.0%), decreased neutrophil count (17.3%), decreased platelet count (14.1%) and decreased white blood cell count (6.7%).¹³

Table 22. TEAEs occurring in ≥20% of patients in either treatment arm (safety population)

TEAE, n (%)	Niraparib (n=255)		Placebo (n=129)	
	Any Grade	Grade ^a ≥3	Any Grade	Grade ^a ≥3
Neutrophil count decreased ^b	167 (65.5)	44 (17.3)	51 (39.5)	2 (1.6)
White blood cell count decreased ^c	166 (65.1)	17 (6.7)	48 (37.2)	1 (0.8)
Anaemia	146 (57.3)	46 (18.0)	34 (26.4)	2 (1.6)
Platelet count decreased ^d	133 (52.2)	36 (14.1)	13 (10.1)	1 (0.8)
Nausea	114 (44.7)	1 (0.4)	24 (18.6)	1 (0.8)
Aspartate transaminase increased	97 (38.0)	1 (0.4)	25 (19.4)	0

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

TEAE, n (%)	Niraparib (n=255)		Placebo (n=129)	
	Any Grade	Grade ^a ≥3	Any Grade	Grade ^a ≥3
Alanine transaminase increased	92 (36.1)	3 (1.2)	30 (23.3)	1 (0.8)
Insomnia	80 (31.4)	0	14 (10.9)	0
γ-Glutamyl transferase increased	73 (28.6)	13 (5.1)	22 (17.1)	3 (2.3)
Fatigue	71 (27.8)	2 (0.8)	19 (14.7)	0
Constipation	54 (21.2)	0	11 (8.5)	0
Vomiting	52 (20.4)	5 (2.0)	12 (9.3)	2 (1.6)

Abbreviations: TEAE = treatment-emergent adverse event

^a Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.

^b Included reports of neutrophil count decreased and neutropenia

^c Included reports of white blood cell count decreased and leukopenia

^d Included reports of platelet count decreased and thrombocytopenia

Source: Li 2023¹³

2.6 Meta-analysis

Although both PRIMA and PRIME evaluated niraparib, a meta-analysis was not considered feasible due to the differences in the patient populations and the lack of data for the high-risk subgroup from PRIME.

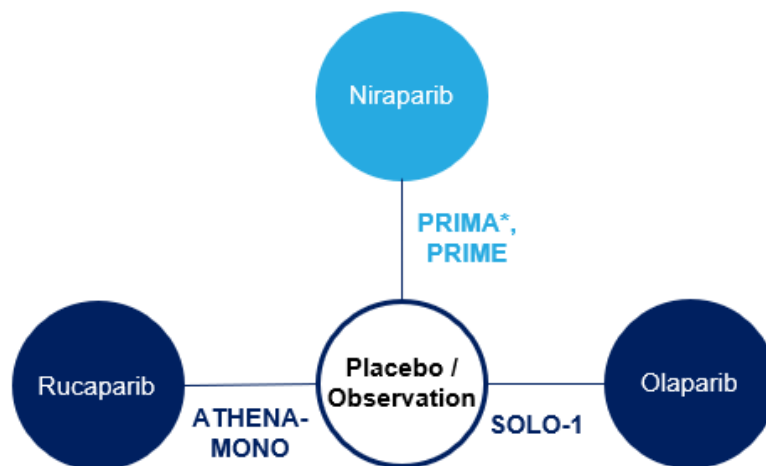
2.7 Indirect and mixed treatment comparisons

As detailed in Appendix B (Section B1.1), the clinical SLR identified eight relevant studies for 1L maintenance in aOC: SOLO-1, PAOLA-1, ATHENA-MONO, PRIME, PRIMA, FLAMES, OVARIO, Oda 2024. Of these eight trials, four were not considered appropriate for the ITC and were excluded. The Oda 2024 trial was excluded on the basis that it was a Phase 2 single-arm trial with limited sample size (N=32), while the FLAMES, OVARIO and PAOLA-1 trials were excluded as they assessed seneparib, niraparib plus bevacizumab and olaparib plus bevacizumab as interventions, respectively, which are not considered relevant comparators for niraparib. The PARPi monotherapy treatment options (olaparib and rucaparib) which are considered relevant comparators for niraparib are listed in Section 1.1, along with the rationale for their relevance.

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

The primary objective of the ITC was to estimate relative effects for i) olaparib vs niraparib in the BRCAm population and ii) rucaparib vs niraparib in the BRCAwt population. Therefore, four unique clinical trials were included in the ITC feasibility assessment (FA): SOLO-1, ATHENA-MONO, PRIME, and PRIMA. Additional details on the feasibility assessment are presented in Appendix B (Section B.1.1.5).

Figure 10. Network of Evidence for ITC FA



Abbreviations: FA = feasibility analysis; ITC = indirect treatment comparison

*Patient-level data are available for PRIMA, whereas aggregate-level data are available for all other studies.

The FA concluded that any ITCs involving these trials are likely inappropriate and fundamentally flawed due to differences in the timing and type of HRD tests administered, and inclusion criteria regarding visible residual disease status (i.e. a greater proportion of patients in the PRIMA trial had high-risk characteristics (e.g., greater proportion with known prognostic factors associated with a high-risk of relapse, such as stage IV disease and NACT), and the trial specifically excluded patients with stage III disease without VRD following primary debulking surgery [i.e., low-risk patients who have the best prognosis], who were included in trials for other PARPis). More information is available in Appendix B (Section B.1.1.5).

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Despite the significant limitations identified in the FA, several exploratory ITCs were conducted. Specifically, comparisons of PFS for niraparib versus olaparib were carried out on the subgroup of BRCAm and high-risk patients (i.e., stage III patients with VRD following PDS and stage IV patients) of SOLO-1 because data were available to facilitate a fairer comparison with respect to visible residual disease status. No OS comparisons were feasible because SOLO-1 did not report any OS data for the high-risk subgroup. Overall, as highlighted in the ITC FA (Section B.1.1.5), data are not available for several important factors for the high-risk subgroup in SOLO-1 (prior bevacizumab, histology, tumour location, timing of surgery, non-visible residual disease status following interval debulking surgery), precluding an appropriate ITC between olaparib and niraparib. An anchored STC was considered for adjusting for observed differences in baseline characteristics between the two studies. However, counter-intuitive associations were observed in the PRIMA trial between PFS and two key prognostic factors and effect modifiers (i.e., ECOG and age; more information provided in the following section), which made population adjustment unreliable (Section 2.7.2). Furthermore, population matching on some key potential effect modifiers, such as type of surgery (PDS vs IDS) and NVRD following surgery, would have been impossible as baseline information on these factors was not available for SOLO-1. Given these limitations, a Bucher ITC was conducted, which may provide an unadjusted and approximate relative effect of niraparib vs olaparib, despite the challenges in adjusting for baseline differences and the unavailability of data on key effect modifiers.

For comparisons vs rucaparib (ATHENA-MONO), subgroup analyses for ATHENA-MONO have not been published in a PRIMA-like population (i.e., excluding the lower-risk stage III patients without VRD). Therefore, it was only possible to compare niraparib (based on data from PRIME rather than PRIMA) with rucaparib (ATHENA-MONO) in a broader population comprising a mix of both low and high-risk patients. However, the proportions of patients with low and high-risk status in each trial were unknown. Importantly, patient-level data are not available for either trial, making Bucher ITCs (i.e. unadjusted comparisons for population differences) the only feasible option. Note that

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

substantial differences were identified in the distributions of effect modifiers (i.e. ECOG, primary tumour location, histology, BRCAm, response to 1L chemotherapy, CA-125) between PRIME and ATHENA-MONO, which are expected to be generally favourable (i.e., higher proportions of patients with improved outcomes) for ATHENA-MONO except for the higher proportion of patients with BRCAm in PRIME (i.e., BRCAm patients are expected to have better efficacy). These differences in the distribution of effect modifiers (Table 92) may bias the results of Bucher ITCs; therefore, to explore the consistency of the effect, ITCs were conducted across all biomarker subgroups.

The following table (Table 23) summarises the ITCs versus each comparator of interest that were conducted, along with the outcomes that were compared and the study populations in which the analyses were conducted.

Table 23. Summary of ITCs

Comparisons	Data Source	ITT	HRd	HRd/BRCAwt	BRCAm	HRp
Niraparib vs Rucaparib	ATHENA-MONO [rucaparib] and PRIME [niraparib])	Bucher ITC for PFS-IRC, OS	Bucher ITC for PFS-IRC, OS	Bucher ITC for PFS-IRC ^a	Bucher ITC for PFS-IRC ^a	Bucher ITC for PFS-IRC
Niraparib vs Olaparib	PRIMA vs SOLO-1 study: High-risk	-	-	-	Bucher ITC (anchored STC explored but found to be infeasible) for PFS-INV	-

Abbreviations: BRCAm = breast cancer mutation; BRCAwt = breast cancer wild type; HRd = homologous recombination deficiency; HRp = homologous recombination proficiency; ITC = indirect treatment comparison; ITT = intent-to-treat; OS = overall survival; PFS-INV = progression-free survival investigator-assessed; PFS-IRC = Progression-free survival indirect review committee-assessed; STC = simulated treatment comparison

^aPRIME reported subgroup results for patients with i) germline BRCAm and ii) non-germline BRCAm and HRd, which were used as proxies for Bucher ITCs vs the BRCAm and HRd / BRCAwt subgroups in ATHENA-MONO. In PRIME, 4.0%-6.4% of niraparib patients were expected to carry only somatic BRCAm variants (Li et al., 2023^{13a}); thus, the

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

germline BRCAm subgroup in PRIME likely does not include all randomized patients with a BRCAm, and the non-germline BRCAm subgroup likely consists of a pool of BRCAwt and somatic BRCAm patients (majority would be BRCAwt). In ATHENA-MONO, 10.8%-13.1% of patients had germline BRCAm, 5.9%-7.2% had somatic BRCAm, and 2.3%-3.6% had an unknown type of BRCAm (Monk et al., 2022¹⁴). In ATHENA-MONO, four BRCA/HRd subgroups were analyzed, consistent with how HRd classification was defined as a stratification factor for randomization: BRCAm (all types, including germline, somatic, and unknown type), BRCAwt / LOH high, BRCAwt / LOH low, BRCAwt / LOH indeterminate. The Bucher ITCs analyzed PFS data for the BRCAm and BRCAwt / LOH high (i.e., HRd) subgroups in ATHENA-MONO to preserve randomization. Although HRs were reported for germline BRCAm and somatic BRCAm subgroups in ATHENA-MONO (abstract by Oaknin et al., 2022⁸⁹), these results are susceptible to bias due to the risk of breaking randomization (i.e., type of BRCAm was not a stratification factor in ATHENA-MONO) and results were only reported for PFS-INV.

2.7.1 Niraparib (PRIME) vs rucaparib (ATHENA-MONO): Bucher ITCs

As described above, an ITC based on PRIMA versus ATHENA-MONO was not possible due to the lack of high-risk data for ATHENA-MONO. Therefore, Bucher ITCs based on published HRs for niraparib from PRIME and for rucaparib from ATHENA-MONO were conducted in a broader population comprising a mix of both low and high-risk patients. The ITC analyses revealed no statistically significant differences across all populations (ITT and subgroups). Across different subgroups and the ITT population, the OS and PFS benefits are likely to be similar between niraparib and rucaparib, regardless of the biomarker subgroup considered. Because equivalence between treatments was consistently observed across all populations considered in our analysis, we expect that these general findings also extend to the BRCAwt subgroup. Nonetheless, given the ITT analysis maintains the randomisation of the trials and maximises the sample size, it can be considered the most reliable relative treatment effect estimate when comparing two treatments of the same drug class with the same mechanism of action.

Table 24. Results of Bucher ITCs Comparing PFS: Niraparib (PRIME) vs Rucaparib (ATHENA-MONO)

Population	Study	Comparison	HR	95% CI LB	95% CI UB	P-value
ITT	PRIME	NIRA vs RS				
	ATHENA-MONO	RUCA vs RS				
	BUCHER ITC	NIRA vs RUCA				

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Population	Study	Comparison	HR	95% CI LB	95% CI UB	P-value
Biomarker subgroups						
BRCAm	PRIME	NIRA vs RS				
	ATHENA-MONO	RUCA vs RS				
	BUCHER ITC	NIRA vs RUCA				
HRd	PRIME	NIRA vs RS				
	ATHENA-MONO	RUCA vs RS				
	BUCHER ITC	NIRA vs RUCA				
HRd/BRCAwt	PRIME	NIRA vs RS				
	ATHENA-MONO	RUCA vs RS				
	BUCHER ITC	NIRA vs RUCA				
HRp	PRIME	NIRA vs RS				
	ATHENA-MONO	RUCA vs RS				
	BUCHER ITC	NIRA vs RUCA				

Abbreviations: BRCAm = breast cancer mutation; BRCAwt = breast cancer wild type; CI = confidence interval; HR = hazard ratio; HRd = homologous recombination deficiency; HRp = homologous recombination proficiency; ITC = indirect treatment comparison; ITT = intent-to-treat; LB = lower bound; NIRA = niraparib; PFS = progression-free survival; RS = routine surveillance; RUCA = rucaparib; UB = upper bound.

[REDACTED]

[REDACTED]

Abbreviations: BRCAm = breast cancer mutation; BRCAwt = breast cancer wild type; CI = confidence interval; HRd = homologous recombination deficiency; HRp = homologous recombination proficiency; ITC = indirect treatment comparison; ITT = intent-to-treat; PFS = progression-free survival.

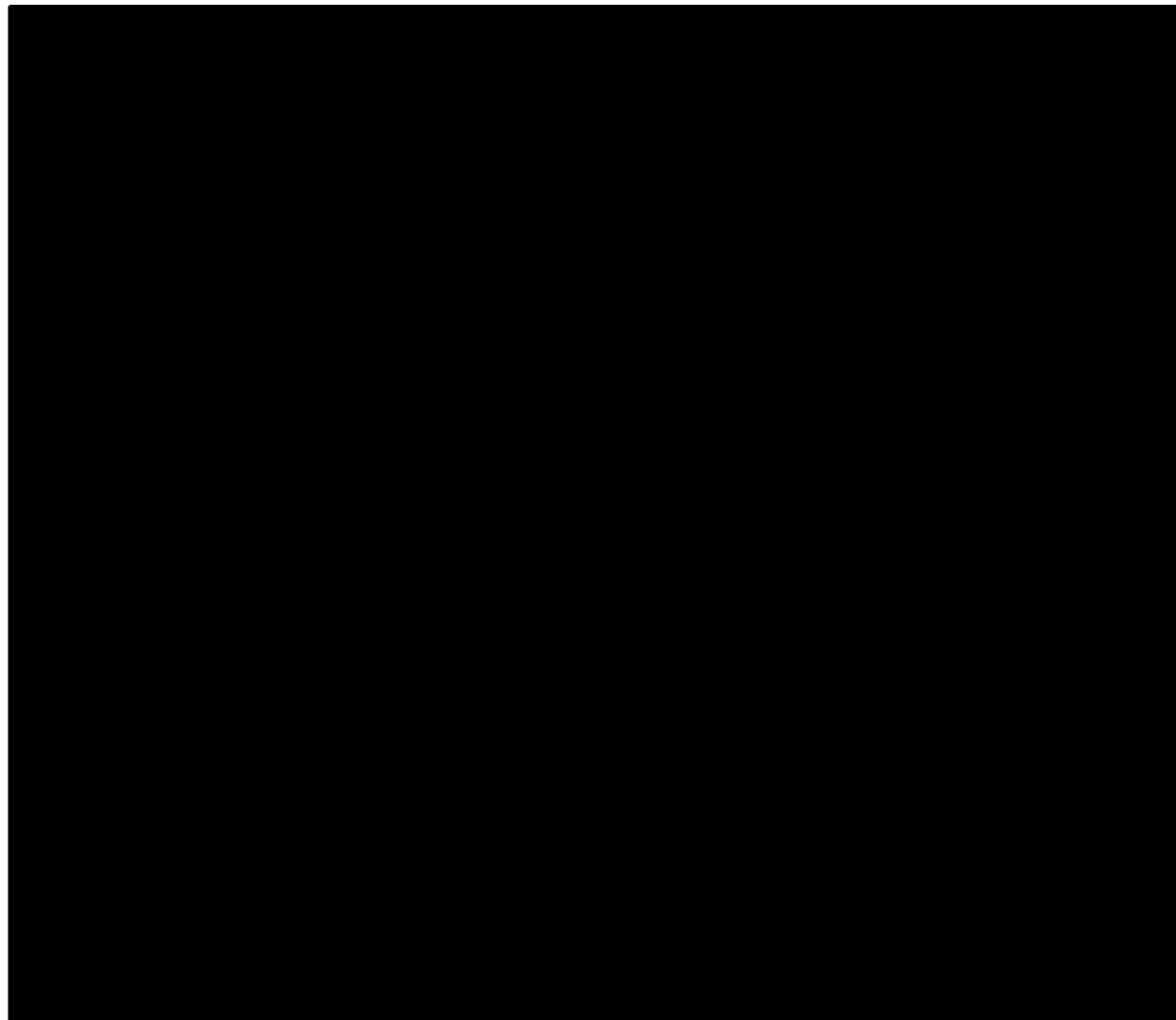
Table 25. Results of Bucher ITCs Comparing OS: Niraparib (PRIME) vs rucaparib (ATHENA-MONO)

Population	Study	Comparison	HR	95% CI LB	95% CI UB	p-value
ITT	PRIME	NIRA vs PBO	[REDACTED]	[REDACTED]	[REDACTED]	

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Population	Study	Comparison	HR	95% CI LB	95% CI UB	p-value
	ATHENA-MONO	RUCA vs PBO				
	BUCHER ITC	NIRA vs RUCA				
HRd	PRIME	NIRA vs PBO				
	ATHENA-MONO	RUCA vs PBO				
	BUCHER ITC	NIRA vs RUCA				

Abbreviations: CI = confidence interval; HR = hazard ratio; HRd = homologous recombination deficiency; ITC = indirect treatment comparison; ITT = intent-to-treat; LB = lower bound; NIRA = niraparib; OS = overall survival; PBO = placebo; RUCA = rucaparib; UB = upper bound.



Abbreviations: HR = hazard ratio; HRd = homologous recombination deficiency; ITC = indirect treatment comparison; ITT = intent-to-treat; OS = overall survival.

2.7.2 Niraparib (PRIMA) vs olaparib (SOLO-1) in BRCAm: Anchored STC

The possibility of conducting an anchored STC for niraparib (PRIMA) vs olaparib (SOLO-1) adjusted for observed differences in treatment effect modifiers across studies was explored. The best fitting distribution was the generalised gamma, identified using goodness of fit statistics (e.g., Akaike's information criteria [AIC] and Bayesian information

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

criteria [BIC]) and observed vs predicted plots of survival probabilities. The generalised gamma regression model adjusting for treatment (i.e., niraparib vs placebo), prognostic factors and effect modifiers as covariates was fitted to the patient-level data in PRIMA. However, the results revealed counter-intuitive regression coefficients for two key prognostic factors and effect modifiers: ECOG and age. Patients receiving placebo who are classified as ECOG 0 had worse PFS compared with patients with ECOG 1 (■■■■■). This association was reversed in the niraparib treatment arm (i.e. ECOG 0 was protective, as expected). Similarly, age <54 years was associated with worse PFS in the placebo and niraparib arms (■■■■■). These counter-intuitive associations in the BRCam subgroup were also observed in the fitted STC model. The treatment-specific acceleration factors for age ≤54 vs >54 years from the generalised gamma fitted model were less than 1 for both arms (placebo: ■■■■, niraparib: ■■■■), indicating worse PFS for younger patients at baseline. The acceleration factor for ECOG 0 vs 1 was ■■■■ for placebo, indicating worse PFS for patients with baseline ECOG 0 (vs 1), and ■■■■ for niraparib, indicating improved PFS for patients with ECOG 0 (vs 1).

These counter-intuitive associations may be explained by the fact that we have focused on a small subset of the data (i.e., BRCam), because associations in the ITT population were either reversed or null. Furthermore, it is important to note that randomisation was not preserved within the BRCam subgroup in PRIMA, as it was not a stratification factor in the trial. Due to the relatively small sample sizes in the BRCam subgroup in PRIMA and the number of variables included in the model, there is also a risk of overfitting. For these reasons, the regression model likely has poor generalisability properties and cannot reliably predict outcomes in the SOLO-1 population. Furthermore, even if the associations with age and ECOG were clinically intuitive, population adjustment would likely remain biased due to the lack of key baseline characteristics needed to minimise bias from cross-trial comparisons (e.g. type of surgery (PDS vs IDS) and NVRD following surgery). Therefore, the STC method was considered unreliable, and only the results from the Bucher ITC were used to inform the cost-effectiveness model.

[REDACTED]

[REDACTED]

Abbreviations: BRCAm = breast cancer mutation; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; ITT = intent-to-treat; PFS-INV = progression-free survival investigator-assessed.

[REDACTED]

[REDACTED]

Abbreviations: BRCAm = breast cancer mutation; CI = confidence interval; HR = hazard ratio; ITT = intent-to-treat; PFS-INV = progression-free survival investigator-assessed.

2.7.3 Niraparib (PRIMA) vs olaparib (SOLO-1): Bucher ITCs

The unadjusted HR (95% CI) for niraparib (PRIMA) vs olaparib (SOLO-1) based on the Bucher ITC was estimated as [REDACTED]. The difference was not statistically significant, and the confidence interval was very wide, consistent with equivalence. Furthermore, observable differences in the relative HR must be interpreted with caution, as it is based on an unadjusted analysis.

Table 26. Results of Bucher ITCs Comparing PFS: niraparib (PRIMA) vs olaparib (SOLO-1)

Comparison	HR	95% CI
PRIMA (niraparib vs PBO)	████	████████
SOLO-1 (olaparib vs PBO)	████	████████
Bucher ITC (niraparib vs olaparib)	████	████████

Abbreviations: CI = confidence interval; HR = hazard ratio; ITC = indirect treatment comparison; PBO = placebo; PFS = progression-free survival.

2.7.4 Uncertainties in the indirect and mixed treatment comparisons

Each of the exploratory ITCs were subject to bias which could not be controlled for with adequate adjustments. For niraparib versus rucaparib comparisons, the lack of relevant data for the high-risk subgroup in ATHENA-MONO meant that conducting an ITC using patient-level data from PRIMA was not feasible. As a result, Bucher ITCs were conducted to indirectly compare PRIME with ATHENA-MONO. Whilst the PRIME trial enrolled a patient population with a more comparable risk profile to ATHENA-MONO than that of PRIMA, imbalances remained in the baseline demographics between trials which could not be adjusted for due to the lack of patient-level data for either trial. In addition, baseline characteristics were reported only for the ITT population in both trials and not for the subgroups. Therefore, the PRIME/ATHENA-MONO Bucher ITCs for the subgroups are inherently subject to an unknown degree of bias due to cross-trial comparisons and the breaking of randomisation. Furthermore, the relative treatment effect specifically within the BRCAwt population, which is relevant to the decision problem, could not be investigated as data for this biomarker subgroup was not reported for ATHENA-MONO.

For ITCs comparing niraparib with olaparib, limited data on baseline characteristics were available for the high-risk BRCAm subgroup from SOLO-1, with key effect modifiers (such as NVRD status) missing. Moreover, comparisons were limited to PFS outcomes due to the absence of OS data from SOLO-1. Although an STC was initially considered, the regression model lacked external validity, compromising the reliability of the analysis. As a result, an unadjusted Bucher ITC was conducted as the next best alternative; however,

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

the absence of detailed patient characteristics makes it impossible to rule out potential imbalances in effect modifiers between studies, reducing the robustness of the findings.

2.8 Effectiveness from real-world evidence (RWE)

The real-world effectiveness of niraparib in 1L maintenance treatment of advanced OC has been demonstrated in studies identified through the previously described SLR (Section 2.2 and Appendix B1.1),⁹⁰ as well as data from the UK SACT database.¹⁹

2.8.1 RWEs identified in the SLR

In the systematic literature review, 23 RWE studies for niraparib as a maintenance treatment in advanced OC following 1L PBC were identified. These RWEs consistently support the key findings from the PRIMA and PRIME trials regarding the efficacy and safety of niraparib, demonstrating its effectiveness in real-world settings (see Appendix B1.4 for a summary of all RWE studies). A summary of the RWEs identified in the SLR are presented in Table 27.

Table 27. RWE of niraparib identified in the SLR

Study, author, year	Study design	Maintenance therapy(s) (n)	Study location	Population/subgroups
Apostol 2023	Retrospective	Niraparib (124)	Italy	Overall population
Salani 2025 Backes 2023 Coleman 2023 Salani 2024 Backes 2025 (CHAR1ZMA)	Retrospective Flatiron Health database	Niraparib (560)	US	Overall population HRd BRCAm/HRd BRCAwt/HRd
Bruno 2024	Retrospective	Niraparib (124)	Italy	Overall population
Chase 2025 Chase 2024 (AR1ZE)	Retrospective Flatiron Health database	Niraparib (453)	US	Overall population (PRIMA-like cohort) Overall population (Stage III NVRD cohort)
Chen 2024	Retrospective	Niraparib (60) Olaparib (104)	China	Overall population
Chase 2024 (PRED1CT)	Retrospective Flatiron Health database	Niraparib (526)	US	Overall population
Ha 2024	Retrospective	Niraparib (64)	South Korea	Overall population

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Study, author, year	Study design	Maintenance therapy(s) (n)	Study location	Population/subgroups
		Olaparib (27)		
Han 2024	Retrospective Korean National Health Insurance Service	Niraparib (118) Olaparib (104)	South Korea	Overall population
Hannaway 2023	Retrospective	Niraparib (83)	Canada	Overall population (all BRCAwt/HRD unknown)
Hashimoto 2023	Retrospective	Niraparib (45)	Japan	Overall population
Khaja 2024	Retrospective	Niraparib (19)	UK	Overall population
Kim 2024	Retrospective	Niraparib (31) Olaparib (80)	South Korea	Matched cohort (all BRCAm)
Li 2022	Retrospective	Niraparib (93)	China	Overall population
Nakamura 2024	Retrospective	Niraparib (60) Olaparib (30) Olaparib + bevacizumab (27)	Japan	Overall population
Piedimonte 2024	Retrospective	Niraparib (52)	Canada	Overall population (all BRCAwt/HRD unknown)
Shin 2021	Retrospective	Niraparib (32)	South Korea	Overall population
Rimel 2024 (SW1TCH)	Retrospective Flatiron Health database	Niraparib (93)	US	Overall population
Wenxin 2023	Retrospective	Niraparib (102)	China	Overall population
Zhao 2023 (NCT05734911)	Retrospective	Niraparib (199)	China	Overall population BRCAm BRCAwt HRd HRp
de la Motte Rouge 2022	Prospective	Niraparib (67)	France	Overall population
Jeong 2024	Prospective	Niraparib (53)	South Korea	Overall population
Zuo 2024 Zheng 2024 (RENI-1)	Prospective	Niraparib (227)	China	Overall population BRCAm BRCAwt
Hasson 2024 (MONITOR-UK)	Ambispective	Niraparib (166)	UK	Overall population Germline BRCAm

Abbreviations: BRCAm = BRCA mutation; BRCAwt = BRCA wild type; HRd = homologous recombination deficiency; HRp = homologous recombination proficient

2.8.1.1 Key highlights of niraparib's efficacy

Consistency of niraparib's effectiveness with PRIMA findings

CHAR1ZMA, a large (N = 560), retrospective cohort study using the Flatiron Health database (US nationwide electronic-health-record-derived data) showed that the median Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

real-world PFS was 11.4 months and the median TTNT was 12.4 months.⁹¹ The benefits of niraparib were more pronounced in the HRd subgroup compared to the overall study population, with a median PFS of 18.2 months and a median TTNT of 19.6 months (Table 28)⁹¹. Within the HRd subgroup, patients with BRCAm had a notably higher median real-world PFS of 25.4 months, indicating particularly favourable prognosis and responsiveness to PARPi in this population (Table 28).⁹¹

Table 28. Real-world PFS and TTNT in the overall population and HRd subgroup of CHAR1ZMA

	Event, n (%)	Median rwPFS (95% CI), months	Median rwTTNT (95% CI), months
Overall (N=560)	341 (60.9)	11.4 (10.1, 12.7)	12.4 (11.5, 13.8)
HRd (n=144)	76 (52.8)	18.2 (13.9, 24.2)	19.6 (14.9, 23.9)
BRCAm (n=66)	30 (45.5)	25.4 (15.9, NR)	24.9 (16.0, NR)
HRd BRCAwt (n=78)	46 (59.0)	14.2 (8.6, 18.6)	15.1 (10.3, 19.8)

Abbreviations: BRCAm = BRCA-mutated; BRCAwt = BRCA wild-type; CI = confidence interval; HRd = homologous recombination-deficient; NR = not reached; PFS = progression-free survival; rw = real-world
Source: Salani 2025⁹¹

Impact of high-risk disease characteristics on clinical outcomes

RWE studies also confirm that HRD and BRCA status are not the only factors that impact patient prognosis and response to niraparib. Findings from the large, retrospective studies such as PRED1CT and AR1ZE, reveal substantial variability in clinical outcomes based on known risk factors such as disease stage, type of debulking surgery, and residual disease after surgery.

In a multivariable analysis of the PRED1CT study, BRCA/HRD status, type of cytoreductive surgery, and residual disease status were statistically significantly associated with TTNT. Patients with BRCAwt/HRd had a shorter TTNT compared to those with BRCAm (Table 29).⁹² Undergoing IDS nearly doubled the risk of TTNT (HR: 1.8) compared to PDS, while having VRD increased the risk of TTNT by 50% (HR: 1.5) compared to NVRD (Table 29).⁹² These data suggest better prognosis and extended

TTNT for patients treated with niraparib in the low-risk group, such as those with stage III NVRD after PDS, who originally were excluded from the PRIMA study.

Table 29. Summary of characteristics significantly associated with TTNT in multivariable analysis in the PREDICT study

Characteristics	Reference arm	HR (95% CI) for TTNT	p-value
BRCA status			
BRCAwt/HRd	BRCAm	2.0 (1.2, 3.2)	0.008
Other	BRCAm	2.0 (1.3, 3.0)	0.001
Unknown	BRCAm	2.9 (1.5, 5.3)	<0.0001
Surgery type			
IDS	PDS	1.8 (1.3, 2.4)	<0.0001
No surgery	PDS	2.7 (1.7, 4.3)	<0.001
Residual disease			
VRD	NVRD	1.5 (1.1, 2.1)	0.005

Abbreviations: BRCA = breast cancer gene; BRCAm = BRCA-mutated; BRCAwt = BRCA wild-type; CI = confidence interval; HR = hazard ratio; HRd = homologous recombination-deficient; IDS = interval debulking surgery; NVRD = no visible residual disease; PDS = primary debulking surgery; TTNT = time to next treatment; VRD = visible residual disease

This is further supported by the results of the AR1ZE study that used the US Flatiron Health database to evaluate survival outcomes in patients with stage III NVRD disease after PDS versus a PRIMA-like cohort.⁹³ The observed real-world median TTNT was doubled for the stage III NVRD cohort compared to the PRIMA-like cohort (22.5 months vs 11.7 months). Similarly, the real-world median PFS was also 2.5 times longer for the stage III NVRD compared to the PRIMA-like cohort (25.2 months vs 10.1 months)⁹³ Since patients with good prognosis and the potential for complete cytoreduction are more likely to receive PDS (Section 1.4.2.2), the AR1ZE findings demonstrate that patients with stage III NVRD after PDS, who were excluded from the PRIMA trial, have a significantly better prognosis and extended survival when treated with niraparib.⁹³ These results reinforce that the outcomes from PRIMA could have been consistent with those of other PARPi monotherapies (olaparib, rucaparib) if it had included both high- and low-risk patients.

External validation of PRIME representativeness for low-risk and high-risk patients.

As the PRIME study accounted for both patient groups, it resulted in a notably longer Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

median PFS in patients treated with niraparib compared to those in PRIMA, which only included high-risk patients. Among the RWE studies identified in SLR, two studies (RENI-1,⁹⁴ Chen 2024⁹⁵) suggest that PRIME is a reasonable representation of what PRIMA outcomes would look like if all patients, both high-risk and low-risk, were included. Both studies demonstrated PFS results closer to those of PRIME and notably higher than those of PRIMA, providing further external validation for PRIME in the real world.

The RENI-1 study prospectively enrolled 227 patients with newly diagnosed OC who received niraparib as a 1L maintenance therapy in China.⁹⁴ With the median follow-up of 23.9 months, the median PFS was not reached any patient group (overall, BRCA and HRd), while the 12-month PFS rates were 69.1%, 87.2% and 76.2%, respectively.⁹⁴ Chen 2024 was a retrospective study based in China that evaluated the efficacy and safety of niraparib (n=60) or olaparib (n=104) as a 1L maintenance therapy for the treatment of newly diagnosed eOC.⁹⁵ Niraparib was primarily administered to patients with BRCAwt (86.7%), while olaparib was predominantly given to patients with BRCAm (88.5%). The median PFS for patients treated with niraparib was 22.1 months (95% CI not evaluable), which was longer than in the PRIMA study and comparable to PRIME (Sections 2.4.2.1 and 2.5.2.1).⁹⁵ Based on Chen 2024, making a direct comparison between olaparib and niraparib was not feasible due to differences in baseline characteristics.⁹⁵

Evidence further supporting the comparability of PARPis and the class effect

One study comparing niraparib and olaparib was identified in the SLR (Kim 2024⁹⁶), which further supported the comparability of niraparib with other PARPi monotherapies and suggests a class effect for PARPi in comparable populations (i.e., including both low-risk and high-risk patients).

Kim 2024 was a retrospective, multicentre cohort study that included data from three Korean institutions to compare PFS in 161 patients with stage III/IV OC with BRCA1/2 mutations who received cytoreductive surgery followed by 1L PBC. The study employed a 3:1 propensity score matching approach to ensure comparable populations for niraparib and olaparib.⁹⁶ After matching, no significant difference was observed between the

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

olaparib and niraparib groups for median PFS (log-rank test $p=0.855$; HR: 1.08; 95% CI: 0.47, 2.52; $p=0.854$), time to subsequent therapy (HR: 1.20; 95% CI: 0.51, 2.81; $p=0.682$) and OS (HR: 0.42; 95% CI: 0.01, 17.61; $p=0.649$), reinforcing the comparability of niraparib with olaparib and indicating that niraparib offers similar efficacy to PARPi monotherapies when used in comparable populations.⁹⁶

2.8.1.2 Key highlights of niraparib's safety

Dose individualisation and real-world safety outcomes

The protocol amendment in PRIMA, which introduced ISD, was associated with reduced AEs (Section 2.4.7.4). This finding is further supported by UK-specific RWE from MONITOR, which confirms that ISD is widely adopted in clinical practice, with the majority of patients initiating niraparib treatment at 200 mg.²⁵

MONITOR-UK is a UK-based observational study that included patients with newly diagnosed or recurrent OC who received niraparib as a maintenance treatment.²⁵ Of the 319 patients enrolled, 165 (52%) were 1L, with 16% receiving an initial dose of 300 mg niraparib and 79% receiving 200 mg.²⁵ Grade ≥ 3 TEAEs were reported in 33% ($n=103$) of all patients (1L and recurrent),²⁵ which is lower than that observed in PRIMA (Section 2.4.7.4). The most common Grade ≥ 3 TEAEs were hypertension, anaemia, low neutrophil count, and low platelet count, occurring in 14%, 8%, 7% and 7% of all patients, respectively.²⁵ Adverse events of special interest were rare and included secondary cancer diagnosis ($n=4$), pneumonitis ($n=2$), AML ($n=1$), and MDS ($n=1$). Despite the predominance of 200 mg dosing, dose reductions occurred in nearly 50% of patients, with few discontinuations reported (5%).²⁵

Thus the MONITOR study demonstrates that niraparib can be considered a manageable and tolerable option for maintenance treatment in OC and supports the use of ISD in clinical practice, emphasising the importance of personalised dosing to optimise patient outcomes and limit risk of AEs.

Furthermore, subgroup results in PRIMA (Section C.1.4.1)⁷⁴ and the NOVA study⁸⁰ for recurrent OC indicated similar efficacy for individualised and fixed dosing. RWE data also support that niraparib's effectiveness is independent of dose.^{97,98} Therefore, ISD helps reduce AEs without compromising efficacy.

2.8.2 SACT dataset

The previous NICE appraisal recommended the commissioning of niraparib through the Cancer Drugs Fund (CDF) to allow managed access and support additional data collection to address clinical uncertainty.²⁶ Patients with advanced OC under the CDF were identified through the NHS England Blueteq[®] system, and real-world data were collected via the SACT database.¹⁹

Between 15 January 2021 and 31 August 2024, 3,100 CDF applications for niraparib were identified in the Blueteq[®] system, with 2,785 unique patients included in the SACT analysis. Data for patients who had a deleterious or suspected deleterious BRCA germline and/or somatic BRCA mutation (N=90) and those who didn't (N=2,695) were analysed separately.¹⁹ Notably, test results for HRD status were unavailable for the majority of patients (83% to 87%). Most patients in both groups initiated niraparib treatment on 200 mg daily (87% and 83% in BRCAm and BRCAwt, respectively), and more than half of patients (BRCAm: 62%, BRCAwt: 54%) had a complete response to PBC.¹⁹ Additionally, the majority of patients had never been exposed to bevacizumab as part of induction therapy (87% in BRCAm and 91% in BRCAwt).¹⁹ Detailed patient characteristics are shown in Table 30.¹⁹

Table 30. Patient characteristics treated with niraparib through the CDF (SACT dataset)¹⁹

Characteristics		BRCAm (N=90)	BRCAwt (N=2,695)
Median age, years		65	70
Age, n (%)	<40	0 (0)	9 (<1)
	40 to 49	3 (3)	101 (4)

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Characteristics		BRCAm (N=90)	BRCAwT (N=2,695)
	50 to 59	20 (22)	407 (15)
	60 to 69	35 (39)	823 (31)
	70 to 79	24 (27)	1,016 (38)
	80+	8 (9)	339 (13)
Performance status, n (%)	0	30 (33)	677 (25)
	1	39 (43)	1,229 (46)
	2	2 (2)	45 (2)
	3	0 (0)	4 (<1)
	4	0 (0)	0 (0)
	Missing	19 (21)	740 (27)
Histologic type, n (%)	High-grade serous adenocarcinoma	90 (100)	2,600 (96)
	High-grade clear cell carcinoma	0 (0)	50 (2)
	High-grade endometrioid adenocarcinoma	0 (0)	43 (2)
	Not captured	0 (0)	2 (<1)
PARPi, n (%)	Never previously received a PARPi	70 (78)	2,668 (99)
	Previously received olaparib monotherapy, which was stopped within 3 months	20 (22)	0 (0)
	Received niraparib as part of a company early access scheme	0 (0)	25 (1)
	Not captured	0 (0)	2 (<1)
Niraparib dose, n (%)	200 mg daily	78 (87)	2,242 (83)
	300 mg daily	12 (13)	451 (17)
	Not captured	0 (0)	2 (<1)
First-line response, n (%)	CR and CA-125 is normal	53 (59)	1,298 (48)
	PR and CA-125 is normal	22 (24)	681 (25)
	CR and CA-125 has not decreased to normal range	3 (3)	165 (6)
	PR and CA-125 has not decreased to normal range	12 (13)	549 (20)
	Not captured	0 (0)	2 (<1)
BRCAm, n (%)	BRCA2 mutation	45 (50)	0 (0)
	BRCA1 mutation	42 (47)	0 (0)
	Both BRCA1 and BRCA2 mutations	3 (3)	0 (0)
Germline or somatic testing, n (%)	Proven germline BRCA mutation	48 (53)	0 (0)
	Proven somatic BRCA mutation	31 (34)	0 (0)
	Somatic BRCA mutation and germline unknown	11 (12)	0 (0)

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Characteristics		BRCAm (N=90)	BRCAwt (N=2,695)
	Negative somatic BRCA mutation test	0 (0)	1,467 (54)
	Negative germline BRCA mutation test with somatic BRCA mutation test not done	0 (0)	1,225 (45)
	Not captured	0 (0)	3 (<1)
HRD status, n (%)	Failed or inconclusive result	0 (0)	36 (1)
	Positive	10 (11)	101 (4)
	Negative	0 (0)	317 (12)
	Not captured	80 (89)	2,241 (83)
Stage surgical management, %	Stage III with NVRD after PDS	18 (20)	494 (18)
	Stage III with VRD after PDS	3 (3)	111 (4)
	Stage III with NVRD after IDS	20 (22)	694 (26)
	Stage III with VRD after IDS	4 (4)	188 (7)
	Stage III no surgery	9 (10)	272 (10)
	Stage IV with NVRD after PDS	3 (3)	72 (3)
	Stage IV with VRD after PDS	4 (4)	56 (2)
	Stage IV with NVRD after IDS	14 (16)	290 (11)
	Stage IV with VRD after IDS	5 (6)	134 (5)
	Stage IV no surgery	10 (11)	382 (14)
Bevacizumab in 1L, n (%)	No bevacizumab	78 (87)	2,455 (91)
	7.5 mg/kg	10 (11)	216 (8)
	15 mg/kg	2 (2)	18 (1)
	Bevacizumab given in combination with platinum-based chemotherapy	0 (0)	4 (<1)
	Not captured	0 (0)	2 (<1)

Abbreviations: BRCAm/wt= breast cancer susceptibility gene mutation/wild type; CA-125 = cancer antigen 125; CDF = Cancer Drug Fund; CR = complete response; IDS = interval debulking surgery; NVRD = no visible residual disease; PARPi = poly (ADP-ribose) polymerase inhibitor; PDS = primary debulking surgery; PR = partial response; SACT = systematic anti-cancer therapy; VRD = visible residual disease

The median treatment duration was 19.5 months (95% CI: 10.3, 25.1) for patients with BRCAm and 8.1 months (95% CI: 7.6, 8.5) for BRCAwt. At the time of analysis, among the 90 BRCAm patients, 54 had ended treatment and 36 were still receiving niraparib, while among the 2,695 BRCAwt patients, 1,991 had ended treatment and 704 were still on treatment (Table 31, Figure 14).¹⁹

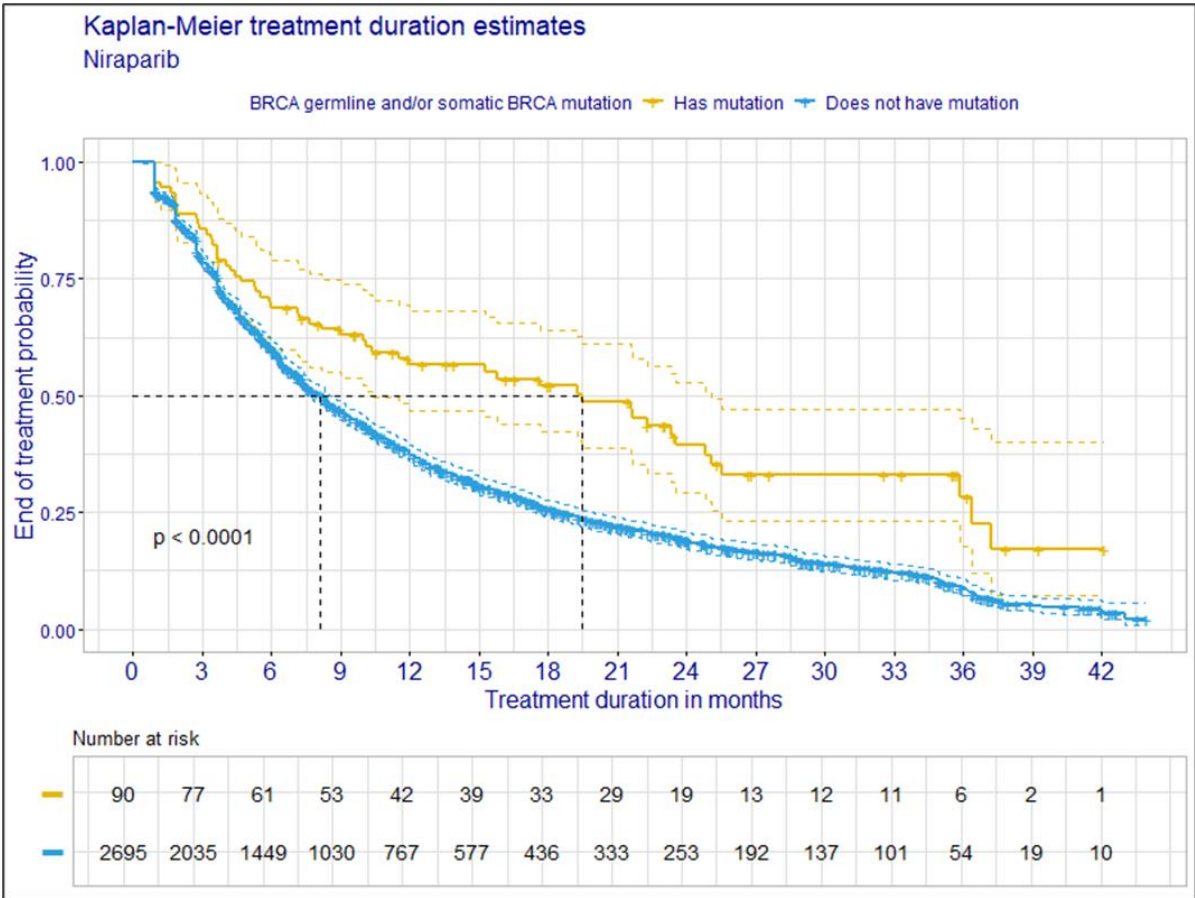
Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Table 31. Treatment duration with niraparib through the CDF (SACT dataset)¹⁹

Characteristics		BRCAm (N=90)	BRCAwt (N=2,695)
Patient died – on treatment, n (%)		0 (0)	15 (1)
Patient died – not on treatment, n (%)		20 (22)	1,111 (41)
Treatment stopped, n (%)		34 (38)	865 (32)
Treatment ongoing, n (%)		36 (40)	704 (26)
Treatment duration at	6 months, % (95% CI)	69 (60, 79)	60 (58, 62)
	12 months, % (95% CI)	56 (47, 68)	38 (36, 40)
	18 months, % (95% CI)	52 (42, 64)	26 (24, 28)
	24 months, % (95% CI)	39 (29, 53)	19 (17, 21)
	36 months, % (95% CI)	28 (18, 45)	9 (7, 11)
Median treatment duration (95% CI), months		19.5 (10.3, 25.1)	8.1 (7.6, 8.5)

Abbreviations: BRCAm/wt= breast cancer susceptibility gene mutation/wild type; CDF = Cancer Drug Fund; CI = confidence interval; SACT = systematic anti-cancer therapy

Figure 14. Kaplan-Meier treatment duration for patients treated with niraparib through CDF (SACT dataset)¹⁹



Abbreviations: BRCA= breast cancer susceptibility gene; CDF = Cancer Drug Fund; SACT = systematic anti-cancer therapy

At a median follow-up time of 17.7 months, among the 90 BRCAm patients, 20 had died and 70 were still alive. Among the 2,695 BRCAwt patients, 1,126 had died and 1,569 were still alive. The median OS was not reached for BRCAm patients, whereas it was 28.8 months (95% CI: 28.0, 30.6) for BRCAwt patients (Table 32, Figure 15).¹⁹

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

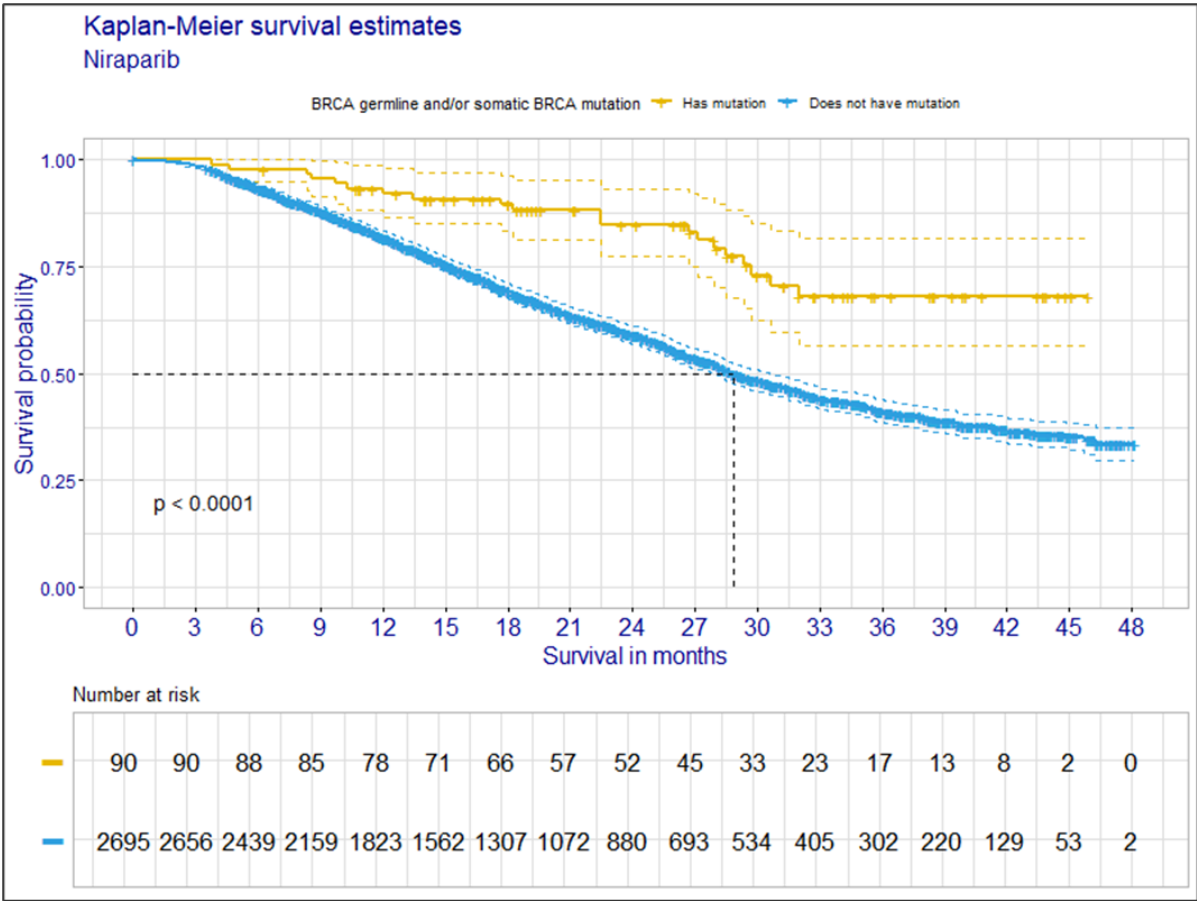
Table 32. Summary of overall survival results for patients treated with niraparib through the CDF (SACT dataset)¹⁹

OS results		BRCAm (N=90)	BRCAwt (N = 2,695)
OS at	6 months, % (95% CI)	98 (95, 100)	93 (92, 94)
	12 months, % (95% CI)	92 (87, 98)	82 (80, 83)
	18 months, % (95% CI)	90 (83, 96)	70 (68, 71)
	24 months, % (95% CI)	85 (77, 93)	59 (57, 61)
	36 months, % (95% CI)	68 (57, 82)	41 (39, 44)
	48 months, % (95% CI)	-	33 (30, 37)
Median OS (95% CI), months		Not reached	28.8 (28.0, 30.6)

Abbreviations: BRCAm/wt= breast cancer susceptibility gene mutation/wild type; CI = confidence interval; OS = overall survival

Median follow-up: 17.7 months (range: 4.8 months to 48.3 months).

Figure 15. Kaplan-Meier survival plot for patients treated with niraparib through the CDF (SACT dataset)¹⁹



Abbreviations: BRCA= breast cancer susceptibility gene; CDF = Cancer Drug Fund; SACT = systematic anti-cancer therapy

Sensitivity analyses of treatment duration (n=2,425) and OS (n=2,725) were conducted for a cohort with at least 6 months of follow-up data in the SACT dataset. The results were consistent with the full analysis cohort, with median OS not reached for BRCAm patients and 28.8 months (95% CI: 27.9, 30.6) for BRCAwt patients.¹⁹

2.9 Ongoing studies

There are no other trials assessing the safety and efficacy of niraparib within the patient population being appraised in this submission (monotherapy maintenance treatment for advanced OC following 1L PBC) that are anticipated in the next 12 months. Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

2.10 Strengths of the clinical evidence

Niraparib is the only PARPi among those approved for maintenance treatment after 1L PBC in advanced OC with efficacy and safety confirmed in two high-quality phase III RCTs – PRIMA and PRIME.^{12,13}

PRIMA was designed as an all-comer trial, enrolling patients regardless of their BRCA or HRD status.¹² This inclusive approach allows for a broader understanding of niraparib's efficacy across various biomarker subgroups, thereby making the findings more applicable to a broader patient population.²⁶

PRIMA also stands out among PARPi trials for disproportionately enrolling those with the highest risk of progression and the greatest unmet need.¹² In contrast to SOLO-1¹⁷ and ATHENA-MONO¹⁸, PRIMA specifically excluded patients with the lowest risk of relapse (i.e., stage III patients with NVRD after PDS) who are known to have a more favourable prognosis and were well represented in the previous PARPi trials (Section 1.4.2.2).¹² Therefore, the PRIMA trial aimed to investigate the utility of PARPi therapy in a population with the highest risk of progression and greatest unmet need.

The PRIME¹³ study complements findings from the PRIMA trial by providing information on niraparib's efficacy regardless of risk of relapse. Notably, PRIME included patients who were not assessed in the PRIMA study (stage III with no residual disease after PDS) and used individualised starting doses, in accordance with the dosing label, from the beginning of the trial, consistent with UK clinical practice. The outcomes across PRIMA and PRIME were similar, demonstrating consistent results between these two pivotal trials and highlighting the efficacy and safety of niraparib in different patient populations and study designs. Notably, PRIME reported numerically longer medians compared to PRIMA, likely reflecting the mix of high- and low-risk patients enrolled in the study.

In summary, the clinical evidence for niraparib is robust, demonstrating its efficacy in a broad range of patients with advanced OC, including those in the high-risk group, and underscoring its potential as a valuable PARPi therapy.

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

2.11 Interpretation of clinical effectiveness and safety evidence

Impact of niraparib on PFS: Across both the PRIMA^{12,16} and PRIME¹³ pivotal trials, the efficacy of niraparib was demonstrated in prolonging the PFS in the 1L maintenance setting regardless of biomarker status. Each of the trials met their primary endpoints, with the more mature PRIMA^{12,16} trial showing a sustained and consistent PFS benefit across the primary, interim and final analysis data cuts.¹²⁻¹⁴ The magnitude of benefit was greatest in the BRCAm and HRd populations; however, niraparib also demonstrated benefit in BRCAwt and HRp patients, who represent those with the highest unmet needs and poorest prognosis.^{12,16,46,49} The improvement in PFS in the PRIMA trial was robust across various prognostic factors, including stage and surgical outcome.^{12,16}

Although PRIMA focused on a higher-risk population, evidence from PRIME¹³ and RWE⁸² demonstrated clinically meaningful benefits for niraparib in a broader population that also included low-risk patients, thus supporting niraparib's use in the relevant population for this appraisal (in line with its marketing authorisation). In PRIME,¹³ the inclusion of lower-risk patients resulted in a median PFS for niraparib that was nearly twice as long as in PRIMA^{12,16} (24.8 months for niraparib in PRIME compared to 13.8 months for niraparib in PRIMA), despite a similar median PFS for placebo in both studies (8.3 months in PRIME and 8.2 months in PRIMA), which demonstrates that niraparib is effective across a broader range of patient risk profiles. Similar results were obtained in the US-based AR1ZE⁸² study, which showed that median real-world PFS in the stage III with no residual disease after PDS cohort was significantly longer (25.2 months) than the PRIMA-like cohort (10.1 months; $p < 0.001$).

Impact of niraparib on OS and other secondary outcomes: PRIMA was a positive trial that successfully met its primary endpoint of PFS.^{12,16} However, it did not achieve the secondary endpoint of OS, with no differences observed in OS between niraparib and placebo in the ITT population or the subgroups analysed.^{12,16} This lack of OS benefit has also been observed in other trials in aOC,^{14,17,64} where extended post-progression

survival can obscure treatment effects and make it more challenging to demonstrate statistically significant differences between arms.

As PRIMA was designed with PFS as the primary endpoint, differences in post-progression treatments between treatment arms and patient management may have impacted OS outcomes. Additionally, potential unblinding after progression to help inform treatment decisions post-progression could introduce performance bias in the assessment of post-progression outcomes such as OS.

Despite not achieving statistical significance for OS, the median OS observed in PRIMA was numerically high; this is particularly noteworthy given the high-risk patient population. Furthermore, the survival outcomes were consistent with the results reported for a similarly high-risk subgroup in the PAOLA-1 trial investigating olaparib as an add-on to bevacizumab in the 1L setting; in the intent-to-treat (ITT) population, PRIMA reported a median OS of 46.6 months with niraparib, compared to 42.2 months for olaparib plus bevacizumab in PAOLA-1, and in the homologous recombination deficient (HRd) population, PRIMA reported a median OS of 71.9 months with niraparib, compared to 67 months for olaparib plus bevacizumab in PAOLA-1. It must be noted that given the differences in trial designs, patient populations, and baseline characteristics these results should be interpreted with caution.¹⁶

Comparison with other PARPis: There are no direct comparisons between niraparib and the relevant comparators (olaparib and rucaparib) in a clinical trial setting in 1L aOC maintenance. Therefore, several exploratory ITCs were conducted despite the ITC feasibility assessment deeming these comparisons inappropriate and fundamentally flawed, in order to aid decision making (Section 2.7.4).

The exploratory ITCs showed no statistically significant differences in PFS outcomes when comparing niraparib (PRIMA) to olaparib (SOLO-1). While the HR point estimate nominally favoured olaparib, likely influenced by unadjusted imbalances in prognostic factors between trial populations, the wide confidence interval supports equivalence

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

between the treatments. Real-world evidence further supports comparable outcomes between olaparib and niraparib in BRCAm patients receiving maintenance therapy, showing no statistically significant differences in PFS, OS, or TFST.⁹⁶ Additionally, English SACT data¹⁹ revealed that OS Kaplan-Meier curves for niraparib and olaparib overlap during the first 27 months, with nearly identical proportions of patients alive at key milestones (6–24 months), further indicating equivalence between the two treatments and reinforcing the potential PARPi class effect (Section B.3.2.6).

Similarly, exploratory ITCs comparing niraparib (PRIME) to rucaparib (ATHENA-MONO) showed no statistically significant differences in PFS or OS outcomes. While the HR point estimate nominally favoured niraparib for the ITT population, the difference was neither clinically nor statistically significant (Section 2.7).

Safety of niraparib: Niraparib was generally well tolerated in both PRIMA and PRIME, demonstrating an acceptable and predictable safety profile, with no new safety signals identified.¹³

It is noteworthy to mention that the frequency of AEs observed in PRIMA was significantly higher compared to PRIME (Section 2.4.7.4 and Section 2.5.7.4) and the more recent UK-specific real-world data (Section 2.8.1.2), likely reflecting the impact of individualised dosing regimens implemented after the PRIMA protocol amendment (Section 2.4.1). In the MONITOR-UK study, where patients started on individualised dosing, Grade ≥ 3 TEAEs were reported in fewer patients than in the PRIMA trial, with the most common being hypertension (14%), anaemia (8%), low neutrophil count (6%), and low platelet count (6%).²⁵

A post-hoc analysis of PRIMA data investigated the efficacy and safety of the individualised starting dose versus the fixed starting dose. No significant differences in efficacy were observed between the two dosing strategies, both in the overall population and the HRd/HRp populations. Furthermore, ISD was associated with a lower incidence of AEs, highlighting improved tolerability without compromising efficacy (xxxxxx 45,

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Appendix C.1.4.1).⁷⁴ Similar conclusions were reported by a real-world evidence study, which found no differences in efficacy between ISD and FSD.⁹⁷

In summary, the PRIMA and PRIME trials, along with real-world evidence studies, demonstrate that individualised dosing of niraparib improves safety versus fixed dosing, while maintaining efficacy.

3 Cost-effectiveness

3.1 Cost-effectiveness summary

- For the purpose of this submission, a de novo model uses a 3-health state partitioned survival structure, as a 4-state model is considered less relevant given that post-progression pathways are similar across first-line PARPi monotherapies
 - Furthermore, a 4-state model results in additional complexity as well as further data requirements which would not have been feasible given the absence of suitable PFS2 data for the relevant comparators
- In addition to standard parametric models, flexible spline models were explored for PFS and OS extrapolations. The most appropriate curves were selected based on clinical feedback and the NICE DSU methods guide ^{99,100}
- In line with previous PARPi NICE appraisals,^{27,28,70} patients alive and progression-free after 10 years were considered to be in long-term remission (“cured”) and were assumed to follow general population mortality thereafter. No adjustments were made to the OS extrapolations, which continued until the OS curve intersected with the PFS curve
- ITCs and RWE from SACT¹⁹ data suggest no clinically meaningful differences in efficacy outcomes between niraparib and the relevant comparators, highlighting the potential for a ‘class effect’ among these treatments; this class effect is more established in the second line setting for aOC where trials are more comparable. Therefore, PARPi equivalence was considered in the base case
- Relative dose intensity was accounted for to reflect dose reductions
 - It is important to note that cost savings are realised only with niraparib, as it is formulated exclusively as 100 mg tablets; therefore, monthly costs depend on the average dose received
 - In contrast, rucaparib and olaparib are available in different strength formulations which are priced identically, meaning dose reductions do not result in corresponding cost savings
 - Therefore, dose reductions were only considered for niraparib in the base case, with the impact of considering RDI for comparators explored in scenario analyses
- Economic analyses demonstrate that niraparib is a cost-effective treatment option in the first-line maintenance setting, regardless of a patient’s BRCA status
- Its availability in routine commissioning will ensure physicians and patients continue to have the choice to select the most appropriate PARPi treatment based on the individual patient characteristics and PARPi safety profile

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

3.2 Published cost effectiveness studies

A systematic literature review (SLR) was conducted to identify published 1L maintenance aOC economic models. The SLR was conducted¹⁰¹ according to the reporting standards of the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA),¹⁰² general methodological requirements outlined in the Cochrane Handbook for Systematic Reviews of Interventions¹⁰³, and key health technology assessment (HTA) bodies, such as NICE¹⁰⁴ and Canada's Drug Agency (CDA)¹⁰⁵. By following the methodologies of these HTA bodies, the SLR complied with the general SLR requirements of most other HTA bodies. Details on the search strategy and inclusion criteria are presented in Appendix E:. The focus of this section is on the UK-related SLR findings, as it is thought these are the most relevant to inform the current appraisal.

Forty-nine cost-effectiveness studies were identified in the SLR for patients with stage III and IV OC treated in the 1L maintenance setting with PR or CR prior to 1L treatment. Of the included studies, 21 were technology appraisals of which 6 were NICE technology appraisal submissions (niraparib, NICE TA673²⁶ 2019; olaparib versus RS, NICE TA598¹⁰⁶ 2019 and NICE TA962⁷⁰ 2024; olaparib + bevacizumab versus bevacizumab, NICE TA693¹⁰⁷ 2021 and NICE TA946⁷⁰ 2024; rucaparib versus placebo, NICE TA1055²⁸, 2024).

Across the 49 studies, cost-effectiveness was primarily analysed using a Markov (n=11), semi-Markov model structure (n=6), or a partitioned survival analysis with a minimum of three health states (n=30), with the remaining two studies appearing to conduct trial-based cost-effectiveness analyses. Most frequently, the health states assessed were progression-free, progressive disease, and death. However, some studies incorporated additional health states to account for multiple disease progressions¹⁰⁸⁻¹¹⁴ as well as one study that utilised disease-specific health states such as haematological complications.¹¹⁵

Among the previous NICE technology appraisal submissions, (TA673²⁶, TA598¹⁰⁶, TA962^{27,70}, TA693¹⁰⁷, TA946⁷⁰ and TA1055²⁸) all utilised a partitioned survival models with either three or four health states (i.e., differentiated according to inclusion of PFS2). Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Table 33 summarises the population, interventions, comparators, country, and perspective of the relevant NICE technology appraisal submissions.

Table 33. Summary of relevant NICE technology appraisal submissions

Study	Population	Intervention	Comparators	Country, Perspective
NICE TAs				
TA946	1L maintenance (HRd-positive)	Olaparib + bevacizumab 1L maintenance	Bevacizumab 1L maintenance*	UK, NHS and PSS
TA962	1L maintenance (BRCAm)	Olaparib	Routine surveillance (RS)	UK, NHS and PSS
TA1055**	1L maintenance (HRd-positive patients with BRCAwt, HRd-negative patients with BRCAwt)	Rucaparib	Wild-type BRCA/HRd-positive: RS, bevacizumab, Olaparib + bevacizumab Wild-type BRCA/HRp: RS, bevacizumab	UK, NHS and PSS

Abbreviations: 1L = First-line; BRCA = Breast Cancer Gene; BRCAm = BRCA-mutated; BRCAwt = BRCA wild-type; HRd = Homologous Recombination Deficient; HRp = Homologous Recombination Proficient; ITT = Intent to Treat; NHS = National Health Service (UK); PSS = Personal Social Services; TA = Technology Assessment

*Routine surveillance initially included but agreed at ACM1 to exclude as it is uncommon for patients not to have any active treatment.

**During the rucaparib submission, an updated analysis focusing on HRp patients, not eligible for bevacizumab, was performed, with RS being the only comparator.

Table 34 summarises the key modelling considerations for the relevant NICE submissions identified. The approach to model efficacy varied across the three reviewed NICE TAs. For PFS, TA946⁷⁰ (olaparib + bevacizumab) and TA962^{27,70} (olaparib) used mixture cure models (MCMs) for PFS to capture long-term responders/survivors. Splines were also included in the exploratory analysis in TA946⁷⁰ (olaparib + bevacizumab). TA1055²⁸ used the PFS K-M curve followed by standard parametric extrapolation, with flexible parametric spline models also being explored for PFS in the bevacizumab-ineligible population. Both TA946²⁷ (olaparib + bevacizumab) and TA962²⁷ (olaparib) considered a landmark cure point at 5 years to justify MCM. PFS2 was modelled using standard parametric fits across all TAs, with the Evidence Assessment Group (EAG) requesting MCMs for PFS2 in Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

TA962²⁷ (olaparib) to be consistent with the PFS modelling approach. OS was frequently modelled using standard parametric extrapolation (TA946⁷⁰, TA962²⁷, and TA1055²⁸), with the EAG requesting MCMs (TA962²⁷) or splines (TA946⁷⁰) to align with the PFS extrapolation approach. All reviewed TAs adopted a lifetime horizon (40-47 years) and monthly cycles.

A comparable OS between the active arm and the comparator arm was observed in TA1055²⁸ for rucaparib. In TA962⁷⁰ (olaparib), the EAG was concerned that OS was similar between olaparib and RS until ~42 months, after which OS separation was observed. A robust clinical rationale could not be provided by the company to explain it, but the overall OS HR (0.55 [0.40 – 0.76]) indicated a survival benefit associated with olaparib use. In TA946⁷⁰ (olaparib + bevacizumab), PAOLA-1 long-term data supported olaparib + bevacizumab OS benefit vs. bevacizumab (HR OS=0.62 [0.45-0.85]) and was thus reflected in the economic model, with EAG-company discussion more focused on which cure fraction/long-term survival extrapolation was more appropriate rather than whether olaparib + bevacizumab results in a survival benefit. In the rucaparib appraisal, OS was still immature, with no KM curves separation observed in the March 2022 data cut (OS HR = 0.96 [0.63-1.47]) and a not statistically significant difference in OS observed in the 2023 data-cut (HR OS = 0.83 [0.58=1.17]). The committee concluded that, despite ATHENA-MONO not showing yet a slowing of PFS hazards to support long-term survivorship, it is likely that some people having rucaparib would experience long-term remission in line with other PARP inhibitors (based on clinical expert opinion). This was reflected in the choice of PFS extrapolations (i.e. log-logistic/log-normal distributions) and OS distributions (log-normal distribution), with the committee (based on clinical expert opinion) assuming the same hazard of death for rucaparib and olaparib + bevacizumab long-term.

Table 34. Key Modelling Considerations for the relevant NICE technology appraisal submissions

Study	Model Structure	Was PFS2 Modeled?	Approach to Efficacy			MCM Used for PFS?	Landmark Cure Point	Time Horizon and Cycle Length
			PFS	PFS2	OS			
NICE TAs								
Olaparib + bevacizumab (TA946)	4- health states partitioned survival model	Yes	Standard parametric fits and MCMs (splines also provided at clarification stage)	Standard parametric fits (splines also provided during technical engagement)	Standard parametric fits (splines also provided during technical engagement)	Yes	5 years	Lifetime horizon (42 years) and 1 month cycle length
Olaparib (TA962)	4-health states partitioned survival model	Yes	Mixture cure model	Standard parametric fits (MCM also provided after EAG request)	Standard parametric fits (MCM also provided after EAG request)	Yes	5 years	Lifetime horizon (47 years) and 1 month cycle length
Rucaparib (TA1055)	4-health states partitioned survival model	Yes	K-M curves until a cutoff time point followed by parametric curves. Flexible parametric spline models were used for the bevacizumab ineligible population	Standard parametric fits	Standard parametric fits	No	NA	Lifetime horizon (40 years) and 1 month cycle length

Abbreviations: K-M = Kaplan-Meier; MCM = Mixture Cure Model; NA = Not applicable; OS = Overall Survival; PFS = Progression-free Survival; PFS2 = Progression-free Survival to second progression; TA = Technology Assessment

3.3 Economic analysis

A *de novo* model was developed to assess the cost-effectiveness, using an NHS and PSS perspective, of niraparib against approved treatments in the 1L maintenance setting for patients who have responded to PBC.

The key features of the *de novo* model are described in the sub-sections that follow.

3.3.1 Patient population

The patient population of the cost-effectiveness model (CEM) is aligned with the NICE scope for this appraisal and the marketing authorisation for niraparib (Section 1.1). The PRIMA trial population forms the basis of the clinical evidence for this evaluation, which considered: adult females (≥ 18 years of age) who are newly diagnosed with stage III or IV high-grade serous or endometrioid ovarian, primary peritoneal, or fallopian tube cancer (collectively referred to as OC) who responded to 1L PBC.

The two populations of interest identified for the submission are:

- **BRCAm:** patients with a BRCA mutation, as defined in the PRIMA trial^{16,82}
- **BRCA wild-type (BRCAwt):** patients without a BRCA mutation, as defined in the PRIMA trial^{16,82}

As described in Sections 1.4.3.1 to 1.4.3.3, the standard of care therapy, and therefore relevant comparator, differs based on BRCA status, with olaparib currently recommended by NICE for BRCAm patients and rucaparib for BRCAwt patients. Therefore, the CEM included separate analyses for the BRCAm and BRCAwt populations to enable comparison of niraparib vs. each of the available PARPi monotherapies, according to BRCA status. While niraparib is approved across all biomarker subgroups in the CDF, the analysis considers the two BRCA-based populations to align with the decision problem and the relevant comparators specified in the final scope.

3.3.2 Model structure

Table 35 summarises the key features of the base-case cost-effectiveness analysis along with a comparison with other 1L aOC models previously considered by NICE.

Table 35. Features of the economic analysis

Factor	Previous NICE evaluations			Current evaluation	
	Olaparib + bevacizumab (TA946)	Olaparib (TA962)	Rucaparib (TA1055)	Chosen values	Justification
Model structure	4- health states partitioned survival model.	4-health states partitioned survival model.	4-health states partitioned survival model.	3-health states partitioned survival model.	There is no standard approach to modelling 1L aOC. Both 3- or a 4-health state partitioned survival models have been used in the published literature. Both structures can capture the key outcomes from the pivotal trial, and the main features of the clinical pathway and patient experience within the NHS, while adhering to the principles of model parsimony and transparency. Our <i>de novo</i> model follows a 3-health state partitioned survival structure. This model structure was selected partly due to the lack of availability of relevant PFS2 data. While PFS2 is available in PRIMA, relevant high-risk population PFS2 data is not available for the comparators outside of the PRIMA trial, limiting the possibility of adequately parametrising the relative effectiveness for niraparib vs. active comparators. Furthermore, the treatment pathway after disease progression with PARPi monotherapy is similar regardless of the first-line PARPi used. As a result, the costs and outcomes associated with subsequent lines of treatment are expected to be uniform across all treatment sequences.

Factor	Previous NICE evaluations			Current evaluation	
	Olaparib + bevacizumab (TA946)	Olaparib (TA962)	Rucaparib (TA1055)	Chosen values	Justification
Time horizon, cycle length and half-cycle correction	Lifetime horizon (42 years) and 1 month cycle length.	Lifetime horizon (47 years) and 1 month cycle length.	Lifetime horizon (40 years) and 1 month cycle length.	Lifetime horizon (between 38 and 44 years depending on the analysis population (i.e. up to 100 years of age)) and 1 month cycle length.	Consistent with previous evaluations.
Treatment waning effect	Not considered.	Not considered.	Not considered.	Not considered.	Given the observed preservation of treatment effect for PFS for niraparib in the PRIMA trial beyond the maximum treatment duration and similar observations from long-term follow-up results from PAOLA-1 and SOLO-1, treatment effect waning was not considered in the economic model for the current appraisal. This is consistent with previous evaluations.
Source of utilities	EQ-5D-5L from PAOLA-1, cross-walked to EQ-5D-3L	EQ-5D-5L from SOLO-1, cross-walked to EQ-5D-3L	EQ-5D-5L from ATHENA-MONO, cross-walked to EQ-5D-3L	EQ-5D-5L from PRIMA, cross-walked to EQ-5D-3L	Consistent with previous evaluations and following NICE reference case
Source of costs	BNF, CMU, NHS reference costs, Unit Costs of Health and Social Care (PSSRU), published literature, previous aOC HTAs and UK clinical expert opinion	BNF, CMU, NHS reference costs, Unit Costs of Health and Social Care (PSSRU), published literature, and UK clinical expert opinion	BNF, eMIT, NHS reference costs	NHS reference costs, BNF, published literature, previous aOC HTAs and UK clinical expert opinion	In line with the NICE reference case

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

A partitioned survival model (PSM) structure was selected with three-health states (Figure 16), including progression-free and alive, progressed and alive, and dead. These states are mutually exclusive and fully exhaustive, meaning that patients must occupy one of the states at any given time.

A PSM approach was adopted based on the following rationale, which is in line with NICE DSU TSD19 guidance:

- PSM approaches are generally considered reasonable for advanced or metastatic cancers, as patients tend to have relatively poor survival prognoses and generally cannot return to the original progression-free state. This is consistent with advanced ovarian cancer, where patients with recurrent disease are expected to be incurable.
- PSMs allow for time-to-event endpoints that are routinely reported in clinical studies for advanced or metastatic cancer treatments (e.g., PFS, OS) to be directly modelled, facilitating easier comparisons for the treatment of interest with external study comparators.
- Given the use of frequently reported time-to-event endpoints, PSMs are intuitive and simple to communicate and allow relatively close replication of within-trial data.
- Updated PFS (76.5% event rate – INV assessed PFS) and OS (62.5% event rate) data from the PRIMA trial are relatively mature, with extrapolations of the outcomes therefore expected to provide reasonable representations of the relationship between progression and mortality.

A PSM approach is also consistent with approaches adopted and accepted in all previous NICE appraisals for 1L PARPi maintenance therapies (TA1055²⁸, TA962⁷⁰, TA946⁷⁰, TA693¹⁰⁷, TA673²⁶, TA598¹⁰⁶).

Typical PSMs include three health states (progression-free and alive, progressed and alive, dead). In some instances, a four-state model that further partitions post-progression patients into first and second progression (PFS2) health states has been

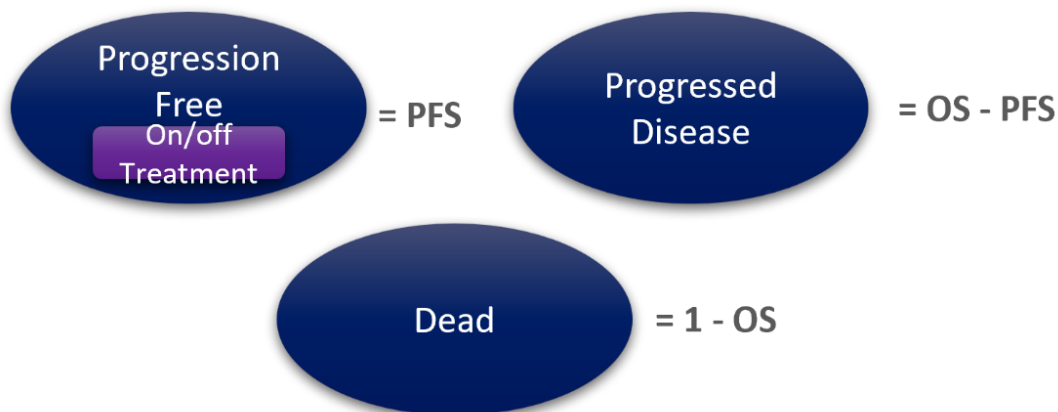
Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

adopted. However, the treatment pathway following disease progression with a PARPi monotherapy is the same regardless of the 1L PARPi used, therefore the costs and outcomes resulting from subsequent lines of treatment are expected to be consistent across each treatment sequence. Furthermore, the lack of relevant PFS2 data for comparators outside of the PRIMA trial (i.e. no PFS2 data stratified by low/high risk) has restricted the ability to adequately parametrise relative effectiveness of PFS2 for niraparib vs. active comparators.

The three-health state model requires survival curves for OS, PFS and TTDD outcomes to estimate the proportions of the model cohort in each of the model states at any point in time. This enables the estimation of treatment costs, disease state costs, and health state utility values to accrue quality-adjusted life years (QALY) and costs over the model time horizon. Visual representations of the three-state approach are shown in Figure 16 and Figure 17.

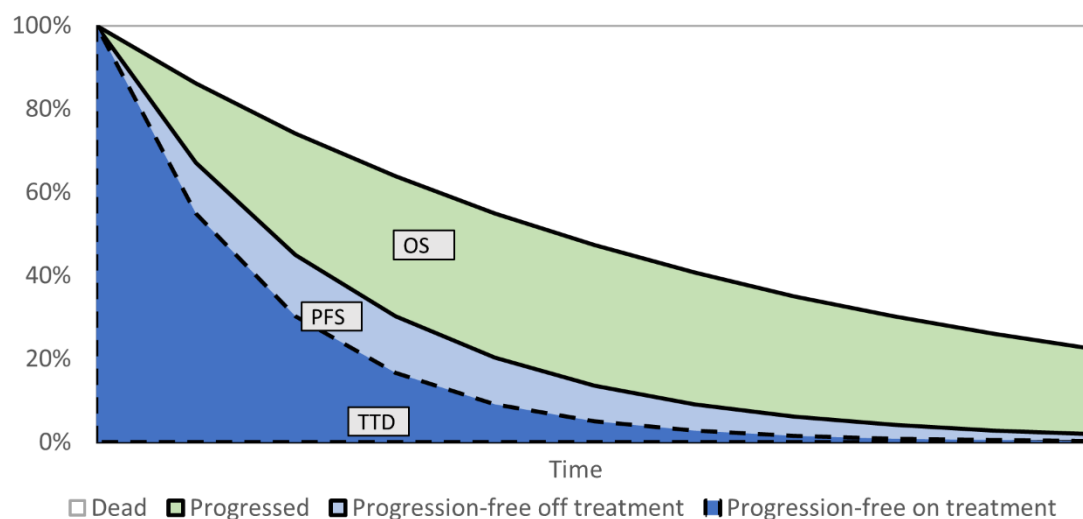
Costs, life years (LYs), and quality-adjusted life years (QALYs) were accrued over time for each health state and aggregated over the chosen time horizon to calculate the overall health and cost outcomes for each intervention. Depending on the health state and on/off treatment status within the progression-free health state, patients were assigned costs related to drug acquisition, administration, follow-up, monitoring and disease management, and adverse events. Utility values were assigned separately to the progression-free and progressed health states. Overall outcomes depend on the duration of treatment, health state membership, resource use, and associated utilities.

Figure 16. Three-State Partitioned Survival Model.



Abbreviations: OS = overall survival; PFS = progression-free survival

Figure 17. Distribution of Patients in Three-State Partitioned Survival Model: Progression-free and On-treatment, Progression-free and Off-treatment, Progressed, and Death Health States



Abbreviations: OS = overall survival; PFS = progression-free survival

3.3.2.1 Model settings

In line with the recommendations in the NICE value assessment framework, the CEM adopted an NHS and personal social services (PSS) perspective.^{116,117} The model therefore included direct costs relating to drug acquisition and administration, healthcare resource use, adverse event management and end-of-life care. Direct health effects for patients are reported as life years (LYs) and quality-adjusted life

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

years (QALYs), with health state utility values estimated using the EQ-5D-5L descriptive system and the EQ-5D-3L mapping function recommended in the NICE manual.

The model considered a 'lifetime horizon,' modelling the patient cohort until a negligible proportion remain alive. Since the mean age of patients across the modelled populations of PRIMA trial ranges from [REDACTED] to [REDACTED] years,⁸² the lifetime horizon refers to a time horizon of [REDACTED] years depending on the analysis population (i.e. up until 100 years of age). A shorter time horizon of 20 years was explored in scenario analysis for both populations.

A monthly time cycle was applied to the model, aligning with previous NICE Technology Appraisals (TA946⁷⁰, TA962⁷⁰, and TA1055²⁸). Costs, LYs and QALYs accrued are half cycle corrected by taking the average of the values at the start and end of each cycle. However, some cost categories were not subject to half-cycle correction, and these include drug acquisition costs, one-off adverse event costs, and one-off medical resource use costs. Given the relatively short cycle length with respect to the lifetime horizon, it is anticipated that half-cycle correction will have a minimal impact on the model outcomes.

The annual discount rate for costs and health outcomes was 3.5%, in line with the NICE reference case.^{104,117} Alternative discount rates of 1.5% were tested in scenario analysis.

3.3.3 Intervention technology and comparators

For the two key populations of interest identified for the submission, the following comparators have been selected:

- **For the BRCAm population:** Olaparib;
- **For the BRCAwt population:** Rucaparib.

The current standard of care for BRCAm patients in the UK is olaparib, with rucaparib not currently recommended in the UK for this population. UK clinical experts consulted by GSK indicated that, given the availability of olaparib and the benefits provided by Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

PARPi in this population, routine surveillance is not considered appropriate a PARPi-eligible population, and that olaparib is the most relevant comparator for the BRCAm population.

Rucaparib is currently recommended for both HRd BRCAwt and non-HRD positive populations, which together constitute the BRCAwt population. Although NICE guidance limits the use of rucaparib to bevacizumab-ineligible patients within HRp or HR-unknown patient populations (Section 1.4.3.2), PARPi monotherapies are generally not considered for patients eligible for bevacizumab in the maintenance phase, and therefore this restriction was not considered relevant for this appraisal given current UK clinical practice. The appropriateness of rucaparib as a comparator was also validated by UK clinical experts, who advised rucaparib would be utilised in place of niraparib for BRCAwt patients should niraparib not be routinely available.

3.4 Clinical parameters and variables

3.4.1 Population characteristics

Baseline characteristics of the patient population of interest were informed by pooled arm estimates for each population from the PRIMA trial as outlined in Table 36. Variable body surface area (BSA) was not reported in the trial and therefore it was estimated using the Du Bois formula: $BSA = 0.007184 * (Height(cm)^{0.725}) * (Weight(kg)^{0.425})$, where the height and weight at baseline was used. These baseline characteristics were used to calculate weight- or BSA-based dosages. Population-specific eGFR was not available; therefore, for any AUC-based dosing, a mean GFR of 93.0 ml/min/1.73m² was used for all populations, based on the estimate adopted in NICE TA962²⁷. Alternative baseline age values, based on median estimates from niraparib SACT data (65 for BRCAm, 70 for BRCAwt), were explored in a scenario analysis.

Table 36. Baseline characteristics by key Population in PRIMA trial

Health States	Characteristic	Mean	SE (N)	Source
BRCAm	Mean age at baseline (years)	████	██████	PRIMA
	Mean weight (kg)	████	██████	
	Mean BSA (m2)	████	██████	
BRCAwT	Mean age at baseline (years)	████	██████	
	Mean weight (kg)	████	██████	
	Mean BSA (m2)	████	██████	

Abbreviations: BSA = body surface area; SE = standard error.

3.4.2 Cure/long-term remission in aOC

There is established evidence to support the potential for long-term remission and functional cure (hereafter referred to as “cure”) in 1L aOC maintenance settings. Clinical experts from previous NICE appraisals (TA248, TA962⁷⁰ and TA946⁷⁰) have highlighted the expectation of cure or long-term survival for a small but significant proportion of patients who remain progression-free. This is also supported by long-term data from the literature, which shows ~20% of patients remain progression free and alive after 10 years, with plateauing observed in the PFS curves^{3,118}. However, given the broader population included in studies identified from the literature and the focus of the PRIMA trial on high-risk patients, further UK clinical expert feedback was sought to support the long-term remission assumption.

During an advisory board, UK clinical experts¹⁰ noted that “cure” was possible even in a PRIMA-like population and across all biomarker subgroups based on BRCA or HRD status. Clinical experts highlighted that relapse (i.e. disease progression) typically occurred within the first 5 years of responding to 1L chemotherapy and maintenance treatment, and patients who remained progression-free after 7-10 years were unlikely to relapse. They also generally agreed that long-term remission is not as established in the relapsed setting, with only a small number of patients able to achieve long-term remission.

Therefore, a user-modifiable cure switch point was incorporated into the economic model, after which patients alive and progression-free (based on PFS) were assumed

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

to be “cured” – i.e., remain progression-free and follow the general population mortality thereafter. In line with previous PARPi NICE appraisals, no adjustments were made to the OS extrapolations, which were assumed to continue beyond the cure point until intersecting with the PFS curve, at which point they were capped by the PFS curve from below. This approach leveraged the mature PFS data from PRIMA, which is expected to more accurately reflect the long-term survival plateau associated with the remission assumption. Furthermore, both PFS and OS were capped to ensure that survival rates per cycle did not drop below the (adjusted) general population mortality at any point. Based on the clinical expert feedback received, a 10-year cure timepoint was used in the base case analysis, with both earlier and later cure time points (8 and 12 years) tested in scenario analyses.

For the BRCAm population, general population mortality applied to PFS after the cure point was adjusted using an HR of 1.26 based on Mai 2009, in line with NICE TA946⁷⁰ and TA962²⁷, and the impact of excluding this HR estimate was explored in scenario analyses.

3.4.3 Approach to survival analysis and curve selection process

PFS and OS survival curves from PRIMA were used to estimate health state membership over time, with TTDD determining the proportion of patients on 1L maintenance treatment over time. Survival curves were extrapolated beyond the observed follow-up period in accordance with NICE DSU guidance.^{99,100} Standard and flexible parametric models were fitted for each biomarker subgroup independently due to the lack of head-to-head comparative trial data between niraparib and olaparib, or with rucaparib.

Standard Parametric Models: Parametric survival models assume that the time-to-event (TTE) outcome follows a parametric distribution. The distributions investigated for PFS, OS, and TTDD included exponential, Weibull, Gompertz, log-logistic, log-normal, gamma, and generalised gamma distributions.

Flexible Parametric Spline Models: an alternative flexible spline modelling approach was explored for PFS and OS, considering that standard parametric models might not necessarily provide reasonable fits to the PRIMA time-to-event data given the Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

flattening of the observed KM data. Based on recent guidance on alternative parametric models¹¹⁹ and their use in recent PARPi CDF exit appraisals, Royston/Parmar flexible spline models were investigated considering all three spline model types (hazards, odds, normal) and 1-3 internal knots.¹²⁰

While mixture cure models (MCMs) were also considered, flexible parametric spline models were considered preferable, as UK health economic experts consulted by GSK¹⁰ highlighted that splines are likely to produce comparable extrapolations to MCMs when mature survival data is available. Furthermore, MCMs pose several implementational challenges, particularly when linking cure fractions across outcomes, as proposed in TA962. This approach requires fitting numerous OS parametric models for each PFS cure fraction, leading to an impractically large number of models to evaluate. Further details on the curve selection process and rationale for model selection are provided in Appendix J. Extrapolations selected for the base case and scenario analyses are summarised in the subsequent sections.

3.4.4 PFS

BRCAm

In the base case analysis, the generalised gamma distribution was chosen to model PFS for the niraparib arm in the BRCAm population from PRIMA. The generalised gamma demonstrated good statistical, visual and hazard profile fit to the observed data, and aligned most closely with feedback obtained from UK clinical experts on long-term PFS expectations for niraparib (Appendix J).  overlays the observed PFS KM curve and the fitted generalised gamma model to PFS, adjusted for the 10-year cure point and capped with general population mortality.

[REDACTED]

[REDACTED]

To explore the impact of PFS curve selection on the model results, lognormal and 1-knot normal spline extrapolations were tested in scenario analyses. These models provided more conservative and more optimistic projections, respectively, compared to the generalised gamma, and reflect the plausible ranges of progression-free survivorship proposed by clinical experts.

BRCAwt

For the base case analysis of the BRCAwt population, the generalised gamma distribution was also selected to model niraparib PFS from PRIMA with the best statistical fit as well as a good visual and hazard profile fit to the observed data, and the best overall alignment with feedback received from one-to-one interviews with three UK clinical experts (Appendix J). [REDACTED] shows the observed PFS KM curve from PRIMA overlaid with the generalised gamma model, including the 10-year cure point and capped with general population mortality.



In a scenario analysis, the 2-knot normal spline model was explored as the best statistical fit among models that provided more optimistic PFS extrapolations and were considered clinically plausible. UK clinical experts estimate that up to 9–10% of patients could remain progression-free and alive at 10 years. A more conservative scenario with PFS below 8% at 10 years was not explored, as these parametric models resulted in overly pessimistic estimates and showed poor visual and statistical alignment with the observed data (Appendix J: Clinical Inputs: Survival Analysis).

Summary

A summary of base case and scenario analysis PFS extrapolations for niraparib is shown in Table 37.

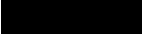
Table 37. Base case and scenario parametric modelling of the niraparib PFS from PRIMA

Population	Parametric model fitted to niraparib arm of PRIMA	Justification
BRCAm		
PFS base case	Generalised gamma	Good statistical, visual and hazard profile fit. Best overall alignment with UK clinical expert feedback
PFS scenario 1	Log-normal	Fairly poor statistical and visual fit to the data, but suggested by one clinical expert as a plausible lower bound in terms of 10-year and 20-year PFS.
PFS scenario 2	1-knot normal spline	Best statistical fit and providing an optimistic alternative long-term projection.
BRCAwt		
PFS base case	Generalised gamma	Good statistical, visual and hazard profile fit. Best overall alignment with UK clinical expert feedback
PFS scenario	2-knot normal spline	Best statistical fit among models closer to upper bound of clinical expert expectations (9-10% at 10 years).

Abbreviations: BRCAm = BRCA mutation; BRCAwt = BRCA wild type; PFS = progression-free survival

3.4.5 OS

BRCAm

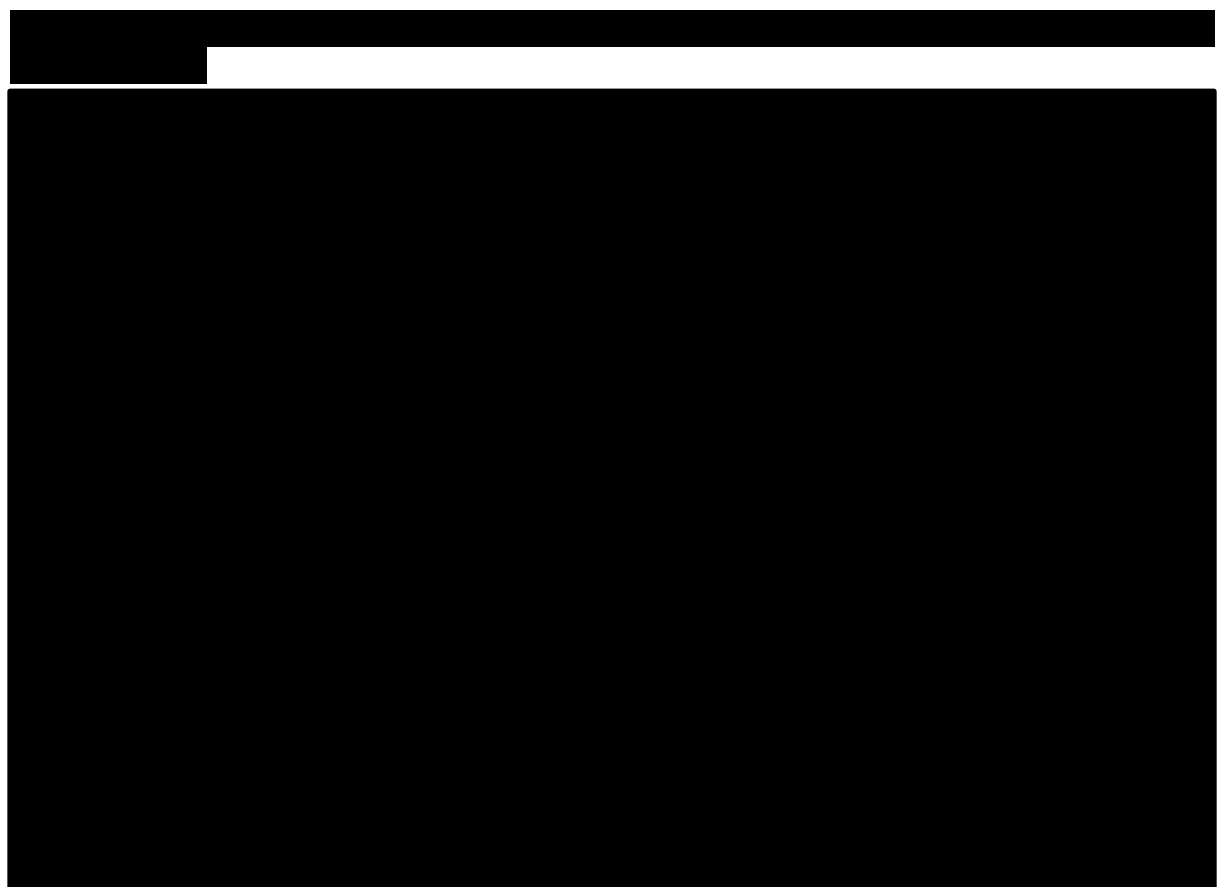
In the base case analysis, the 1-knot normal spline model was selected to model OS for niraparib in the BRCAm population, as it demonstrated the best overall statistical fit to the data (best AIC and 0.2 BIC difference from lowest), a good visual and hazard profile fit, and the best overall alignment with the feedback from four UK clinical experts (Appendix J).  overlays the observed niraparib arm OS KM curve in PRIMA with the 1-knot normal spline model and includes the base case PFS extrapolation (generalised gamma) to show the impact of capping of OS curve from below by PFS.

[REDACTED]

Two additional scenarios were also explored: a more pessimistic extrapolation based on the lognormal distribution, and a more optimistic projection based on the generalised gamma distribution (consistent with clinical expert feedback on clinically plausible survival expectations).

BRCAwt

For the base case analysis of the BRCAwt population, the 1-knot hazard spline distribution was selected to model OS for niraparib. This model provided a good statistical fit to the observed data as well as a good visual and hazard profile fit, and the best overall alignment with feedback on long-term survival extrapolations from three UK clinical experts (Appendix J). [REDACTED] overlays the observed niraparib arm OS KM curve with the 1-knot hazard spline model, along with the base case generalised gamma PFS model used to cap OS from below.



Two alternative OS distributions were also considered for the BRCAwt population. The lognormal model, preferred by one of the three UK clinical experts based on the PFS crossing point, was explored as a pessimistic scenario. The generalised gamma distribution was then explored as a more optimistic survival extrapolation scenario, based on UK clinical expert feedback on clinically plausible survival expectations (i.e., ~15% of patients are alive at 10 years).

Summary

A summary of base case and scenario analysis PFS extrapolations for niraparib is shown in Table 38.

Table 38. Base case and scenario parametric modelling of niraparib from PRIMA

Population	Parametric model fitted to niraparib arm of PRIMA	Justification
BRCAm		
OS base case	1-knot normal spline	Joint best overall statistical fit to the data and good visual and hazard profile fit. Good alignment with overall feedback obtained from UK clinical experts.
OS scenario 1	Log-normal	Good statistical fit and good visual fit, but worse visual fit than generalised gamma and spline models. Model preferred by one of the UK clinical experts consulted and explored as lower bound scenario.
OS scenario 2	Generalised gamma	Joint best overall statistical fit and good visual fit. Explored as upper bound scenario given UK clinical expert feedback.
BRCAwT		
OS base case	1-knot hazard spline	Good statistical, visual and hazard profile fit. Best overall reflection of feedback on long-term survival extrapolations from UK clinical experts.
OS scenario 1	Log-normal	Best statistical fit according to BIC, although slightly worse visual fit to tail of observed data than generalised gamma and splines. Preferred model of one of the clinical experts; explored as lower bound survival scenario.
OS scenario 2	Generalised gamma	Better statistical in terms of AIC, with marginally better statistical fit than flexible spline models. Explored as upper bound scenario given UK clinical expert feedback.

3.4.6 PFS and OS: Modelling of external comparators

There are no direct comparisons between niraparib and the relevant comparators (olaparib and rucaparib) in a clinical trial setting in 1L aOC maintenance. Therefore, an ITC feasibility assessment was conducted, which concluded that any ITCs involving comparison of niraparib (PRIMA, PRIME) trials vs. olaparib (SOLO-1) and rucaparib (ATHENA-MONO) trials are likely inappropriate and fundamentally flawed, as described in Section 2.7.

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

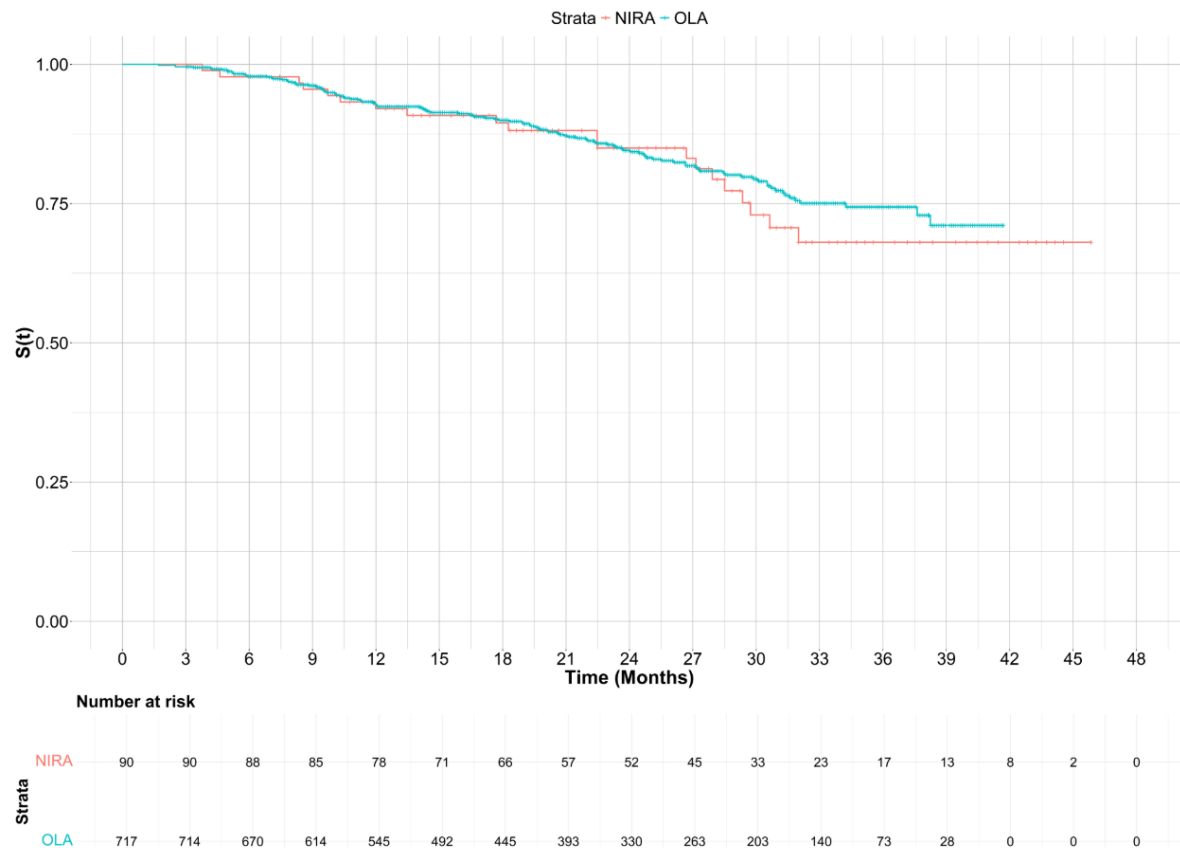
Despite the significant limitations identified in the ITC FA, several exploratory ITCs were conducted, to obtain relative treatment effects across different outcomes and treatments and within each population of interest (see Section 2.7).

The exploratory ITC using PRIMA and SOLO-1 indicated no statistically significant differences in PFS outcomes for niraparib compared to olaparib in the BRCaM population. While the unadjusted Bucher ITC nominally favoured olaparib, the result was not statistically significant [REDACTED], and numerical differences were likely due to differences in the PRIMA and SOLO-1 trial design and populations. Furthermore, the absence of detailed patient characteristics for the high-risk BRCaM population subgroup of SOLO-1 (including key prognostic factors such as NVRD status) made it impossible to rule out potential imbalances in effect modifiers between studies that would impact the results of an unadjusted analysis. As noted in Section 2.7, population-adjusted methods (STC) were initially considered but the regression model lacked external validity.

Exploratory ITCs for niraparib versus rucaparib using PRIME and ATHENA-MONO (Section 2.7), in the absence of high-risk data for rucaparib, also indicated no statistically significant differences in PFS across all populations and for OS for the ITT and HRd populations (other subpopulation specific OS data was not available from PRIME).

In the absence of OS outcomes for high-risk patients from SOLO-1, OS data for BRCaM patients receiving olaparib and niraparib from the SACT was reviewed, to assess whether survival differences between niraparib and olaparib survival could be expected. As shown in Figure 22, the SACT OS KM curves for niraparib and olaparib overlap for the first 27 months, before only deviating slightly at the tails where low numbers of patients at risk are available to inform the niraparib curve. Furthermore, the proportion of patients alive at key SACT milestones (6-24 months) is similar between niraparib and olaparib, as summarised in Table 39.

Figure 22. Comparison of OS SACT Data for BRCAm Patients: Niraparib vs Olaparib



Abbreviations: NIRA = niraparib; OLA = olaparib; OS = overall survival; SACT = Systemic Anti-Cancer Therapy

Table 39. Comparison of OS SACT Data Milestones for BRCAm Patients: Niraparib vs Olaparib

Time Period	NIRA OS (%)	OLA OS (%)
6 months	98% [95% CI: 95%, 100%]	98% [95% CI: 96%, 99%]
12 months	92% [95% CI: 87%, 98%]	93% [95% CI: 91%, 95%]
18 months	90% [95% CI: 83%, 96%]	90% [95% CI: 87%, 92%]
24 months	85% [95% CI: 77%, 93%]	85% [95% CI: 81%, 87%]
36 months	68% [95% CI: 57%, 82%]	74% [95% CI: 69%, 79%]
Median OS	Not reached	Not reached
Median follow-up in SACT overall	17.7 months (538 days)	22.9 months
Number of events	20 events (22.2%) out of 90 patients	116 (16.2%) out of 717

Abbreviations: CI = confidence interval; NIRA = niraparib; OLA = olaparib; OS = overall survival; SACT = Systemic Anti-Cancer Therapy

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Real-world evidence studies comparing PARPis effectiveness in 1L aOC maintenance are currently limited, thus restricting the use of RWE comparative effectiveness for the CEM (Section 2.8.1). Nevertheless, equivalence in niraparib and olaparib efficacy is supported by a recent real-world evidence study⁹⁶ (South Korea) in BRCAm patients, where similar outcomes between olaparib and niraparib when used as maintenance therapy were demonstrated, with no statistically significant differences in PFS (HR: 1.08; 95% CI: 0.47, 2.52; p=0.854), TFST (HR: 1.20; 95% CI: 0.51, 2.81; p=0.682) or OS (HR: 0.42; 95% CI: 0.01, 17.61; p=0.649 – note that only 2 deaths were observed in the olaparib arm and none in the niraparib arm).

Clinical expert feedback also supports the expectation of a class effect for PARPis, with no meaningful differences in efficacy across the approved drugs. This 'class effect' is more evident in the relapsed setting where pivotal trials of PARPi treatments are more comparable.²¹⁻²³ Experts highlighted that the alignment between UK SACT OS data for niraparib and olaparib, along with supportive findings from the above mentioned South Korean study⁹⁶, provides valuable evidence of this class effect. Experts also noted that PFS and OS outcomes for niraparib from PRIMA and rucaparib from ATHENA-MONO²⁸ were also considered comparable, despite differences in study design and patient characteristics, with no clinically meaningful differences between hazard ratios across biomarker populations. However, experts acknowledge that interpreting OS data, particularly for some subgroups, was more challenging due to differences in data maturity between the two studies.

The assumptions for modelling external comparators are summarised in Table 40. For the BRCAm population, the use of a constant HR of ■■■ for niraparib compared to olaparib was explored based on the explorative Bucher ITC estimate to test the robustness of the results to changes in assumptions related to comparative efficacy, although this was considered to be a conservative scenario analysis.

Table 40. Comparator Survival Estimate HR

Comparator (population)	Outcome	Inputs	Assumptions
Olaparib (BRCAm)	PFS:	HR = 1.00	Assumed equivalence in base case. Scenario analysis conducted with constant HR = [REDACTED] based on Bucher ITC of PRIMA vs SOLO-1
	OS:	HR = 1.00	Assumed equivalence based on SACT OS data comparison
Rucaparib (BRCAwt)	PFS:	HR = 1.00	Assumed equivalence supported by Bucher ITC of PRIME vs ATHENA-MONO
	OS:	HR = 1.00	

Abbreviations: OS = overall survival; PFS = progression-free survival; TTDD = time to treatment discontinuation; ITC = indirect treatment comparison.

3.4.7 TTDD

Niraparib

Although the niraparib SmPC does not specify a maximum duration of treatment, both PRIMA and PRIME trial protocols specified a 36-month stopping rule, which is typically adhered to by clinicians in UK clinical practice. While some patients in the trial continued niraparib beyond this period, feedback from UK clinical experts during an advisory board suggested that only a very small proportion of patients in UK clinical practice would be expected to continue treatment beyond 36 months. This is primarily due to risk benefit ratio as there is a lack of clinical trial evidence demonstrating the efficacy and safety beyond 3 years and concerns regarding cumulative toxicity and the associated risks of AML and MDS with prolonged PARPi use. As a result, continued treatment with PARPi is likely to be limited to patients with visible disease who remain progression-free and continue to respond to treatment after three years. Clinical experts also noted that discontinuing niraparib after 36 months is unlikely to impact efficacy outcomes.

According to clinical experts, the proportion of patients remaining on niraparib treatment after 36 months is estimated to range from 5% to 10%, influenced by factors such as surgical outcomes and the extent of residual disease, which can vary across

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

regions due to differences in healthcare practices and access to care prior to initiating and during PARPi treatment.

Therefore, in the base case scenario, it was assumed that 90% of patients will discontinue niraparib after 36 months, while 10% will remain on treatment. Those remaining beyond the stopping rule are assumed to follow the same TTDD curve projection as applied prior to the stopping rule.

For the base case analysis, PRIMA TTDD data were utilised to align with use of PRIMA data for PFS and OS in the model. Given the limited need to extrapolate TTDD beyond the observed data based on clinical expert feedback, the statistical and visual fit of parametric models for niraparib TTDD were used as the primary selection criteria, in line with NICE DSU TSD14 guidance⁹⁹. However, as none of the models demonstrated particularly strong visual fits to the observed data (Appendix J: Clinical Inputs: Survival Analysis), TTDD was modelled using the available KM data from PRIMA combined with the parametric model that provided the best statistical fit for each population (exponential for BRCAm, log-logistic for BRCAwt) to extrapolate beyond the observed data.

Comparators- olaparib and rucaparib

For external comparators, published TTDD KM curves were available for olaparib from SOLO-1 and SACT data; however, comparable TTDD curves were not available for rucaparib. Median time on treatment estimates were available from both SOLO-1 for olaparib (24.6 months) and ATHENA-MONO for rucaparib (14.7 months). However, median treatment duration data were available only for the overall population from ATHENA-MONO, which is likely to overestimate time on treatment for a BRCAwt population.

To ensure a consistent approach across PARPi comparators and to produce a more conservative estimate for rucaparib, TTDD curves were instead generated by adjusting the base case PFS curves for each treatment arm with AE discontinuation probabilities. For olaparib in the BRCAm population, a constant AE discontinuation rate was estimated based on the probability of AE-related discontinuation (11.92%)

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

and the median treatment exposure (24.6 months) from SOLO-1.¹⁷ Similarly, for rucaparib in the BRCAwt population, a constant AE discontinuation rate was calculated based on the probability of AE-related discontinuation (11.76%) and the median treatment exposure (14.7 months) from ATHENA-MONO.¹⁴

SOLO-1¹⁷ and olaparib SACT data showed that some patients continued treatment beyond 24 months. However, as cumulative toxicity and the associated risks of AML and MDS with prolonged PARPi use are class-wide concerns, the assumption that 10% of patients would continue treatment beyond the stopping rule for niraparib was also applied to olaparib and rucaparib in the base-case analyses for the BRCAm and BRCAwt populations, respectively. However, this assumption may underestimate the true costs of olaparib and rucaparib as clinical experts noted that in clinical practice there was greater scope for continuing treatment beyond the stopping rule for these therapies (relative to niraparib) as the overall exposure is shorter; suggesting that the proportion continuing on olaparib or rucaparib is likely to be higher due to the earlier treatment stopping rule at 24 months.

xxxxxx ■ outlines the base case TTDD extrapolations for niraparib and olaparib in the BRCAm population, while xxxxxx ■ shows the base case niraparib and rucaparib TTDD curves for the BRCAwt population.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Given some of the uncertainty around PARPi treatment continuation and TTDD extrapolation assumptions, the following TTDD related scenario analyses were also conducted, including use of available SACT data for niraparib and olaparib:

- Niraparib SACT TTDD data and assume that 90% of patients discontinue treatment after 36 months. Uses the available KM data combined with the best statistically fitting survival distribution (lognormal for BRCAm, generalised gamma for BRCAwt)
- Assume all patients discontinue at the stopping rule time point (36 months for niraparib, 24 months for olaparib and rucaparib) across all comparators
- Derivation of the TTDD curve for the comparators using simple exponential models fitted using the median time on treatment estimates for olaparib and rucaparib (24.6 months for olaparib, 14.7 months for rucaparib)
- **Additional scenario for BRCAm only:**
 - Use of niraparib and olaparib SACT TTDD KM data to the approximate end of available follow-up (42 months and 38 months, respectively), then assume all patients discontinue treatment

Plots of the resulting TTDD curves for each of these scenarios are presented in Appendix J: Clinical Inputs: Survival Analysis.

3.4.8 Summary of base-case survival extrapolations

A summary of the survival extrapolation settings for PFS, OS and TTDD across populations and comparators is shown in Table 41.

Table 41. Summary of Survival Parameters Used in the Model

Category	Inputs	
	BRCAm	BRCAwt
PFS Distribution: Niraparib	Gen. gamma	Gen. gamma
PFS approach: Comparators	Assume equivalence (i.e. HR=1)	
PFS Cure Landmark (% cured)	10 years (100%)	
OS Distribution: Niraparib	1-knot normal spline	1-knot hazard spline

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Category	Inputs	
	BRCAm	BRCAwt
OS approach: Comparators	Assume equivalence (i.e. HR=1)	
TTDD Distribution: Niraparib	KM + Exponential	KM + Log-logistic
Treatment stopping time point: Niraparib	36 months	
Proportion discontinuing at stopping rule: Niraparib	90%	
TTDD Approach: Comparators	Generated from PFS combined with AE discontinuation data from SOLO-1	Generated from PFS combined with AE discontinuation data from ATHENA-MONO
Treatment stopping time point: Comparators	24 months	
Proportion discontinuing at stopping rule: Comparators	90%	

Abbreviations: PFS = Progression-free survival; OS = Overall survival; TTDD = Time to treatment discontinuation; ITC = Indirect treatment comparison.

3.4.9 Treatment waning

Treatment effect waning was not considered relevant across any of the 1L PARPi CDF exit appraisals for olaparib + bevacizumab (TA946⁷⁰), olaparib (TA962²⁷) or rucaparib (TA1055²⁸), or across identified model publications reviewed. Omission of waning is consistent with the clinical intent of PARPi, which is to maintain remission beyond the first 2-3 years following PBC when the risk of relapse is greatest. Patients who remain progression-free beyond this period are considered to be at low risk of progression. Therefore, incorporating treatment waning following discontinuation of PARPi in survival modelling was not considered appropriate.

3.4.10 Adverse events

In the CEM, grade 3 or above treatment-related AEs that occurred in more than 5% of patients in either arm of each study were considered to capture impact on costs and health-related quality of life (HRQoL), in alignment with the approach previously adopted for niraparib in NICE TA 673.²⁶ The impact of AEs on healthcare resource utilisation costs, and HRQoL were captured as one-off costs and one-off QALY loss at treatment initiation (i.e., in the first modelled cycle), respectively, as in previous NICE TAs (TA946⁷⁰, TA962²⁷, TA1055²⁸). While AEs can occur at any point during

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

treatment, they are assumed to occur primarily after treatment initiation and require only acute care.

AE probabilities for niraparib were extracted from both the PRIMA trial and from the MONITOR-UK study⁷⁵, while those for the comparators olaparib and rucaparib were obtained from their respective pivotal trials (Table 42). For the base case analysis, MONITOR-UK data were used for niraparib as the starting dose distribution (16% on 300mg, 79% on 200mg, 5% on 100mg) was more reflective of UK clinical practice, and also more comparable to the SACT data used to model the niraparib dose distribution in the base case analysis (see Section 3.6.1). This approach was validated during one-to-one follow-up interviews with three UK clinical experts, who confirmed that the AE frequencies observed in MONITOR-UK were appropriate and more reflective of niraparib use in UK clinical practice.

Although phase 3 trial data were used to model AEs for olaparib and rucaparib, real-world evidence for olaparib¹²¹ suggests that its AE profile is fairly similar to that observed in SOLO-1. In contrast, the differences observed between AEs in the real-world and PRIMA could be attributed largely to a greater proportion of patients starting on the 300 mg dose which is associated with higher rates of AEs and lower tolerability. Additionally, niraparib is the only PARPi treatment where the marketing authorisation mandates weekly blood count tests for the first month of treatment followed by monthly tests for the following 9 months. Clinicians noted that AEs are generally lower at the 200 mg dose; individualised dosing schedule combined with proactive monitoring and pre-emptive AE management, helps reduce the incidence of serious AEs. A GSK sponsored patient support program is in place which provides blood testing and blood pressure monitoring services at home to patients being treated with niraparib. This minimises patient barriers to testing services which are required by the SmPC and serves to proactively manage incidences of adverse effects.

AE data for PARPi's was also assumed to be consistent across population subgroups. This approach is consistent with previous TAs (TA946⁷⁰, TA962²⁷, TA1055²⁸). Application of PRIMA AE estimates was explored in scenario analysis.

Table 42. Grade 3+ Adverse Event Incidence

Regimens	Anaemia	Hypertension	Increased ALT/AST	Neutropenia	Neutrophil count decreased	Platelet count decreased	Thrombocytopenia	N	Source
Niraparib	9.8%	15.2%	0.0%	0.0%	7.7%	11.0%	0.0%	165	MONITOR-UK
								484	PRIMA
Rucaparib	28.7%	0.0%	10.6%	14.6%	0.0%	0.0%	7.1%	425	ATHENA MONO
Olaparib	21.9%	0.0%	0.0%	8.5%	0.0%	0.0%	0.8%	260	SOLO1

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase.

3.5 Measurement and valuation of health effects

3.5.1 Health-related quality-of-life data from clinical trials

In PRIMA, patient HRQoL was a secondary end point and was assessed using the European Organisation for Research and Treatment of Cancer [EORTC] Quality of Life Questionnaire [EORTC QLQ-C30], the EORTC Quality of Life Questionnaire Ovarian Cancer module [EORTC QLQ-OV28]), the FOSI, and the EQ-5D-5L.⁶⁹ A statistical analysis of HRQoL data from PRIMA conducted by GSK was used to capture HRQoL differences between progression-free and progressed patients (progression effects). EQ-5D-5L response data from PRIMA were converted to EQ-5D-3L scores using the Hernandez-Alava 2020 cross-walk algorithm in line with NICE recommendations.^{104,117}

Potential differences in HRQoL were assessed using a generalised estimating equation (GEE) model with an identity link function, with various GEE models explored including progression, treatment arm and population subgroup as covariates. However, given the lack of significant differences in health state specific utilities by treatment arm and population subgroup, and in line with prior NICE appraisals, the same set of utility estimates derived from the overall PRIMA trial population were considered for both BRCAm and BRCAwt populations.

3.5.2 Mapping

As per NICE guidance [50], EQ-5D-5L response data from PRIMA were converted to EQ-5D-3L scores using the Hernandez-Alava 2020 cross-walk algorithm, as stated in Section 3.4.1. No other mapping was performed.

3.5.3 Health-related quality-of-life studies

The clinical SLR identified four studies evaluating 1L PARPi maintenance treatments with relevant HRQoL data. These studies relate to the RCTs for niraparib¹², rucaparib¹⁴, olaparib¹⁵ and olaparib plus bevacizumab⁶⁴ main clinical trial publications. Data on EORTC QLQ-C30 and EQ-5D were available from two RCTs each (PAOLA-1 and PRIMA, and SOLO-1 and PRIMA, respectively). To note that in both PRIMA (niraparib) and SOLO-1 (olaparib), similar EQ-5D-5L scores were seen regardless of Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

treatment arm. One additional study was identified from the non-clinical searches that reported caregiver HRQoL.¹²²

Full details of the clinical SLRs can be found in Appendix B:. Full details of the non-clinical SLR and its findings, including PRISMA diagram and outcomes are detailed in Appendix G:.

Given alignment with data primarily utilised otherwise in the base case analysis, data from the PRIMA trial was considered most relevant for sourcing health state utility values in the base case analysis, with alternative health state utility values and adverse event disutility estimates sourced from the literature.

3.5.4 Adverse reactions

The model accounts for adverse event (AE) disutility that may arise with 1L maintenance treatment, which are applied as one-off QALY losses at the start of the model.

Disutility estimates and durations for each AE were aligned with those used in the NICE appraisal for rucaparib (TA1055²⁸), and are presented in Table 43 with the QALY loss per AE calculated from the AEs incidence, disutility and duration. Due to a lack of data availability, the SEs for disutility and duration values are assumed as 10% of the mean.

Table 43. AE QALY Losses

Adverse Events	Disutility	SE	Duration (weeks)	SE	Estimated QALY Loss Per AE	Source
Anaemia	-0.0800	0.0080	1.0000	0.1000	-0.0015	NICE TA1055
Hypertension	-0.1300	0.0130	1.5714	0.1571	-0.0039	NICE TA1055
Increased ALT/AST	-0.0900	0.0090	1.6000	0.1600	-0.0028	NICE TA1055
Neutropenia	-0.0900	0.0090	1.3286	0.1329	-0.0023	NICE TA1055
Neutrophil count decreased	-0.0900	0.0090	1.3286	0.1329	-0.0023	NICE TA1055
Platelet count decreased	-0.0900	0.0090	1.3286	0.1329	-0.0023	Assumed same as neutropenia, as in NICE TA1055 (rucaparib TA) and NICE TA673 (Original niraparib TA)
Thrombocytopenia	-0.0900	0.0090	1.3286	0.1329	-0.0023	Assumed same as neutropenia, as in TA1055 (rucaparib TA) and TA673 (niraparib TA)

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; NICE = National Institute for Health and Care Excellence; QALY = quality-adjusted life year; SE = standard error

One-off QALY losses for each comparator were estimated by combining the base case adverse event probabilities in Table 42 with QALY losses per AE in Table 43. Exclusion of AE-related QALY losses was also explored in scenario analysis.

Table 44. Overall One-off QALY Loss per Comparator

Regimens	One-off AE-related QALY loss
Niraparib	-0.00117
Rucaparib	-0.00123
Olaparib	-0.00055

Abbreviations: AE = adverse event; QALY = quality-adjusted life year.

3.5.5 Health-related quality-of-life data used in the cost-effectiveness analysis

The utility values derived from the PRIMA study and used in the base case analysis are summarised in Table 45. Alternative health state utility estimates from NICE TA962 (0.81 for progression free and 0.76 for progressed, with utility sample reference age of 53.2 years) were explored in scenario analysis.

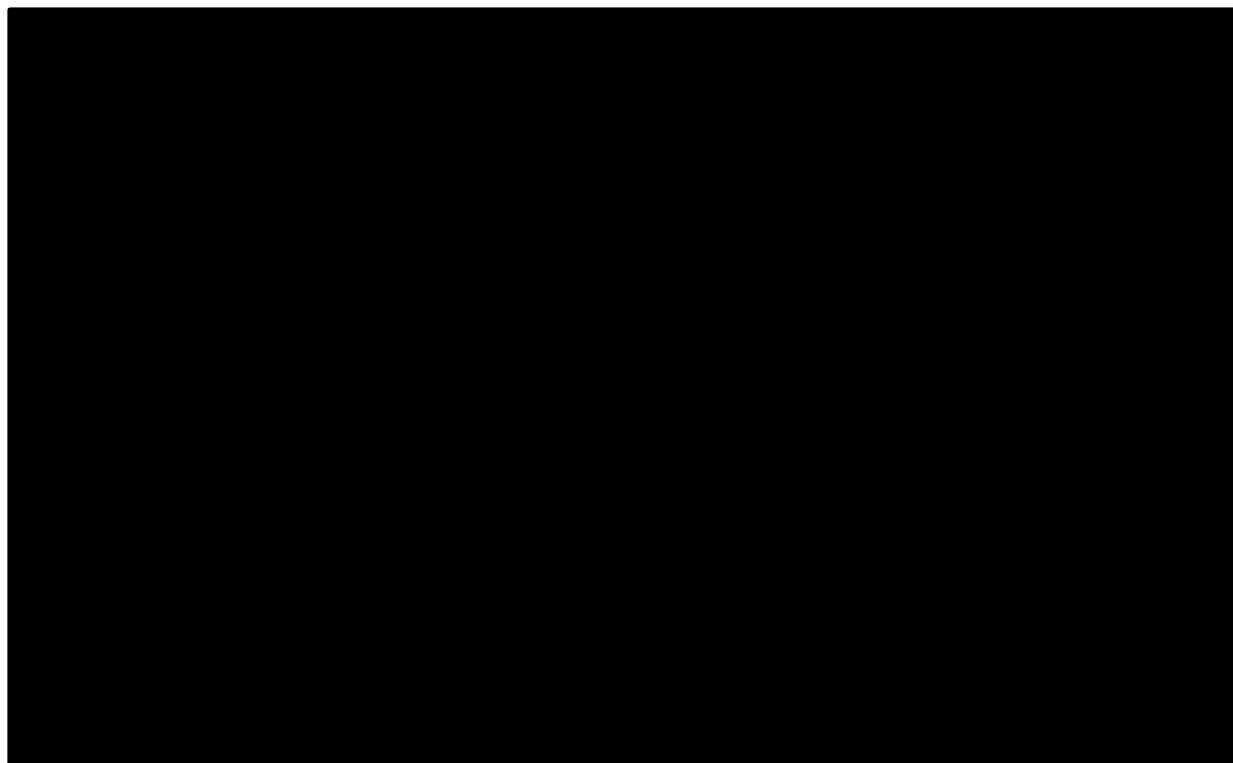
Table 45. Base-case utilities (PRIMA)

Health States	Mean	SE	Utility Sample Reference Age (Years)	Source
Progression Free	██████	██████	██████	PRIMA
Progressed	██████	██████		

Abbreviations: SE = Standard error.

Utility values were applied to each health state in the model (progression free and progressed) to capture patient QoL associated with treatment and disease outcomes and were assumed to be the same regardless of the treatment (i.e., utility values are assumed to remain unchanged regardless of treatment arms). This assumption is in line with clinical advice to the EAG in TA1055²⁸, which highlighted that HRQoL is not likely to differ by subgroups.

Utility values in the model are adjusted by age to reflect decreases in HRQoL over time using a multiplicative approach¹²³ (NICE guidance 4.3.7^{104,117}). In line with NICE guidance, these adjustments were made to account for the expected decline in QoL associated with age and to prevent health state utilities exceeding those of the age-matched UK general population. UK general population utility norms were sourced from the Hernandez-Alava 2022 NICE DSU report, where general population utility was derived from an adjusted limited dependent variable mixture model (ALDVMM) fitted to UK Health Survey for England EQ-5D-3L data.¹⁷



No specific adjustments were included for patients in long-term remission, who are assumed to continue experiencing the same quality of life as progression-free patients, in line with prior PARPi appraisals.^{28,70,106}

3.6 Cost and healthcare resource use identification, measurement and valuation

Thirteen studies were identified for the SLR that reported on HCRU/costs, including the three NICE technology appraisals previously reviewed (TA962²⁷, TA946⁷⁰ and TA1055²⁸). Search terms are summarised in Appendix G:. Full details on the findings of the HCRU/costs SLR including PRISMA diagram and outcomes are detailed in Appendix G:. Given their recency and use of a UK NHS and PSS payer perspective, the recent three prior PARPi NICE technology appraisals were considered most relevant for informing cost category inclusion and sourcing of cost inputs compared to other publications identified.

Based on review of published economic studies and prior NICE appraisals, the model included the following cost categories: drug acquisition and administration, adverse event management, follow-up and monitoring, terminal care and subsequent treatment costs. The following sections describe the assumptions and the inputs used for each cost category included in the model.

3.6.1 Intervention and comparators' costs and resource use

Drug Acquisition Costs

Drug acquisition costs for each treatment regimen were calculated based on cost per package and dosing regimen (including dose per administration and number of administrations) reported in the respective prescribing information and/or clinical trials. Unit cost per package was obtained from (i) latest data from British National Formulary and (ii) the latest drugs and pharmaceutical electronic market information tool (eMIT).^{116,124}

If multiple formulations of a treatment with similar strength were available, an average cost was calculated for use in the model. For treatments with multiple formulations with different strengths, the least expensive formulation that aligns with the prescribed dosing was selected.

An overview of the label-based dosing for each comparator is summarised in Table 46.

Table 46. Dosing, route of administration and regimen of drugs used in 1L aOC maintenance

Maintenance regimens	Niraparib		Rucaparib	Olaparib
	NIRA 200 mg Dose*	NIRA 300 mg Dose*		
Treatment				
Dosing type	Fixed	Fixed	Fixed	Fixed
Route	Oral	Oral	Oral	Oral
Dose	200 mg QD	300 mg QD	600 mg BID	300 mg BID

Abbreviations: 1L = First-Line; aOC = Advanced Ovarian Cancer; BID = twice a day; QD= once a day
 * 200 mg QD: body weight of <77 kg and/or a platelet count of <150,000/ μ ; 300 mg QD: body weight of $\geq$ 77 kg and a platelet count of $\geq$ 150,000/ μ L

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Niraparib is an oral monotherapy with a recommended starting dose of 200 mg (two 100 mg capsules), taken once daily (OD). For patients who weigh ≥ 77 kg and have baseline platelet count $\geq 150,000/\mu\text{L}$, the recommended starting dose of niraparib is 300 mg OD (three 100 mg capsules). In the base case analysis, the modeling approach for niraparib dosing considered the proportion of patients starting on 200 mg versus 300 mg and incorporated the relative dose intensity for patients starting on each dose. The distribution of patients starting on 200mg or 300mg, as provided by the SACT data was seen as the most accurate reflection of UK clinical practice and is also aligned with available dose distribution data from the MONITOR-UK study²⁵, which clinical experts stated was a more accurate reflection of niraparib use in UK clinical practice.

Relative dose intensity (RDI) was considered to account for the impact that dose modifications have on drug costs, with niraparib RDI estimates sourced from PRIMA in the absence of available information from other data sources. RDI for niraparib is expected to be lower as patients tend to get down dosed frequently as observed in RWE (such as MONITOR-UK²⁵ and Bruno et al.⁹⁷), which was also noted by UK clinical experts (see Section 3.4.10).

RDI is particularly relevant for niraparib due to its linear pricing structure, distinguishing it from olaparib and rucaparib. While dose reductions are observed across all PARPis, cost savings are only realised with niraparib. Niraparib is formulated as 100 mg tablets which are used to make up daily doses of 100 mg, 200 mg or 300mg per day. In this regard niraparib is linearly priced, with the monthly cost per patient dependent on the average dose received within that month. Conversely, rucaparib is formulated as a 300 mg, 250 mg or 200 mg tablet, each packaged as a 60-tablet pack with the same cost-per-pack as outlined in Table 48. Therefore, dose adjustments which result in a dose reduction from the recommended starting dose of 600 mg per day down to 500 mg or 400 mg per day do not impact on the average daily cost. Similarly in the case of olaparib, 56-tablet packs of 150 mg and 100 mg tablet packs are also flat priced meaning dose adjustments will not impact on the average monthly cost. Furthermore, unlike in the case of niraparib, dose adjustments for rucaparib and olaparib, particularly those occurring mid-cycle, are likely to result in wastage and increased

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

monthly costs. Unused tablets from discontinued pack strengths are discarded, requiring patients to switch to a lower pack strength. Data on mid-cycle dose adjustments are not available for olaparib and rucaparib and so are conservatively not accounted for in the cost-effectiveness analysis. Given this, RDI parameters were not applied for olaparib and rucaparib in the base case analyses, with RDIs for olaparib (96.0%) and rucaparib (88.0%) applied in NICE TA1055 explored in scenario analysis for the BRCAm and BRCAwt populations, respectively.

Table 47 shows the niraparib starting dose distribution and the relative dose intensity parameters for niraparib, olaparib and rucaparib by population.

Table 47. Niraparib starting dose distribution and Relative dose intensity parameters

Dosing approach: Individualised starting dose	BRCAm	BRCAwt	Source
Niraparib 200mg	87%	83%	SACT data (BRCAm cohort and BRCAwt cohort, respectively)
Niraparib 300mg	13%	17%	
Relative dose intensity			
Niraparib 200mg	■%	■%	PRIMA, data on file
Niraparib 300mg	■%	■%	
Olaparib	100.0%	---	Assumption based on flat pricing across packs. Values from NICE TA1055 of 96.0% for olaparib and 88.0% explored in scenario analysis.
Rucaparib	---	100.0%	

To test the impact of application of alternative niraparib dosing data, the following scenario analyses were also conducted:

- Using the 200mg (■% for BRCAm, ■% for BRCAwt) vs 300mg (■% for BRCAm, ■% for BRCAwt) starting dose distribution based on population-specific data from the PRIMA trial, which was expected to be an overestimate of usage of the 300mg dose in UK clinical practice

- Applying the average niraparib dose received in the PRIMA trial (■■■■■mg for BRCAm, ■■■■■mg for BRCAwt). Note that RDI was not applied for this scenario since it was assumed to already be captured within the average dose estimate
- Applying the proportion of patients receiving each of the three niraparib doses (100 mg, 200 mg, 300 mg) per month over the PRIMA trial duration. As for the average dose approach, this approach assumes that the RDI was captured as part of the dose distribution. Data applied for this scenario analysis are summarised in Appendix K: Detailed niraparib dosing approach used in scenario analyses
- Using the relative 200mg (82.8%) vs 300mg (17.2%) starting dose distribution based on data from the MONITOR-UK study²⁵

A summary of the pack prices used for each comparator are shown in Table 48.

Table 48. Unit Costs per package

Drugs	Unit size 1 (mg)	Pack size 1	List price per pack for pack size 1 (£)	Source
Niraparib	100.0 mg	56	£ 4,500.00	BNF ⁴¹
Niraparib	100.0 mg	84	£ 6,750.00	BNF ⁴¹
Rucaparib	200.0 mg	60	£ 3,562.00	BNF ⁴¹
Rucaparib	250.0 mg	60	£ 3,562.00	BNF ⁴¹
Rucaparib	300.0 mg	60	£ 3,562.00	BNF ⁴¹
Olaparib	100.0 mg	56	£ 2,317.50	BNF ⁴¹
Olaparib	150.0 mg	56	£ 2,317.50	BNF ⁴¹

The resulting acquisition costs by subpopulation and comparator per model cycle for the base case analysis are summarised in Table 49, including the cost of niraparib with and without the proposed PAS discount of ■■■■.

Table 49. Acquisition costs per model cycle

Population	Treatment	Dose	Acquisition cost per model cycle w/o list price discount for niraparib	Acquisition cost per model cycle with PAS discount for niraparib
BRCAm	Niraparib Weight <77 kg or Platelet <150,000/mcL	200.00 mg	£ [REDACTED]	£ [REDACTED]
	Niraparib Weight ≥77 kg & Platelet ≥150,000/mcL	300.00 mg	£ [REDACTED]	£ [REDACTED]
	Olaparib	300.00 mg	£4,837	
BRCAwT	Niraparib Weight <77 kg or Platelet <150,000/mcL	200.00 mg	£ [REDACTED]	£ [REDACTED]
	Niraparib Weight ≥77 kg & Platelet ≥150,000/mcL	300.00 mg	£ [REDACTED]	[REDACTED]
	Rucaparib	600.00 mg	£6,361	

Drug Administration Costs

Following approaches in previous TAs (TA946 and TA962), oral drug administered at home were assumed not to incur any administration related costs.^{27,70}

3.6.2 Health-state unit costs and resource use

Based on previous NICE TA economic evaluations^{27,28,70} and clinical expert feedback, follow-up and monitoring cost consists of outpatient oncologist consultation, laboratory tests for complete blood count and imaging procedures (CT-scan). Resource utilisation was modelled separately for the following health states.

- Progression-free - On maintenance treatment
- Progression-free - Off maintenance treatment
- Progressed disease

Annual frequency of resources incurred in the above-mentioned health states can be stratified by treatment in the model. In the absence of available data to differentiate

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

monitoring frequencies by treatment within health states, the same health-state specific frequencies were generally applied to all treatments, with two exceptions. The model allows for additional one-off monitoring costs in the first cycle, which was applied for niraparib to account for additional blood tests required in the first cycle, calculated as 2.67 completed blood tests to produce 4 total blood tests when combined with the monthly frequency of 1.33 blood tests applied in the progression-free on treatment health state, as per UK SMPC.²⁴

In line with NICE TA962²⁷ and TA946⁷⁰, a 7-year stopping rule was applied in the base case, meaning patients no longer incur resource use costs in the progression-free on-treatment health state after this time point. A scenario analysis was also conducted where no stopping rule was applied to progression-free on-treatment health state resource use.

Monthly resource use frequencies by health state are outlined in Table 50.

Table 50. Monthly frequency of resource use.

Monthly Frequency of Resource Use				Source
Health state	Outpatient Oncologist Visit	Complete Blood Count	CT scan	NICE TA1055 ²⁸ and NICE TA946 ⁷⁰ Niraparib SMPC ²⁴
Progression free- on treatment – first cycle (niraparib only)	-	2.67	-	
Progression free - on treatment (up to 7 years)	1.33	1.33	0.17	
Progression free - off treatment	0.33	0.33	0.08	
Progressed disease	1.33	1.33	0.33	

Abbreviations: CT = computed tomography

The unit cost of each treatment monitoring resource identified above was derived from the latest version of NHS reference costs (2023/24) and generally aligned with cost codes used in prior NICE TAs (Table 51).

Table 51. Cost of Resources

	Outpatient Oncologist Visit	Complete Blood Count	CT scan
Unit Cost	£ 191.00	£ 7.66	£ 110.42
Source	NHS Reference Cost (WF01A) ¹²⁵	NHS Reference Cost (PATH05) ¹²⁵	NHS Reference Cost (RD20A - RD27Z) ¹²⁵
Description	Non-admitted face to face attendance, Consultant led; follow-up (503; gynaecological oncology)	Directly Accessed Pathology Services; 370 (Medical Oncology Service), Directly Accessed Pathology Services; 800 (Clinical Oncology Service)	Diagnostic Imaging; Computerised Tomography Scan - Weighed average of the different scan types (w/o contrast) and number of areas
Notes	Assumed consultant led follow-up visits	Weighted average of only oncology services (medical oncology, clinical oncology)	Aligned with OLA TA

A summary of the resulting monthly resource use costs by health state is outlined in Table 52.

Table 52. Summary: Monthly resource use cost.

Regimens	Monitoring Cost per Cycle
Progression free - on treatment – first cycle (niraparib only)	£ 20.43
Progression free - on treatment	£ 283.32
Progression free - off treatment	£ 75.39
Progressed disease	£ 301.65

3.6.3 Adverse reaction unit costs and resource use

AE costs are estimated as a sum product of AE incidence (see Table 42) and unit costs (Table 53) and, similar to AE QALY losses, were applied as one-off costs in the first model cycle. AE unit costs were derived from NHS reference costs¹²⁶ with NHS reference cost code use broadly aligned with previous NICE TAs.

Table 53. Adverse Event Unit Costs

Treatment	Cost of AE Per Episode	NHS Reference Codes	Description/Notes
Anaemia	£802.00	SA04G	Iron Deficiency Anaemia with CC Score 14+, Non-elective inpatient - short stay
Hypertension	£759.00	EB04Z	Total unit cost
Increased ALT/AST	£15.00	PATH04	Clinical Biochemistry: Directly assessed pathology services (370): Medical oncology service Note: Based on the rucaparib TA estimate PATH04 code for blood test in medical oncology best match the value when assumed that 3 tests were required (£5 x 3).
Neutropenia	£636.47	SA08G SA08H	Non-elective short stays for Other Haematological or Splenic Disorders, with CC Score 3-5 and 6+ Note: comparable to previous appraisals
Neutrophil count decreased	£636.47	SA08G SA08H	Aligned with prior NICE TAs where equal cost as neutropenia was assumed
Platelet count decreased	£752.58	SA12G SA12H	Thrombocytopenia with CC Score 0-1, 2.-4, 5-7, 8+, non-elective inpatient-short stay Note: Followed same approach as prior TSA and assumed platelet count decreased is equal to thrombocytopenia.
Thrombocytopenia	£752.58	SA12J SA12K	

The resulting overall one-off AE costs by comparator are summarised in Table 54.

Table 54. Summary of AE Costs

Regimens	One-off AE Costs
Niraparib	£ 325.38
Rucaparib	£ 377.78
Olaparib	£ 235.47

3.6.4 Subsequent treatment costs

A proportion of patients that experience progression are expected to receive additional drug-based interventions, including platinum- and non-platinum chemotherapy regimens. Although PARPi use in subsequent treatment lines was observed in the intervention arms across the relevant PRAPi trial, including PRIMA, PARPi re-

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

treatment is not allowed in UK clinical practice, as noted in prior PARPi NICE appraisals (TA962²⁷, TA946⁷⁰ and TA1055²⁸), with clinical experts in TA962²⁷ indicating the lack of evidence to support the efficacy of PARPi re-treatment. This assumption was also validated with UK clinical experts at one-to-one interviews, with clinical experts noting the lack of clinically meaningful improvement when PARPi's are given in subsequent lines.¹²⁷ This assumption was also validated with UK clinical experts at one-to-one interviews, with clinical experts noting the lack of clinically meaningful improvement when PARPi's are given in subsequent lines.¹²⁷

In the model, distributions and durations of subsequent treatments are differentiated between second-line and third-line plus treatment to help to reflect potential differences in subsequent treatment based on the line of therapy. Subsequent treatment costs were applied to the estimated incidence of progression based on the per-cycle change of the progression health state adjusted for mortality (i.e. accounting for the proportion of patients from the previous cycle that would die based on per-cycle OS risk).

The proportion of patients receiving each subsequent treatment upon progression with a PARPi is derived from treatment usage observed within the PRIMA trial. Subsequent treatment distributions applied in the model were derived in several stages:

- The proportions applied in the model were calculated as percentages of the total niraparib patients with a first progression event (n=■ for BRCAm, n=■ for BRCAwt) for 2L subsequent treatments and of patients with a second progression event (n=■ for BRCAm, n=■ for BRCAwt) for 3L+ subsequent treatments in PRIMA.
- Given that PARPi retreatment and bevacizumab are not permitted as subsequent line treatments in NHS practice, but are recorded as subsequent treatment in the PRIMA trial, the proportion of patients receiving these treatments are redistributed proportionally to each of the other chemotherapy agents. These proportions were validated with UK clinicians who confirmed them to be representative of subsequent treatments used in clinical practice.

- 3L+ treatment distributions were also multiplied by the proportion of first progression patients in PRIMA who also reported experiencing a PFS2 event, i.e. a second relapse, calculated as ████% of the BRCAm population and ████% of the BRCAwt population.

The final proportions applied in the model for each population are summarised in Table 55.

Table 55. Distribution of subsequent treatments applied in the economic model – base case (PRIMA)

Subsequent treatment	<u>BRCAm</u>		<u>BRCAwt</u>	
	<u>2L</u>	<u>3L+</u>	<u>2L</u>	<u>3L+</u>
Proportion of first progression patients experiencing second progression	-	████%	-	████%
Proportion of progressed patients receiving subsequent treatment				
Carboplatin	████%	████%	████%	████%
Cisplatin	████%	████%	████%	████%
Cyclophosphamide	████%	████%	████%	████%
Paclitaxel	████%	████%	████%	████%
Doxorubin (PLD)	████%	████%	████%	████%
Gemcitabine	████%	████%	████%	████%

Subsequent treatment dosing was broadly aligned with UK labels and prior NICE TAs and validated during one-to-one interviews with UK clinical experts consulted by GSK. Dosing and average duration estimates for subsequent treatments are shown in Table 56.

Table 56. Dosing and duration of subsequent treatments applied in the economic model

Subsequent treatment	Dose	Duration (months)	
		2L	3L+
Carboplatin	4 mg/ml/min every 3 or 4 weeks	5.00	4.14
Cisplatin	75 mg/m ² every 3 or 4 weeks	5.00	5.00
Cyclophosphamide	50mg twice every 4 weeks	5.00	5.00
Paclitaxel	80 mg/m ² weekly	5.00	5.00
Doxorubicin (PLD)	40 mg/m ² every 4 weeks	6.00	6.00
Gemcitabine	1,000 mg/m ² twice every 3 weeks	5.00	5.00

Drug wastage was also considered in the model for IV-administered subsequent treatments and assumed to be 100%. Drug wastage was calculated by assuming no vial sharing and determining the number of vials needed based on the average weight, body surface area (BSA) or area under the curve (AUC)-based dosing calculations rounding up the number of vials to the nearest integer. No wastage was assumed for oral drugs.

Subsequent treatment administration costs were calculated based on the administration schedule of each treatment and the unit cost per type of administration (Table 57).

Table 57. Unit costs for the administration of subsequent treatments

Route of Administration	Cost	Description	Source
Deliver Exclusively Oral Chemotherapy	£ 240.00	Deliver Exclusively Oral Chemotherapy	National schedule of NHS costs - Year 2023/24 (SB11Z)
Deliver more Complex Parenteral Chemotherapy at First Attendance	£ 184.00	Deliver simple chemotherapy at first attendance; Overall time of 60 minutes nurse time and up to 120 minutes chair time for the delivery of a complete cycle	National schedule of NHS costs - Year 2023/24 (SB13Z)

Abbreviations: NHS = National Health Service

A summary of the total one-off subsequent treatment cost applied is outlined in Table 58 by population.

Table 58. Summary of subsequent treatment costs

Population	Total Subsequent Treatment Cost	
	2L	3L+
BRCAm	£ 5,444.25	£ 4,646.92
BRCAwT	£ 4,713.10	£ 5,026.01

3.6.5 Miscellaneous unit costs and resource use

Terminal Care Costs

In line with NICE TA946⁷⁰ and TA962²⁷, patients incur a one-off terminal care cost applied at the time of death, with the same estimate applied to all death events. The unit cost was derived from recent nice appraisals (NICE TA946⁷⁰ and TA962²⁷) which used an estimate from Guest et al. [2006]¹²⁸ using the £8,053.63 estimate from those appraisals and inflated from 2021 to 2024 costs based on PSSRU inflation indices. Also in line with NICE TA946⁷⁰ and TA962²⁷, the model assumes that 51.28% of patients will receive end-of-life care based on data from a UK study by Gao et al. 2013.¹²⁹ Due to a lack of identified uncertainty data, SEs are assumed equal to 10% of the mean value.

Table 59. Terminal care costs.

End of Life Costs	Mean	SE	Source	Notes
Unit Cost	£ 9,248.28	£ 924.83	Guest 2006	Inflated from NICE TA946/NICE TA962 estimate to 2024 costs
Proportion of patients receiving end-of-life care	51.28%	5.1%	Gao 2013	In line with all recent NICE PARPi TA's
Average terminal care cost per death	£ 4,742.52			

Genetic Testing Costs

Genetic testing costs were not included in the model as these tests are now part of routine NHS care and are not expected to differ between PARPi treatments.

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

3.7 Severity

In line with NICE's health technology evaluation manual of process and methods, absolute and proportional QALY shortfall was calculated for the two populations of interest to assess the severity of the condition.¹¹⁷

Average ages of the female populations used to calculate shortfall are shown in Table 60, and are aligned with patient characteristics data used in the model and described in Table 36. The cohort characteristics for the two subpopulations in the PRIMA trial were assumed to be representative of the population of interest in the UK.

Table 60 Summary features of QALY shortfall analysis

Parameter	BRCAm	BRCAwt	Source
Mean starting age, years	██████	██████	PRIMA, data on file

For the calculation of QALYs for patients without the condition over the remaining life expectancy, UK life tables and UK age and sex adjusted utilities based on Hernandez Alava et al.¹³⁰ have been used, using the shortfall calculator developed by Schneider et al. 2021.¹³¹

Table 61. Summary of QALY shortfall analysis

Population	Comparator	Expected total QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	Absolute / Proportional shortfall	QALY weight
BRCAm	Olaparib	13.7983	6.4375	7.361 / 53.35%	1.0
BRCAwt	Rucaparib	11.7163	3.7264	7.990 / 68.19%	1.0

3.8 Uncertainty

There are no specific uncertainties beyond those inherent to any evaluation in this indication. To assess the level of uncertainty associated with the model, a DSA was Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

conducted to evaluate individual parameter uncertainty, and a PSA was conducted to evaluate overall parameter uncertainty. Additionally, various scenario analyses were performed to assess different methodological assumptions and uncertainties. See Section 3.11 for more detail.

3.9 Summary of base-case analysis inputs and assumptions

3.9.1 Summary of base-case analysis inputs

An overview of the key economic model variables applied in the base-case analysis are presented in Table 169 (Appendix L: Base case inputs and assumptions), alongside the justification for the setting and corresponding reference in the submission document.

3.10 Base-case results

The total and incremental costs, QALYs, and LYG, along with the incremental cost per QALY and incremental Net Monetary Benefit (NMB) for the base case with PAS discount, are presented below in Table 62 for BRCAm and Table 63 for BRCAwt population. In the BRCAm population, niraparib compared to olaparib resulted in cost savings of [REDACTED] with the PAS price for niraparib. The health outcomes were largely equivalent with only a very marginal difference in QALYs of [REDACTED] due to nominal differences in AE incidence estimates applied. The resulting incremental NMB indicated niraparib to be highly cost-effective, amounting to [REDACTED] at a willingness-to-pay threshold (WTP) of £30,000 per QALY when including the niraparib PAS price discount.

For the BRCAwt population, niraparib compared with rucaparib resulted in cost savings of [REDACTED] when including the niraparib PAS price discount, with marginally lower incremental QALYs of [REDACTED] making niraparib dominant over rucaparib. The resulting incremental NMB was £[REDACTED] at a WTP of £30,000 per QALY, when including the niraparib PAS price discount.

Estimates of clinical outcomes included in the cost-effectiveness analysis and tabulated disaggregated base-case incremental cost-effectiveness analysis results are presented in Appendix H.

Table 62. Base-case results with niraparib PAS discount - BRCAm

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)	Incremental NMB at £20,000	Incremental NMB at £30,000
Niraparib		8.21		xx xxxxxx	0.00		Less costly, less effective	x xxxxxx	x xxxxxx
Olaparib	£ 127,738	8.21	6.27						

Abbreviations: ICER = incremental cost-effectiveness ratio; LYG = life years gained; QALYs = quality-adjusted life years; NMB = net monetary benefit

Table 63. Base-case results with niraparib PAS discount - BRCAwt

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)	Incremental NMB at £20,000	Incremental NMB at £30,000
Niraparib		4.75			0.00		Less costly, more effective		
Rucaparib	£ 117,381	4.75	3.50						

Abbreviations: ICER = incremental cost-effectiveness ratio; LYG = life years gained; QALYs = quality-adjusted life years; NMB = net monetary benefit

3.11 Exploring uncertainty

This section will provide a comprehensive assessment of uncertainty, examining the relative impact of various types of uncertainty on cost-effectiveness estimates. It will evaluate whether any potential uncertainties around modelling assumptions included in the analyses have been adequately captured and will identify any uncertainties that are unlikely to be mitigated by additional evidence or expert input.

3.11.1 Probabilistic sensitivity analysis

PSA was conducted to assess the parameter uncertainty and mean PSA result was used as the base case. All key parameters were assigned probability distributions and point estimates were drawn using Monte Carlo simulation techniques. The PSA was run for 5,000 iterations as this was found to be sufficient to produce stable results. Results from the PSA for both the BRCAm (vs. olaparib) and BRCAwt (vs. rucaparib) population base-case analyses are presented in Table 64 and Table 65, using the PAS price for niraparib. The results demonstrate good consistency with the deterministic analysis and show that niraparib remains a cost-effective treatment strategy versus olaparib and rucaparib, resulting in cost savings.

The cost-effectiveness plane for niraparib versus olaparib and versus rucaparib is presented in [REDACTED] and [REDACTED], respectively. At a willingness to pay threshold of £30,000, niraparib has a 100% probability of being cost-effective compared with olaparib and rucaparib. The cost-effectiveness acceptability curves of niraparib versus olaparib and versus rucaparib are not presented, since niraparib is cost-effective with 100% probability up to very large willingness to pay thresholds.

Table 64. Probabilistic base-case results with niraparib PAS discount – BRCAm

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)	Incremental NMB at £20,000	Incremental NMB at £30,000
Niraparib		8.42			0.00		Less costly, less effective		
Olaparib	£128,298	8.42	6.41						

Abbreviations: ICER = incremental cost-effectiveness ratio; LYG = life years gained; QALYs = quality-adjusted life years; NMB = net monetary benefit

Table 65. Probabilistic base-case results with niraparib PAS discount – BRCAwt

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)	Incremental NMB at £20,000	Incremental NMB at £30,000
Niraparib		4.78			0.00		Less costly, more effective		
Rucaparib	£ 117,424	4.78	3.52						

Abbreviations: ICER = incremental cost-effectiveness ratio; LYG = life years gained; QALYs = quality-adjusted life years; NMB = net monetary benefit

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

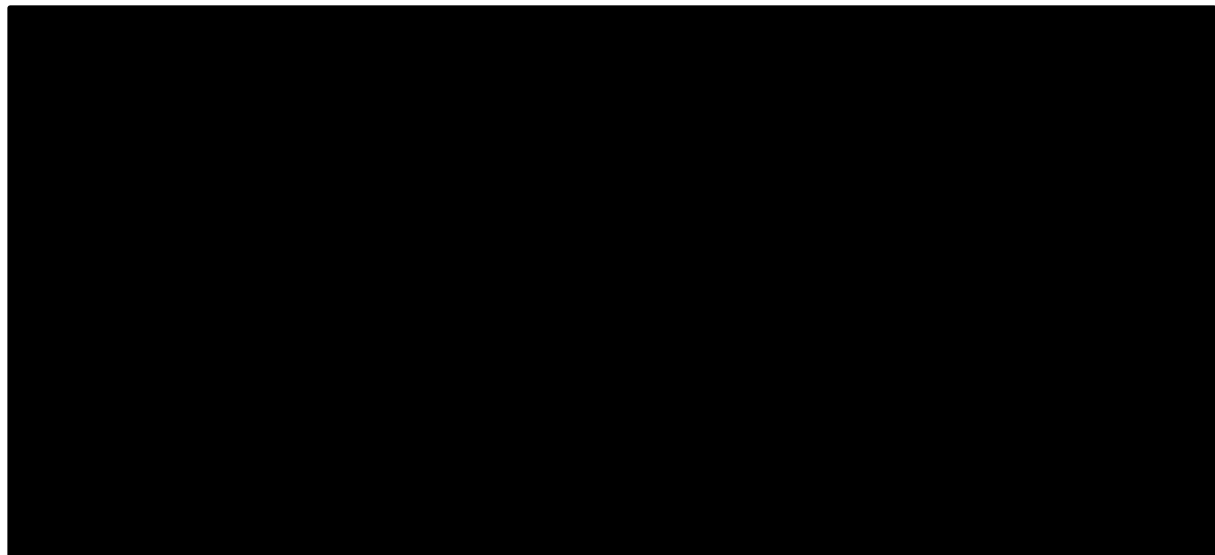
3.11.2 Deterministic sensitivity analysis

A one-way deterministic sensitivity analysis (DSA) was conducted to identify key model drivers. Each parameter was varied individually between its upper and lower 95% confidence intervals. These intervals were determined using standard errors Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

when available, or estimated based on a $\pm 10\%$ variation around the mean when measures of variance were not available. The details of the parameters varied are outlined in Table 169.

The results of the DSA for the 10 most influential parameters on incremental net monetary benefit are presented in [REDACTED] for the BRCAm population (niraparib vs. olaparib) and in [REDACTED] for the BRCAwt population (niraparib vs. rucaparib). The DSA outcomes indicate that the most influential parameters against olaparib included parameters determining PFS and TTDD for niraparib, the likelihood of AE discontinuations and treatment exposure for AE-related discontinuation for olaparib and niraparib RDI. Similarly, against rucaparib, the most influential parameters were the parameters determining the PFS parametric fit and TTDD for niraparib and the likelihood of AE discontinuations and treatment exposure for AE-related discontinuation for rucaparib.

[REDACTED]



Note: PFS parametric fit P1 and P2 are the first and second coefficients of the parametric survival model. TTDD KM random sample is the random number used to vary, with the SE, the TTDD Kaplan-Meier curve.

[REDACTED]

[REDACTED]

Note: PFS parametric fit P1 and P2 are the first and second coefficients of the parametric survival model. TTDD KM random sample is the random number used to vary, with the SE, the TTDD Kaplan-Meier curve.

3.11.3 Scenario analysis

Scenario analyses conducted showed that the base case analysis versus olaparib (BRCAm) and rucaparib (BRCAwt) is robust to variations in input parameters as outlined in Table 66 and Table 67. In all scenarios, niraparib remained less costly compared to olaparib (BRCAm) and rucaparib (BRCAwt), with all resulting INMBs being positive. Detail breakdown of the total cost and total QALY by comparator is summarised in H1.3.

Table 66. Results of scenario analyses – niraparib versus olaparib (BRCAm)

Scenario	Base case value/assumptions	Scenario analysis value/assumptions	Incremental Cost	Incremental QALY	Incremental NMB at £30,000
Base case	-	-			
Time horizon	years	20 years			
Discount Rate	3.5%	1.5%			
Median Age	Mean age PRIMA: years	Median age from SACT data: 65 years			
Alternative cure point	10 years	8 years to test application of earlier cure point based on UK advisory board feedback and aligned with approximate end of available follow-up from PRIMA			
	10 years	12 years to test application of later cure point based on UK KOL feedback			
PFS distribution	Gen. gamma	Lognormal			

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Scenario	Base case value/assumptions	Scenario analysis value/assumptions	Incremental Cost	Incremental QALY	Incremental NMB at £30,000
	Gen. gamma	1-knot normal spline	████████	████████	████████
PFS HR	HR=1 (equivalence)	HR=████ based on Bucher ITC HR of PRIMA vs SOLO-1	████████	████████	████████
OS distributions	1-knot normal spline	Lognormal	████████	████████	████████
	1-knot normal spline	Gen. gamma	████████	████████	████████
G Excess mortality vs general population	HR = 1.26	HR =1	████████	████████	████████
TTDD	PRIMA TTDD - 90% of patients discontinuing at 36 months	SACT TTDD - 90% of patients discontinuing at 36 months	████████	████████	████████
	PRIMA TTDD data - 90% of patients discontinuing at 36 months	SACT TTDD until 42 months and 38 months for NIRA and OLA, respectively, then assume all patients discontinue	████████	████████	████████
	90% of patients discontinuing after stopping rule	100% of patients discontinue treatment according to product label-based stopping rules	████████	████████	████████
Comparator TTDD	PFS combined with AE-related discontinuation from SOLO-1	Simple exponential models fitted through the median time on treatment estimates	████████	████████	████████
Niraparib dosing	Individualised starting dose based on SACT data	Applies detailed 100/200/300mg dose per cycle based on PRIMA	████████	████████	████████

Scenario	Base case value/assumptions	Scenario analysis value/assumptions	Incremental Cost	Incremental QALY	Incremental NMB at £30,000
	Individualised starting dose based on SACT data	Applies population specific mean dose calculated across the PRIMA data	████████	████████	████████
	Individualised starting dose based on SACT data	Applies the proportion of patients starting at 200 vs. 300mg based on PRIMA data	████████	████████	████████
	Individualised starting dose based on SACT data	Applies the proportion of patients starting at 200 vs. 300mg based on MONITOR-UK data	████████	████████	████████
Olaparib dosing	RDI not included	RDI = 96% as in NICE TA 1055	████████	████████	████████
Follow-up and monitoring	7-year stopping rule	Excludes stopping rule for follow-up and monitoring costs applied to patients who remain progression free for at least 7 years	████████	████████	████████
AEs	Grade 3+ incidence AEs from NIRA RWE (MONITOR-UK)	Use Grade 3+ incidence AEs from PRIMA	████████	████████	████████
Health state utility	████ for progression-free and █████ for progressed based on PRIMA	0.81 for progression-free and 0.76 for progressed based on NICE TA962	████████	████████	████████
AE disutility	Include AE disutility	Exclude AE disutility	████████	████████	████████

Abbreviations: AE = adverse event; KOL = key opinion leader; NICE = National Institute for Health and Care Excellence; NIRA = niraparib; OS = overall survival; PFS = progression-free survival; QALY = quality-adjusted life year; SACT = Systemic Anti-Cancer Therapy; TTDD = time to discontinuation or death.

Table 67. Results of scenario analyses – niraparib versus rucaparib (BRCAwt)

Scenario	Base case value	Scenario analysis value	Incremental Cost	Incremental QALY	Incremental NMB at £30,000
Base case	-	-			
Time horizon	years	20 years			
Discount Rate	3.5%	1.5%			
Median Age	Mean age PRIMA: years	Median age from SACT data: 70 years			
Alternative cure point	10 years	8 years to test application of earlier cure point based on UK advisory board feedback and aligned with approximate end of available follow-up from PRIMA			
	10 years	12 years to test application of later cure point based on UK KOL feedback			
PFS distribution	Gen. gamma	2-knot normal spline			
OS distributions	1-knot normal spline	Lognormal			
	1-knot normal spline	Gen. gamma			
TTDD	PRIMA TTDD - 90% of patients discontinuing at 36 months	SACT TTDD - 90% of patients discontinuing at 36 months			
	PRIMA TTDD - 90% of patients discontinuing at 36 months	SACT TTDD until 42 months, then assume all patients discontinue			

Scenario	Base case value	Scenario analysis value	Incremental Cost	Incremental QALY	Incremental NMB at £30,000
	90% of patients discontinuing after stopping rule	100% of patients discontinue treatment according to product label-based stopping rules			
Comparator TTDD	PFS combined with AE-related discontinuation from ATHENA-MONO	Simple exponential models fitted through the median time on treatment estimates			
Niraparib dosing	Individualised starting dose based on SACT data	Applies detailed 100/200/300mg dose per cycle based on PRIMA			
	Individualised starting dose based on SACT data	Applies population specific mean dose calculated across the PRIMA data			
	Individualised starting dose based on SACT data	Applies the proportion of patients starting at 200 vs. 300mg based on PRIMA data			
	Individualised starting dose based on SACT data	Applies the proportion of patients starting at 200 vs. 300mg based on MONITOR-UK data			
Rucaparib dosing	RDI not included	RDI = 88% as in NICE TA 1055			
Follow-up and monitoring	7-year stopping rule	Excludes stopping rule for follow-up and monitoring costs applied to patients who			

Scenario	Base case value	Scenario analysis value	Incremental Cost	Incremental QALY	Incremental NMB at £30,000
		remain progression free for at least 7 years			
AEs	Grade 3+ incidence AEs from NIRA RWE (MONITOR-UK)	Use Grade 3+ incidence AEs from PRIMA			
Health state utility	for progression-free and for progressed based PRIMA	0.81 for progression-free and 0.76 for progressed based on NICE TA962			
AE disutility	Include AE disutility	Exclude AE disutility			

Abbreviations: AE = adverse event; KOL = key opinion leader; NICE = National Institute for Health and Care Excellence; NIRA = niraparib; OS = overall survival; PFS = progression-free survival; QALY = quality-adjusted life year; SACT = Systemic Anti-Cancer Therapy; TTDD = time to discontinuation or death.

3.12 Subgroup analysis

No other subgroup analyses were conducted for the submission.

3.13 Benefits not captured in the QALY calculation

Having more than a single treatment available to help delay disease progression in 1L OC maintenance is essential for optimizing patient care and maximising population health. Such benefits are poorly captured within conventional cost-utility analysis. Every individual responds differently to medications due to factors such as genetics, age, lifestyle, comorbidities, and disease progression. Offering a variety of treatments enables healthcare providers to tailor therapies to meet the unique needs of each patient, enhancing efficacy, minimizing adverse effects and improving health outcomes overall. Furthermore, the availability of diverse treatments fosters innovation, encourages competition, and drives continual improvement in therapeutic approaches, ultimately improving health outcomes and ensuring that more patients can access effective care suited to their circumstances.

3.14 Validation

Technical validation process leveraged external published validation guidelines¹³² to ensure the model was implemented accurately.

The validation process was conducted in three main steps. At the end of draft model implementation, the project team conducted the following standardised checks to identify implementation issues and ensure that the model is ready for technical verification by an experienced team member that was not involved in the project. Unexpected model behaviours after each step was examined to ensure that it stems from the model design and not from implementation error, with any inconsistencies or identified issues recorded and corrected.

- Step 1A - Functionality testing (FT). A procedure for testing a model during which all key buttons (e.g. buttons to run a simulation, buttons to run sensitivity analyses) and toggles (e.g. dropdowns) are clicked or switched and the impact on the model interface, outcomes, or both is evaluated.

- Step 1B - Extreme value testing (EVT). A procedure for testing a model during which all key model inputs (e.g. efficacy, safety, costs, utility) are varied to low and high extreme values (determined on a case by case basis by parameter type) with the impact evaluated on the direct outcomes (e.g. high/low values for drug unit cost evaluated on total drug cost predicted by the model)
- Step 1C – Scenario/Logic check testing. A procedure for testing a model during which a pre-defined list of scenarios/logic checks is set up in the model and the scenario/logic checks results compared with the expected outcomes (i.e. model outcomes of each scenario/logic check should align with a priori expectations).

Technical verification (Step 2) was then performed by an internal peer reviewer not involved with the original programming. This technical validation reviewed the interface, parameters, calculations, engine, results sheet, DSA, PSA, and any other ancillary code (e.g. VBA). Unexpected model behaviour, implementation, and typing errors identified by this review was updated in the model and resolved.

In addition, a team member independent to the project team reviewed the extracted model inputs (Step 3A), to verify the accuracy of data input extraction by comparison of values to original data sources (including transformations of parameters to derive model inputs are correctly calculated - e.g. rate to probability conversions). Furthermore, internal predictive validation (Step 3B) was conducted (e.g. comparison of survival analyses predictions calculated in the economic model vs. statistical report outputs and observed data from the original study), with any identified discrepancies addressed.

Once technical validation was completed, discussion with UK clinical and health economic experts was also conducted to help validate key model assumptions (e.g. cure plausibility, parametric survival model approach) and conduct predictive validation of long-term survival extrapolations for niraparib. An advisory board was conducted with three UK clinical experts and two UK health economic modelling experts. A one-to-one interview with an additional clinical expert not included in the advisory board was undertaken, along with three further one-to-one interviews with Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

each of the UK clinical experts included in the advisory board. A one-to-one interview with an additional UK health economics expert (not involved in the advisory board) was also conducted.

3.15 Interpretation and conclusions of economic evidence

A *de novo* cost-utility model was developed to evaluate the cost-effectiveness of niraparib compared to relevant comparators as maintenance treatment in women with newly diagnosed advanced OC. This evaluation considered two patient populations of interest according to their BRCA status: patients with a BRCA mutation and patients without a BRCA mutation, BRCAwt. This bespoke evaluation by (sub-)population reflects both differences in treatment options and differences in prognosis.

In the BRCAm population, and compared to olaparib, the cost-effectiveness deterministic base-case results indicated that niraparib may be cost saving (██████████ with the PAS price for niraparib) and equivalent, with a minor non-clinically relevant QALY difference (incremental QALY of ██████████). The estimated incremental net monetary benefit at a £30,000 per QALY gained cost-effectiveness threshold is ██████████, with similar estimate when using a £20,000 per QALY gained threshold value. In patients with BRCAwt, niraparib is considered cost-effective compared to rucaparib with cost savings amounting to £██████████ with niraparib PAS price, and marginal difference in incremental QALYs (of ██████████). Thus, niraparib is less costly than rucaparib, at almost equivalent QALYs. However, these estimates do not take into account any confidential net price discounts.

Probabilistic base-case results are closely aligned with the deterministic base-case results outlined. Considering that different decision rules are applicable to both populations as simulations fall on different quadrants of the cost-effectiveness plane, the probability of niraparib being cost-effective in both populations is 100% across a range of cost-effectiveness thresholds (from £0 to £350,000).

For both the BRCAm and BRCAwt populations, the results of one-way deterministic sensitivity analyses indicated that results are robust to changes in key economic model parameters.

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Given the results obtained, niraparib can be considered a cost-effective treatment option regardless of a patient's BRCA status in the 1L maintenance setting, where patients still have limited treatment options, i.e. olaparib for mutated and rucaparib for non-mutated.

The main strengths of the economic analysis performed are:

- Niraparib's efficacy data is primarily sourced from the PRIMA trial, a high-quality multicentre phase III randomised trial of patients with advanced stage III-IV ovarian cancer. PRIMA included UK patients with aOC, enhancing its representativeness of 1L aOC UK patients. The maturity of the PRIMA trial survival data is considered high at 76.5% for PFS and 62.5% for OS.
- The economic model has been populated by randomised trial data but also informed by relevant published literature and leveraged UK real world evidence.
- Survival outcomes predictions and key modelling assumptions have been thoroughly validated by UK clinical expert opinion, reflecting the most up to date UK clinical practice.
- Health state utility values, independent of treatment, were derived from the PRIMA trial, which is the most relevant evidence to inform the health-related quality of life of these populations.
- All health care resource consumption and costs used in the economic model have been sourced from UK published sources, with inflation to 2024 prices where needed. Health care resource use estimates were validated by UK clinical experts.

The main limitations of the economic analysis performed are:

- No direct head-to-head evidence is available to inform the comparative effectiveness between niraparib and the relevant PARPi comparators. In addition, available data does not allow for robust, adjusted, indirect comparisons. However, PARPi equivalence is supported by results of

exploratory ITC analysis (Section 2.7), RWE and UK clinical expert opinion. Scenario analysis explored alternatives to the base case assumptions.

- Economic model requirements implied that clinical benefits beyond the duration of the PRIMA trial were estimated through the fitting of standard and flexible parametric distributions to patient level survival data to estimate long-term PFS, OS, and TTDD. Although PRIMA trial survival data is considered mature, survival modelling assumptions inherently imply some level of uncertainty. The methods for survival extrapolation followed the NICE DSU guidelines and the survival extrapolations were validated by UK clinical experts. Alternative parametric survival distributions (pessimistic and optimistic) were evaluated in scenario analysis, although, given the equivalence of PFS and OS between niraparib and comparator treatments, these are unlikely to be a driver of economic model results.
- Given evidence from relevant published literature, previous appraisals and UK clinical expert opinion, in the economic model it was assumed that if patients remained progression-free for 10 years, long-term remission is considered. Thus, although uncertain, in the base case analysis a PFS cure landmark was considered at 10 years. Early and later cure points were evaluated in scenario analysis but with no significant impact on base case results.
- TTDD data for niraparib from PRIMA was complemented by UK clinical expert opinion and RWE to inform assumptions regarding the proportion of patients who remained on niraparib treatment post-36 months. In the absence of TTDD KM data for the comparator therapies from their pivotal trials, these were estimated based on PFS and AE-related discontinuation in the base case. Uncertainty in TTDD was explored through scenario analysis and did not substantially affect interpretation of the base case cost-effectiveness results for either population.

Results indicate that niraparib is a cost-effective option compared to olaparib and rucaparib in the BRCAm and BRCAwt populations, respectively.

4 References

1. González-Martín A, Harter P, Leary A, et al. Newly diagnosed and relapsed epithelial ovarian cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol* 2023;34(10):833-848. (In eng). DOI: 10.1016/j.annonc.2023.07.011.
2. Cancer Research UK. What is ovarian cancer? 25 November 2024 (<https://www.cancerresearchuk.org/about-cancer/ovarian-cancer/what-is-ovarian-cancer>).
3. Pitiyarachchi O, Friedlander M, Java JJ, et al. What proportion of patients with stage 3 ovarian cancer are potentially cured following intraperitoneal chemotherapy? Analysis of the long term (≥ 10 years) survivors in NRG/GOG randomized clinical trials of intraperitoneal and intravenous chemotherapy in stage III ovarian cancer. *Gynecol Oncol* 2022;166(3):410-416. (In eng). DOI: 10.1016/j.ygyno.2022.07.004.
4. Berek JS, Renz M, Kehoe S, Kumar L, Friedlander M. Cancer of the ovary, fallopian tube, and peritoneum: 2021 update. *Int J Gynaecol Obstet* 2021;155 Suppl 1(Suppl 1):61-85. (In eng). DOI: 10.1002/ijgo.13878.
5. National Institute for Health and Care Excellence. Ovarian cancer: recognition and initial management. Clinical guideline [CPG122].
6. National Institute for Health and Care Excellence. Maximal cytoreductive surgery for advanced ovarian cancer. Interventional procedures guidance [IPG757].
7. National Cancer Institute. Ovarian Epithelial, Fallopian Tube, and Primary Peritoneal Cancer Treatment (PDQ®)—Health Professional Version. 12 February 2025.
8. Lord R, Rauniyar J, Morris T, et al. Real world outcomes in platinum sensitive relapsed ovarian, fallopian tube, or peritoneal cancer treated in routine clinical practice in the United Kingdom prior to poly-ADP ribose polymerase inhibitors. *Int J Gynecol Cancer* 2020;30(7):1026-1033. (In eng). DOI: 10.1136/ijgc-2019-000973.
9. Lambert HE, Gregory WM, Nelstrop AE, Rustin GJ. Long-term survival in 463 women treated with platinum analogs for advanced epithelial carcinoma of the ovary: life expectancy compared to women of an age-matched normal population. *Int J Gynecol Cancer* 2004;14(5):772-8. (In eng). DOI: 10.1111/j.1048-891X.2004.014507.x.
10. GlaxoSmithKline. Meeting report. GSK UK PRIMA CDF Exit Health Technology Assessment Advisory Board. 22 May 2025 2025.
11. González-Martín A, Desauw C, Heitz F, et al. Maintenance olaparib plus bevacizumab in patients with newly diagnosed advanced high-grade ovarian cancer: Main analysis of second progression-free survival in the phase III PAOLA-1/ENGOT-ov25 trial. *Eur J Cancer* 2022;174:221-231. (In eng). DOI: 10.1016/j.ejca.2022.07.022.
12. González-Martín A, Pothuri B, Vergote I, et al. Niraparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. *N Engl J Med* 2019;381(25):2391-2402. (In eng). DOI: 10.1056/NEJMoa1910962.
13. Li N, Zhu J, Yin R, et al. Treatment With Niraparib Maintenance Therapy in Patients With Newly Diagnosed Advanced Ovarian Cancer: A Phase 3 Randomized Clinical Trial. *JAMA Oncol* 2023;9(9):1230-1237. (In eng). DOI: 10.1001/jamaoncol.2023.2283.
14. Monk BJ, Parkinson C, Lim MC, et al. A Randomized, Phase III Trial to Evaluate Rucaparib Monotherapy as Maintenance Treatment in Patients With Newly Diagnosed Ovarian Cancer (ATHENA-MONO/GOG-3020/ENGOT-ov45). *J Clin Oncol* 2022;40(34):3952-3964. (In eng). DOI: 10.1200/jco.22.01003.

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

15. Moore K, Colombo N, Scambia G, et al. Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. *N Engl J Med* 2018;379(26):2495-2505. (In eng). DOI: 10.1056/NEJMoa1810858.
16. Monk BJ, Barretina-Ginesta MP, Pothuri B, et al. Niraparib first-line maintenance therapy in patients with newly diagnosed advanced ovarian cancer: final overall survival results from the PRIMA/ENGOT-OV26/GOG-3012 trial. *Ann Oncol* 2024;35(11):981-992. (In eng). DOI: 10.1016/j.annonc.2024.08.2241.
17. DiSilvestro P, Banerjee S, Colombo N, et al. Overall Survival With Maintenance Olaparib at a 7-Year Follow-Up in Patients With Newly Diagnosed Advanced Ovarian Cancer and a BRCA Mutation: The SOLO1/GOG 3004 Trial. *J Clin Oncol* 2023;41(3):609-617. (In eng). DOI: 10.1200/jco.22.01549.
18. 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]. Committee Papers. 2024.
19. National Disease Registration Service. Niraparib for maintenance treatment of advanced ovarian, fallopian tube, and peritoneal cancer - data review. 2025.
20. GlaxoSmithKline. Systematic Literature Review for Niraparib as First-Line Maintenance Treatment for Patients with Advanced or Metastatic Ovarian Cancer - non-interventional study report. 2025.
21. Hettle R, Sackeyfio A, Gill J, Siddiqui K, Nussey F, Friedlander M. Comparative Efficacy And Safety Of Olaparib 300 Mg Tablets Bid And Niraparib 300 Mg Tablets QD As Maintenance Treatment After Response To Chemotherapy In Patients With Platinum-Sensitive Relapsed Germline BRCA-Mutated Ovarian Cancer (PSROC). *Value in Health* 2017;20(9):A412. DOI: 10.1016/j.jval.2017.08.088.
22. Staropoli N, Ciliberto D, Del Giudice T, et al. The Era of PARP inhibitors in ovarian cancer: "Class Action" or not? A systematic review and meta-analysis. *Crit Rev Oncol Hematol* 2018;131:83-89. (In eng). DOI: 10.1016/j.critrevonc.2018.08.011.
23. Wang H, Wu M, Liu H, et al. Comparison of the Efficacy and Safety of PARP Inhibitors as a Monotherapy for Platinum-Sensitive Recurrent Ovarian Cancer: A Network Meta-Analysis. *Front Oncol* 2021;11:785102. (In eng). DOI: 10.3389/fonc.2021.785102.
24. GlaxoSmithKline UK Limited. Zejula 100 mg film-coated tablets. Summary of Product Characteristics (SPC). 4 June 2024 2024.
25. Hasson S, P., Bowen R, Ang J, E., et al. MONITOR-UK: An initial analysis of a multicentre, observational study of maintenance niraparib in ovarian cancer. *ESMO Open* 2024;9(S5).
26. National Institute for Health and Care Excellence. Niraparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy. Technology appraisal guidance [TA673]. 17 February 2021 2021.
27. National Institute for Health and Care Excellence. Olaparib for maintenance treatment of BRCA mutation-positive advanced ovarian, fallopian tube or peritoneal cancer after response to first-line platinum-based chemotherapy. Technology appraisal guidance [TA946]. 28 March 2024 2024.
28. National Institute for Health and Care Excellence. Rucaparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

lineplatinum-based chemotherapy. Technology appraisal guidance [TA1055]. 9 April 2025 2025.

29. European Commission. Commission implementing decision of 16.11.2017 granting marketing authorisation under Regulation (EC) No 726/2004 of the European Parliament and of the Council for "Zejula - niraparib", an orphan medicinal product for human use. 16 November 2017 2017.

30. European Commission. Commission implementing decision of 27.10.2020 amending granted by Decision C(2017)7804(final) for

"Zejula - niraparib", an orphan medicinal product for human use. 27 October 2020 2020.

31. National Institute for Health and Care Excellence. Niraparib [Specialist drug]. Medical forms. (<https://bnf.nice.org.uk/drugs/niraparib-specialist-drug/medical-forms>).

32. Frey MK, Pothuri B. Homologous recombination deficiency (HRD) testing in ovarian cancer clinical practice: a review of the literature. Gynecol Oncol Res Pract 2017;4:4. (In eng). DOI: 10.1186/s40661-017-0039-8.

33. Cancer Genome Atlas Research Network. Integrated genomic analyses of ovarian carcinoma. Nature 2011;474(7353):609-15. (In eng). DOI: 10.1038/nature10166.

34. Pennington KP, Walsh T, Harrell MI, et al. Germline and somatic mutations in homologous recombination genes predict platinum response and survival in ovarian, fallopian tube, and peritoneal carcinomas. Clin Cancer Res 2014;20(3):764-75. (In eng). DOI: 10.1158/1078-0432.Ccr-13-2287.

35. Cancer Research UK. Stages and grades of ovarian cancer. 5 December 2024 (<https://www.cancerresearchuk.org/about-cancer/ovarian-cancer/stages-grades>).

36. Cortez AJ, Tudrej P, Kujawa KA, Lisowska KM. Advances in ovarian cancer therapy. Cancer Chemother Pharmacol 2018;81(1):17-38. (In eng). DOI: 10.1007/s00280-017-3501-8.

37. Cancer Research UK. Symptoms of ovarian cancer. 25 November 2024 (<https://www.cancerresearchuk.org/about-cancer/ovarian-cancer/symptoms>).

38. Zakkak N, Barclay ME, Swann R, et al. The presenting symptom signatures of incident cancer: evidence from the English 2018 National Cancer Diagnosis Audit. Br J Cancer 2024;130(2):297-307. (In eng). DOI: 10.1038/s41416-023-02507-4.

39. Dilley J, Burnell M, Gentry-Maharaj A, et al. Ovarian cancer symptoms, routes to diagnosis and survival - Population cohort study in the 'no screen' arm of the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS). Gynecol Oncol 2020;158(2):316-322. (In eng). DOI: 10.1016/j.ygyno.2020.05.002.

40. National Disease Registration Service. Cancer incidence and mortality. (https://nhsd-ndrs.shinyapps.io/incidence_and_mortality/).

41. Cabasag CJ, Arnold M, Rutherford M, et al. Shifting incidence and survival of epithelial ovarian cancer (1995-2014): A SurvMark-2 study. Int J Cancer 2023;152(9):1763-1777. (In eng). DOI: 10.1002/ijc.34403.

42. Cancer Research UK. Ovarian cancer statistics. (<https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/ovarian-cancer#heading-Zero>).

43. Cancer Research UK. Early Cancer Diagnosis Data Hub. (<https://crukcancerintelligence.shinyapps.io/EarlyDiagnosis/>).

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

44. International Agency for Research on Cancer. Global Cancer Observatory: Cancer Today. (<https://gco.iarc.fr/today/en>).
45. Xu-Vuillard A, Guerin-Charbonnel C, Bocquet F, et al. Efficacy of chemotherapy after progression during or following PARPi exposure in ovarian cancer. *ESMO Open* 2024;9(9):103694. (In eng). DOI: 10.1016/j.esmoop.2024.103694.
46. Chase D, Perhanidis J, Gupta D, Kalilani L, Golembesky A, González-Martín A. Association of Multiple High-Risk Factors on Observed Outcomes in Real-World Patients With Advanced Ovarian Cancer Treated With First-Line Therapy. *JCO Clin Cancer Inform* 2023;7:e2200189. (In eng). DOI: 10.1200/cci.22.00189.
47. Cabasag CJ, Butler J, Arnold M, et al. Exploring variations in ovarian cancer survival by age and stage (ICBP SurvMark-2): A population-based study. *Gynecol Oncol* 2020;157(1):234-244. (In eng). DOI: 10.1016/j.ygyno.2019.12.047.
48. Gaitskell K, Hermon C, Barnes I, et al. Ovarian cancer survival by stage, histotype, and pre-diagnostic lifestyle factors, in the prospective UK Million Women Study. *Cancer Epidemiol* 2022;76:102074. (In eng). DOI: 10.1016/j.canep.2021.102074.
49. Sims TT, Sood AK, Westin SN, et al. Correlation of HRD status with clinical and survival outcomes in patients with advanced-stage ovarian cancer. *Journal of Clinical Oncology* 2021;39(15_suppl):5568-5568. DOI: 10.1200/JCO.2021.39.15_suppl.5568.
50. Huang YW. Association of BRCA1/2 mutations with ovarian cancer prognosis: An updated meta-analysis. *Medicine (Baltimore)* 2018;97(2):e9380. (In eng). DOI: 10.1097/md.00000000000009380.
51. Allen I, Hassan H, Walburga Y, et al. Second Primary Cancer Risks After Breast Cancer in BRCA1 and BRCA2 Pathogenic Variant Carriers. *J Clin Oncol* 2025;43(6):651-661. (In eng). DOI: 10.1200/jco.24.01146.
52. Moss E, Taylor A, Andreou A, et al. British Gynaecological Cancer Society (BGCS) ovarian, tubal and primary peritoneal cancer guidelines: Recommendations for practice update 2024. *Eur J Obstet Gynecol Reprod Biol* 2024;300:69-123. (In eng). DOI: 10.1016/j.ejogrb.2024.06.025.
53. Irodi A, Rye T, Herbert K, et al. Patterns of clinicopathological features and outcome in epithelial ovarian cancer patients: 35 years of prospectively collected data. *Bjog* 2020;127(11):1409-1420. (In eng). DOI: 10.1111/1471-0528.16264.
54. Tookman L, Green C, Leonard K, et al. Diagnosis, treatment and burden in advanced ovarian cancer: a UK real-world survey of healthcare professionals and patients. *Future Oncol* 2024;20(23):1657-1673. (In eng). DOI: 10.1080/14796694.2024.2358742.
55. Cesario SK, Nelson LS, Broxson A, Cesario AL. Sword of Damocles cutting through the life stages of women with ovarian cancer. *Oncol Nurs Forum* 2010;37(5):609-17. (In eng). DOI: 10.1188/10.Onf.609-617.
56. Matulonis UA, Kornblith A, Lee H, et al. Long-term adjustment of early-stage ovarian cancer survivors. *Int J Gynecol Cancer* 2008;18(6):1183-93. (In eng). DOI: 10.1111/j.1525-1438.2007.01167.x.
57. Mirabeau-Beale KL, Kornblith AB, Penson RT, et al. Comparison of the quality of life of early and advanced stage ovarian cancer survivors. *Gynecol Oncol* 2009;114(2):353-9. (In eng). DOI: 10.1016/j.ygyno.2009.05.009.
58. Chase DM, Wenzel L. Health-related quality of life in ovarian cancer patients and its impact on clinical management. *Expert Rev Pharmacoecon Outcomes Res* 2011;11(4):421-31. (In eng). DOI: 10.1586/erp.11.41.

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

59. Reb AM. Transforming the death sentence: elements of hope in women with advanced ovarian cancer. *Oncol Nurs Forum* 2007;34(6):E70-81. (In eng). DOI: 10.1188/07.Onf.E70-e81.
60. Colombo N, Lorusso D, Scollo P. Impact of Recurrence of Ovarian Cancer on Quality of Life and Outlook for the Future. *Int J Gynecol Cancer* 2017;27(6):1134-1140. (In eng). DOI: 10.1097/igc.0000000000001023.
61. Simmons D, Blank SV, ElNaggar AC, Chastek B, Bunner SH, McLaurin K. Health Care Resource Utilization and Costs Associated with Disease Progression in Ovarian Cancer. *Adv Ther* 2022;39(6):2544-2561. (In eng). DOI: 10.1007/s12325-022-02086-5.
62. Gilbert L, Ramanakumar AV, Festa MC, et al. Real-world direct healthcare costs of treating recurrent high-grade serous ovarian cancer with cytotoxic chemotherapy. *J Comp Eff Res* 2020;9(8):537-551. (In eng). DOI: 10.2217/ce-2020-0032.
63. Martinez Castro P, Vargas L, Mancheño A, et al. Malignant Bowel Obstruction in Relapsed Ovarian Cancer With Peritoneal Carcinomatosis: An Occlusive State. *Int J Gynecol Cancer* 2017;27(7):1367-1372. (In eng). DOI: 10.1097/igc.0000000000001049.
64. Ray-Coquard I, Pautier P, Pignata S, et al. Olaparib plus Bevacizumab as First-Line Maintenance in Ovarian Cancer. *N Engl J Med* 2019;381(25):2416-2428. (In eng). DOI: 10.1056/NEJMoa1911361.
65. National Institute for Health and Care Excellence. Bevacizumab in combination with paclitaxel and carboplatin for first-line treatment of advanced ovarian cancer [TA284].
66. NHS England. National Cancer Drugs Fund List. 2025.
67. Perren TJ, Swart AM, Pfisterer J, et al. A Phase 3 Trial of Bevacizumab in Ovarian Cancer. *New England Journal of Medicine* 2011;365(26):2484-2496. DOI: doi:10.1056/NEJMoa1103799.
68. Richardson DL, Quintanilha JCF, Danziger N, et al. Effectiveness of PARP Inhibitor Maintenance Therapy in Ovarian Cancer by BRCA1/2 and a Scar-Based HRD Signature in Real-World Practice. *Clin Cancer Res* 2024;30(20):4644-4653. (In eng). DOI: 10.1158/1078-0432.Ccr-24-1225.
69. Roche Products Limited. Avastin 25 mg/ml concentrate for solution for infusion. Summary of Product Characteristics (SPC). 4 July 2023 2023.
70. National Institute for Health and Care Excellence. Olaparib with bevacizumab for maintenance treatment of advanced high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer. Technology appraisal guidance [TA946]. 17 January 2024 2024. (<https://www.nice.org.uk/guidance/ta946>).
71. GlaxoSmithKline UK Limited. Zejula 100 mg hard capsules. Summary of Product Characteristics (SPC). 10 January 2024 2024.
72. Staropoli N, Ciliberto D, Luciano F, et al. The impact of PARP inhibitors in the whole scenario of ovarian cancer management: A systematic review and network meta-analysis. *Crit Rev Oncol Hematol* 2024;193:104229. (In eng). DOI: 10.1016/j.critrevonc.2023.104229.
73. Ray-Coquard I, Leary A, Pignata S, et al. Olaparib plus bevacizumab first-line maintenance in ovarian cancer: final overall survival results from the PAOLA-1/ENGOT-ov25 trial. *Ann Oncol* 2023;34(8):681-692. (In eng). DOI: 10.1016/j.annonc.2023.05.005.
74. Mirza MR, González-Martín A, Graybill WS, et al. Prospective evaluation of the tolerability and efficacy of niraparib dosing based on baseline body weight and platelet

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

count: Results from the PRIMA/ENGOT-OV26/GOG-3012 trial. Cancer 2023;129(12):1846-1855. (In eng). DOI: 10.1002/cncr.34706.

75. de la Motte Rouge T, Selle F, Kfoury M, et al. First real-life data on niraparib maintenance in newly-diagnosed advanced ovarian cancer: A descriptive analysis of the temporary authorisation for use (ATU) cohort. Int J Gynecol Cancer 2022;32:2:A1-A504.

76. Tesaro I, . A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study of Niraparib Maintenance Treatment in Patients with HRD-Positive Advanced Ovarian Cancer Following Response on Front-Line Platinum-Based Chemotherapy. 12 February 2018 2018.

77. Tesaro I, . Statistical Analysis Plan. A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study of Niraparib Maintenance Treatment in Patients with Advanced Ovarian Cancer Following Response on Front-Line Platinum-Based Chemotherapy. Protocol PR-30-5017-C 19 June 2019 2019.

78. Zai Lab. A Statistical Analysis Plan for A Phase 3, Randomized, DoubleBlind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of ZL-2306 (Niraparib) as Maintenance Therapy in Patients with Advanced Ovarian, Fallopian Tube, or Primary Peritoneal Cancer (collectively referred to as ovarian cancer) Following Response to First-Line Platinum-Based Chemotherapy. 26 October 2021 2021.

79. Zai Lab. Clinical Study Protocol. A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of ZL-2306 (Niraparib) as Maintenance Therapy in Patients with Advanced Ovarian, Fallopian Tube, or Primary Peritoneal Cancer

(collectively referred to as ovarian cancer) Following Response on First-Line Platinum-Based Chemotherapy. 9 April 2021.

80. Berek JS, Matulonis UA, Peen U, et al. Safety and dose modification for patients receiving niraparib. Ann Oncol 2018;29(8):1784-1792. (In eng). DOI: 10.1093/annonc/mdy181.

81. National Institute for Health and Care Excellence. Single Technology Appraisal. Niraparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to firstline platinum-based chemotherapy [ID1680]. Committee Papers. May 2020 2020.

82. González-Martín A, Pothuri B, Vergote I, et al. Progression-free survival and safety at 3.5years of follow-up: results from the randomised phase 3 PRIMA/ENGOT-OV26/GOG-3012 trial of niraparib maintenance treatment in patients with newly diagnosed ovarian cancer. Eur J Cancer 2023;189:112908. (In eng). DOI: 10.1016/j.ejca.2023.04.024.

83. GlaxoSmithKline. Niraparib PR-30-5017-c A phase 3, randomized, double-blind, placebo-controlled, multicenter study of niraparib maintenance treatment in patients with advanced ovarian cancer following response on front-line platinum-based chemotherapy – clinical study report. 2019.

84. GlaxoSmithKline. Final Overall Survival Analysis Clinical Study Report. A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study of Niraparib Maintenance Treatment in Patients with Advanced Ovarian Cancer Following Response on Front-Line Platinum-Based Chemotherapy. 2024.

85. Lorusso D, Monk B, Barretina-Ginesta M, et al. Updated patient-reported outcomes in the PRIMA/ENGOT-OV26/GOG-3012 trial of niraparib first-line maintenance therapy in

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

patients with newly diagnosed advanced ovarian cancer. 26th European Congress on Gynecological Oncology. Rome, Italy 2025.

86. Pothuri B, Han S, Chase DM, et al. Health-related quality of life in patients with newly diagnosed advanced ovarian cancer treated with niraparib vs placebo: Results from the phase 3 randomized PRIMA/ENGOT-OV26/GOG-3012 trial. *Gynecol Oncol* 2024;184:168-177. (In eng). DOI: 10.1016/j.ygyno.2024.01.021.
87. GlaxoSmithKline. Subsequent treatments in PRIMA trial [Data on File]. 2025.
88. GlaxoSmithKline. BRCAwt stats [Data on File]. 2025.
89. Oaknin A, Moore K, Colombo N, et al. 995PD - Time to second progression (PFS2) and second subsequent therapy (TSST) for patients (pts) with newly diagnosed, advanced ovarian cancer (OC) and a BRCA mutation (BRCAm) treated with maintenance (mt) olaparib (ola): Phase III SOLO1 trial. *Annals of Oncology* 2019;30:v405. DOI: <https://doi.org/10.1093/annonc/mdz250.003>.
90. Appiah K, Dusen Rv, Sarri G, et al. Systematic Literature Review for Niraparib as First-Line Maintenance Treatment for Patients with Advanced or Metastatic Ovarian Cancer. September 2024 2024.
91. Salani R, Calderón Boyle TA, Lim J, et al. Real-world outcomes of first-line maintenance niraparib monotherapy in patients with epithelial ovarian cancer. *Future Oncol* 2025;21(2):213-219. (In eng). DOI: 10.1080/14796694.2024.2441654.
92. Chase DM, Shukla S, Moore J, et al. Patient Characteristics Associated with Time to Next Treatment in Patients with Ovarian Cancer Treated with Niraparib: The PRED1CT Real-World Study. *Oncol Ther* 2024;12(3):599-607. (In eng). DOI: 10.1007/s40487-024-00294-3.
93. Chase DM, Hanna M, Lim JT, et al. Niraparib as First-Line Maintenance Therapy in Patients with Stage III Ovarian Cancer and No Visible Residual Disease: AR1ZE Real-World Study. *Oncol Ther* 2025;13(1):253-262. (In eng). DOI: 10.1007/s40487-024-00318-y.
94. Zheng Z, Zuo J, Wang K, et al. RENI-1 efficacy and safety of niraparib as first-line maintenance therapy in newly diagnosed ovarian cancer: A prospective, multicenter real-world study, updated in 24-month follow-up. *Annals of Oncology* 2024;35(S4).
95. Chen J, Zhang M, Li K, et al. PARP inhibitor maintenance treatment for newly diagnosed ovarian cancer patients: a real-world study from China. *Front Oncol* 2024;14:1336616. (In eng). DOI: 10.3389/fonc.2024.1336616.
96. Kim JH, Kim SI, Park EY, et al. Comparison of survival outcomes between olaparib and niraparib maintenance therapy in BRCA-mutated, newly diagnosed advanced ovarian cancer. *Gynecol Oncol* 2024;181:33-39. (In eng). DOI: 10.1016/j.ygyno.2023.11.037.
97. Bruno M, Apostol AI, Boccia SM, et al. Effects of niraparib dose reduction on short-term outcomes in ovarian cancer patients. *Int J Gynecol Cancer* 2024;34(10):1588-1595. (In eng). DOI: 10.1136/ijgc-2024-005363.
98. Apostol AI, Sassu CM, Lardino S, et al. The effects of niraparib dose reduction on long-term outcomes in ovarian cancer patients: a large retrospective, observational study. Abstract No. 709. *Int J Gynecol Cancer* 2023.
99. National Institute for Health and Care Excellence. NICE DSU Technical Support Document 14: Survival Analysis for Economic Evaluations Alongside Clinical Trials - Extrapolation with Patient-Level Data. March 2013 2013.

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

100. Rutherford M, et al. NICE DSU Technical Support Document 21: Flexible Methods for Survival Analysis. . University of Sheffield, 2020.
101. University of Sheffield. NICE DSU Technical Support Document 1: Introduction to Evidence Synthesis for Decision Making. 2022
(https://www.sheffield.ac.uk/sites/default/files/2022-02/TSD1-Introduction.final_08.05.12.pdf).
102. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *Syst Rev* 2021;10(1):89. (In eng). DOI: 10.1186/s13643-021-01626-4.
103. Higgins JPT, Thomas J, Chandler J, et al. *Cochrane Handbook for Systematic Reviews of Interventions* version 6.5. 2024.
104. NICE. NICE health technology evaluations: the manual. 13 May 2025.
105. Canadian Agency for Drugs and Technologies in Health. Indirect Evidence: Indirect Treatment Comparisons in Meta-Analysis. 2009.
106. National Institute for Health and Care Excellence. Olaparib for maintenance treatment of BRCA mutation-positive advanced ovarian, fallopian tube or peritoneal cancer after response to first-line platinum-based chemotherapy. Technology appraisal guidance [TA598]. 28 August 2019 2019. (<https://www.nice.org.uk/guidance/TA598>).
107. National Institute for Health and Care Excellence. Olaparib plus bevacizumab for maintenance treatment of advanced ovarian, fallopian tube or primary peritoneal cancer. Technology appraisal guidance [TA693]. 28 April 2021 2021. (<https://www.nice.org.uk/guidance/ta693>).
108. Cedillo S, Garí C, Aceituno S, et al. Cost-effectiveness of olaparib plus bevacizumab versus bevacizumab monotherapy in the maintenance of patients with homologous recombination deficiency-positive advanced ovarian cancer after response to first-line platinum-based chemotherapy. *Int J Gynecol Cancer* 2024;34(2):277-284. (In eng). DOI: 10.1136/ijgc-2023-004786.
109. Elsea D, Fan L, Mihai A, et al. Cost-Effectiveness Analysis of Olaparib in Combination with Bevacizumab Compared with Bevacizumab Monotherapy for the First-Line Maintenance Treatment of Homologous Recombination Deficiency-Positive Advanced Ovarian Cancer. *Pharmacoecon Open* 2022;6(6):811-822. (In eng). DOI: 10.1007/s41669-022-00338-2.
110. Fan L, Muston D, Elsea D, et al. Olaparib in combination with bevacizumab compared to bevacizumab monotherapy for the first-line maintenance treatment of advanced ovarian cancer: a cost-effectiveness analysis. *Gynecologic Oncology* 2021;162:S216-S217. DOI: [https://doi.org/10.1016/S0090-8258\(21\)01063-5](https://doi.org/10.1016/S0090-8258(21)01063-5).
111. Moya-Alarcón C, González-Domínguez A, Ivanova-Markova Y, et al. Olaparib as first line in BRCA-mutated advanced ovarian carcinoma: Is it cost-effective in Spain? *Gynecol Oncol* 2022;164(2):406-414. (In eng). DOI: 10.1016/j.ygyno.2021.11.011.
112. Perez-Fidalgo JA, Lleti ACC, Manso L, et al. Cost-effectiveness of Olaparib plus Bevacizumab versus Bevacizumab in the maintenance of patients with HRD+ advanced ovarian cancer after response to first-line platinum-based chemotherapy in Spain. *Journal of Clinical Oncology* 2022;40(16_suppl):e17591-e17591. DOI: 10.1200/JCO.2022.40.16_suppl.e17591.
113. Tan DS, Chan JJ, Hettle R, Ghosh W, Viswambaram A, Yu CC. Cost-effectiveness of olaparib versus routine surveillance in the maintenance setting for patients with BRCA-

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

mutated advanced ovarian cancer after response to first-line platinum-based chemotherapy in Singapore. *J Gynecol Oncol* 2021;32(2):e27. (In eng). DOI: 10.3802/jgo.2021.32.e27.

114. Yong CM, Yehgambaram PAP, Lee SWH. Cost-effectiveness analysis of olaparib maintenance therapy for BRCA mutation ovarian cancer in the public sector in Malaysia. *PLoS One* 2024;19(2):e0298130. (In eng). DOI: 10.1371/journal.pone.0298130.

115. Wolford JE, Bai J, Minion LE, et al. Cost-effectiveness of maintenance therapy in advanced ovarian cancer: Paclitaxel, bevacizumab, niraparib, rucaparib, olaparib, and pembrolizumab. *Journal of Clinical Oncology* 2018;36(15_suppl):5508-5508. DOI: 10.1200/JCO.2018.36.15_suppl.5508.

116. National Institute for Health and Care Excellence. British National Formulary (BNF). (<https://bnf.nice.org.uk/>).

117. NICE. NICE health technology evaluations: the manual [PMG36]. 31 October 2023.

118. Szamreta EA, Monberg MJ, Desai KD, Li Y, Othus M. Prognosis and conditional survival among women with newly diagnosed ovarian cancer. *Gynecol Oncol* 2024;180:170-177. (In eng). DOI: 10.1016/j.ygyno.2023.11.018.

119. Palmer S, Borget I, Friede T, et al. A Guide to Selecting Flexible Survival Models to Inform Economic Evaluations of Cancer Immunotherapies. *Value Health* 2023;26(2):185-192. (In eng). DOI: 10.1016/j.jval.2022.07.009.

120. Royston P, Parmar MK. Flexible parametric proportional-hazards and proportional-odds models for censored survival data, with application to prognostic modelling and estimation of treatment effects. *Stat Med* 2002;21(15):2175-97. (In eng). DOI: 10.1002/sim.1203.

121. Bellier C, Gladieff L, Le Du F, et al. Olaparib First-Line Maintenance Monotherapy in BRCA-Mutated Epithelial Ovarian Cancer: Descriptive Analysis of the First French Real-World Data Study. *Drugs Real World Outcomes* 2023;10(2):207-213. (In eng). DOI: 10.1007/s40801-022-00349-9.

122. Shukla S, de Courcy J, Ellis H, et al. PCR211 VOCAL (Views of Ovarian Cancer Patients and Their Caregivers-How Maintenance Therapy Affects Their Lives) Study: Cancer-Related Burden and Quality of Life of Caregivers. *Value in Health* 2022;25(12):S430-S431. DOI: 10.1016/j.jval.2022.09.2144.

123. AstraZeneca UK Limited. Lynparza 100 mg film-coated tablets. Summary of Product Characteristics (SPC). 9 December 2024 2024.

124. GOV.UK. Drugs and pharmaceutical electronic market information tool (eMIT). (<https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit>).

125. NHS England. National schedule of NHS costs - Year 2023/24. 2024.

126. Liu J, Hawkes C, Walder L, et al. Budget impact analysis of niraparib for first-line maintenance therapy in advanced ovarian cancer from a US payer perspective. *J Manag Care Spec Pharm* 2021;27(10):1377-1387. (In eng). DOI: 10.18553/jmcp.2021.27.10.1377.

127. Pujade-Lauraine E, Selle F, Scambia G, et al. Maintenance olaparib rechallenge in patients with platinum-sensitive relapsed ovarian cancer previously treated with a PARP inhibitor (OREO/ENGOT-ov38): a phase IIb trial. *Ann Oncol* 2023;34(12):1152-1164. (In eng). DOI: 10.1016/j.annonc.2023.09.3110.

128. Guest JF, Ruiz FJ, Greener MJ, Trotman IF. Palliative care treatment patterns and associated costs of healthcare resource use for specific advanced cancer patients in the UK.

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Eur J Cancer Care (Engl) 2006;15(1):65-73. (In eng). DOI: 10.1111/j.1365-2354.2005.00623.x.

129. Gao W, Ho YK, Verne J, Glickman M, Higginson IJ. Changing patterns in place of cancer death in England: a population-based study. PLoS Med 2013;10(3):e1001410. (In eng). DOI: 10.1371/journal.pmed.1001410.

130. Hernández Alava M, Pudney S, Wailoo A. Estimating EQ-5D by age and sex for the UK. (<https://www.sheffield.ac.uk/sites/default/files/2022-02/DSU%20Age%20based%20utility%20-%20Final%20for%20website.pdf>).

131. Schneider P, McNamara S, Love-Koh J, Doran T, Gutacker N. QALY Shortfall Calculator. (<https://shiny.york.ac.uk/shortfall>).

132. Büyükkaramikli NC, Rutten-van Mölken M, Severens JL, Al M. TECH-VER: A Verification Checklist to Reduce Errors in Models and Improve Their Credibility. Pharmacoeconomics 2019;37(11):1391-1408. (In eng). DOI: 10.1007/s40273-019-00844-y.

133. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. Bmj 2019;366:l4898. (In eng). DOI: 10.1136/bmj.l4898.

134. Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. Bmj 2016;355:i4919. (In eng). DOI: 10.1136/bmj.i4919.

135. GlaxoSmithKline. Systematic Literature Review for Niraparib as First-Line Maintenance Treatment for Patients with Advanced or Metastatic Ovarian Cancer - non-interventional study listing. 2025.

136. Hettle R, McCrea C, Lee CK, Davidson R. Population-adjusted indirect treatment comparison of maintenance PARP inhibitor with or without bevacizumab versus bevacizumab alone in women with newly diagnosed advanced ovarian cancer. Ther Adv Med Oncol 2021;13:17588359211049639. (In eng). DOI: 10.1177/17588359211049639.

137. Hardesty MM, Krivak TC, Wright GS, et al. OVARIO phase II trial of combination niraparib plus bevacizumab maintenance therapy in advanced ovarian cancer following first-line platinum-based chemotherapy with bevacizumab. Gynecol Oncol 2022;166(2):219-229. (In eng). DOI: 10.1016/j.ygyno.2022.05.020.

138. Oda K, Shintani D, Mori M, et al. 777P A phase II study of the efficacy of olaparib maintenance monotherapy for patients with HRD-positive, newly diagnosed, advanced, high-grade ovarian cancer, evaluated by whole-exome sequencing (MSBM-OL). Annals of Oncology 2024;35:S585. DOI: 10.1016/j.annonc.2024.08.838.

139. Wu X, Liu J, Wang J, et al. Senaparib as first-line maintenance therapy in advanced ovarian cancer: a randomized phase 3 trial. Nat Med 2024;30(6):1612-1621. (In eng). DOI: 10.1038/s41591-024-03003-9.

140. Hashimoto K, Kawakami K, Yokokawa T, et al. Serum Creatinine Elevation as a Risk Factor for Niraparib-induced Hematologic Toxicity. Anticancer Res 2023;43(10):4533-4541. (In eng). DOI: 10.21873/anticancer.16647.

141. Zhao M, Qiu S, Wu X, et al. Efficacy and Safety of Niraparib as First-Line Maintenance Treatment for Patients with Advanced Ovarian Cancer: Real-World Data from a Multicenter Study in China. Target Oncol 2023;18(6):869-883. (In eng). DOI: 10.1007/s11523-023-00999-x.

142. Shin W, Noh JJ, Baek SH, Kim BG, Lim MC, Park SY. Real-world Experience of Niraparib in Newly-diagnosed Epithelial Ovarian Cancer. Anticancer Res 2021;41(9):4603-4607. (In eng). DOI: 10.21873/anticancer.15273.

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

143. Zheng H, Gao Y, Guo H, et al. Real-world Experience of Olaparib Treatment in Patients with Ovarian Cancer: A Chinese Multicenter Study. *Mol Cancer Ther* 2021;20(9):1735-1742. (In eng). DOI: 10.1158/1535-7163.Mct-20-1064.
144. Nakamura K, Matsuoka H, Yorimitsu M, et al. Efficacy and safety of olaparib, olaparib plus bevacizumab and niraparib maintenance treatment in Japanese patients with platinum-sensitive advanced ovarian cancer. *Jpn J Clin Oncol* 2024;54(1):31-37. (In eng). DOI: 10.1093/jjco/hyad125.
145. Li J, Chen Y, He M, et al. First evidence of olaparib maintenance therapy in patients with newly diagnosed homologous recombination deficient positive/BRCA wild-type ovarian cancer: real-world multicenter study. *Front Med* 2024;18(6):1026-1034. (In eng). DOI: 10.1007/s11684-024-1083-5.
146. Thaker PH, Areli Calderón Boyle T, Burns S, et al. Characteristics and real-world outcomes of patients with epithelial ovarian cancer who received niraparib plus bevacizumab first-line maintenance therapy in the COMB1NE study. *Int J Gynecol Cancer* 2024;34(12):1924-1931. (In eng). DOI: 10.1136/ijgc-2024-005611.
147. Ha HI, Yoon HJ, Song C, et al. Clinical Outcomes of Poly(ADP-Ribose) Polymerase Inhibitors as Maintenance Therapy in Patients with Ovarian Cancer in the Southeastern Region of Korea. *Curr Oncol* 2024;31(11):6711-6722. (In eng). DOI: 10.3390/curroncol31110495.
148. Rimel B, Boyle TAC, Burns S, et al. Real-World First-Line Maintenance Niraparib Monotherapy Use Following Chemotherapy Plus Bevacizumab: The SW1TCH Study. *Oncol Ther* 2024;12(3):465-475. (In eng). DOI: 10.1007/s40487-024-00281-8.
149. Lee YJ, Shin YK, Kim NR, et al. Chemotherapy response score no longer predicts survival outcomes in high-grade serous ovarian cancer patients with BRCA mutation and/or maintenance therapy. *J Gynecol Oncol* 2024;35(6):e73. (In eng). DOI: 10.3802/jgo.2024.35.e73.
150. Jeong YW, Kim DE, Kim JH, et al. Time-Trend Analysis and Risk Factors for Niraparib-Induced Nausea and Vomiting in Ovarian Cancer: A Prospective Study. *Cancer Res Treat* 2024 (In eng). DOI: 10.4143/crt.2024.899.
151. Adjei NN, Haas A, Zhao H, et al. Real-world trends in the use of maintenance therapy in ovarian cancer across the United States from 2017 to 2021. *Gynecol Oncol* 2024;190:255-261. (In eng). DOI: 10.1016/j.ygyno.2024.08.026.
152. Han GH, Kim HR, Yun H, Kim JH, Cho H. Comparison of Adverse Events Between PARP Inhibitors in Patients with Epithelial Ovarian Cancer: A Nationwide Propensity Score Matched Cohort Study. *Target Oncol* 2024;19(2):251-262. (In eng). DOI: 10.1007/s11523-024-01037-0.
153. GlaxoSmithKline. Systematic Literature Review of Non-Clinical Outcomes Associated with First-Line Maintenance Treatment of Patients with Advanced or Metastatic Ovarian Cancer. 06 June 2025.
154. Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. *Bmj* 1996;313(7052):275-83. (In eng). DOI: 10.1136/bmj.313.7052.275.
155. Cohn DE, Barnett JC, Wenzel L, et al. A cost-utility analysis of Gynecologic Oncology Group protocol 218: The importance of incorporating prospectively collected quality-of-life scores in health outcomes research. *Gynecologic Oncology* 2014;133:4. DOI: 10.1016/j.ygyno.2014.03.025.

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

156. Tan DS, Chan JJ, Loke JK, et al. 231P - Cost-effectiveness of olaparib vs routine surveillance in the maintenance setting for patients with BRCA-mutated advanced ovarian cancer after response to first-line platinum-based chemotherapy in Singapore. *Annals of Oncology* 2019;30:ix79-ix80. DOI: <https://doi.org/10.1093/annonc/mdz426.007>.
157. Wolford JE, Liang SY, Tewari KS, et al. An economic analysis: Examining the cost-effectiveness of bevacizumab and olaparib as upfront maintenance treatment of advanced ovarian cancer. *Gynecologic Oncology* 2019;154:25. DOI: 10.1016/j.ygyno.2019.04.060.
158. Penn CA, Wong MS, Walsh CS. Cost-effectiveness of Maintenance Therapy Based on Molecular Classification Following Treatment of Primary Epithelial Ovarian Cancer in the United States. *JAMA Netw Open* 2020;3(12):e2028620. (In eng). DOI: 10.1001/jamanetworkopen.2020.28620.
159. Huepenbecker S, Deshmukh A, Sun C, et al. Cost-utility analysis of management strategies after frontline treatment of women with epithelial ovarian cancer (339). *Gynecologic Oncology* 2022;166:S174-S175. DOI: [https://doi.org/10.1016/S0090-8258\(22\)01561-X](https://doi.org/10.1016/S0090-8258(22)01561-X).
160. Okumura L, Massaoka MH, Areas I, Licursi C, Mihai A, Ryan J. EE50 Olaparib As Maintenance Therapy for Women with Ovarian Cancer and Homologous Recombination Deficiency in Brazil: What Clinical and Cost Data Have Highest Impact on Cost-Effectiveness Analysis? *Value in Health* 2022;25(7):S345. DOI: 10.1016/j.jval.2022.04.304.
161. Lim S, Moss H, Havrilesky L, et al. A novel, out-of-pocket, cost-effectiveness analysis comparing a frontline niraparib-for-all to a biomarker-based strategy in patients with advanced ovarian cancer. *Gynecologic Oncology* 2021;162:S77. DOI: [https://doi.org/10.1016/S0090-8258\(21\)00786-1](https://doi.org/10.1016/S0090-8258(21)00786-1).
162. Molina Hernández JP, Solorzano J, Murtiera S, Perichon S, Cercone J, Leon A. PCN96 OLAPARIB COST-EFFECTIVENESS AS A MAINTENANCE TREATMENT OPTION FOR NEWLY DIAGNOSED BRCA-MUTATED OVARIAN CANCER WHO ARE IN RESPONSE AFTER FIRST-LINE PLATINUM-BASED CHEMOTHERAPY IN COSTA RICA. *Value in Health* 2020;23:S40. DOI: 10.1016/j.jval.2020.04.1595.
163. Castillo-Fernandez O, Murtiera S, Solorzano J, et al. PCN85 COST-EFFECTIVENESS OF OLAPARIB AS A MAINTENANCE TREATMENT OPTION FOR NEWLY DIAGNOSED BRCA-MUTATED OVARIAN CANCER WHO ARE IN RESPONSE AFTER FIRST-LINE PLATINUM-BASED CHEMOTHERAPY IN PANAMA. *Value in Health* 2020;23:S38. DOI: 10.1016/j.jval.2020.04.1586.
164. Muston D, Hettle R, Monberg M, et al. Cost-effectiveness of olaparib as a maintenance treatment for women with newly diagnosed advanced ovarian cancer and BRCA1/2 mutations in the United States. *Gynecol Oncol* 2020;159(2):491-497. (In eng). DOI: 10.1016/j.ygyno.2020.08.013.
165. Barrington DA, Tubbs C, Smith HJ, Straughn JM, Jr., Senter L, Cohn DE. Niraparib maintenance in frontline management of ovarian cancer: a cost effectiveness analysis. *Int J Gynecol Cancer* 2020;30(10):1569-1575. (In eng). DOI: 10.1136/ijgc-2020-001550.
166. Gonzalez R, Havrilesky LJ, Myers ER, et al. Cost-effectiveness analysis comparing "PARP inhibitors-for-all" to the biomarker-directed use of PARP inhibitor maintenance therapy for newly diagnosed advanced stage ovarian cancer. *Gynecol Oncol* 2020;159(2):483-490. (In eng). DOI: 10.1016/j.ygyno.2020.08.003.
167. Gonzalez R, Havrilesky LJ, Secord AA, Myers ER, Dottino JA, Moss HA. Just OK is not OK: How well does PARP inhibitor frontline maintenance therapy need to work in biomarker negative ovarian cancer for universal treatment to represent a value-based

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

therapeutic option? *Gynecologic Oncology* 2020;159:21-22. DOI: 10.1016/j.ygyno.2020.06.043.

168. Armeni P, Borsoi L, Fornaro G, Jommi C, Colombo N, Costa F. Cost-Effectiveness and Net Monetary Benefit of Olaparib Maintenance Therapy Versus No Maintenance Therapy After First-line Platinum-based Chemotherapy in Newly Diagnosed Advanced BRCA1/2-mutated Ovarian Cancer in the Italian National Health Service. *Clin Ther* 2020;42(7):1192-1209.e12. (In eng). DOI: 10.1016/j.clinthera.2020.04.015.

169. Muston D, Hettle R, McLaurin K, Fan L, Monberg MJ. PCN72 Biomarker Testing to Guide Cost Effective Use of PARPi in Patients with Newly Diagnosed Ovarian Cancer. *Value in Health* 2020;23:S434. DOI: 10.1016/j.jval.2020.08.209.

170. Richardson MT, Kapp DS, Chan JE, et al. Upfront maintenance with anti-vascular versus PARP inhibitors in advanced ovarian cancer: A cost-effective analysis. *Gynecologic Oncology* 2020;159:21. DOI: 10.1016/j.ygyno.2020.06.042.

171. Zhu Y, Liu K, Cao H, Zhu H. The cost-effectiveness analysis of maintenance olaparib plus Bevacizumab in patients with advanced ovarian cancer: based on the final survival results from PAOLA-1 trial. *J Ovarian Res* 2023;16(1):168. (In eng). DOI: 10.1186/s13048-023-01257-4.

172. Zhu Y, Yang Q, Liu K, Cao H, Zhu H. Olaparib plus bevacizumab as a first-line maintenance treatment for patients with advanced ovarian cancer by molecular status: an updated PAOLA-1 based cost-effectiveness analysis. *J Gynecol Oncol* 2024;35(1):e2. (In eng). DOI: 10.3802/jgo.2024.35.e2.

173. Giuliani J, Mantoan B, Ferrario L, Candela MV, Aprile G. Cost-effectiveness of poly-(ADP-ribose) polymerase (PARP)-inhibitors for the maintenance treatment after responding to first- and second-line chemotherapy in advanced ovarian cancer. *J Oncol Pharm Pract* 2023;29(2):457-464. (In eng). DOI: 10.1177/10781552221137705.

174. Perrier L, Zarca K, Cadet T, et al. EE63 Cost-Effectiveness of Olaparib Plus Bevacizumab First-Line Maintenance in Ovarian Cancer Alongside the PAOLA-1 Trial. *Value in Health* 2023;26(12):S61-S62. DOI: 10.1016/j.jval.2023.09.335.

175. Canada's Drug Agency - L'Agence des Medicaments du Canada. Lynparza for Newly Diagnosed Ovarian Cancer – Final Economic Guidance Report. 05 December 2019 2019. (<https://www.cda-amc.ca/lynparza-newly-diagnosed-ovarian-cancer-details>).

176. Scottish Medicines Consortium. Olaparib 100mg and 150mg film-coated tablets (Lynparza®) [SMC2368]. 05 November 2021 2021. (<https://scottishmedicines.org.uk/medicines-advice/olaparib-lynparza-full-smc2368/>).

177. Scottish Medicines Consortium. Niraparib 100mg hard capsules (Zejula®) [SMC2338]. 09 April 2021 2021. (<https://scottishmedicines.org.uk/medicines-advice/niraparib-zejula-full-smc2338/>).

178. Scottish Medicines Consortium. Olaparib 100mg and 150mg film-coated tablets (Lynparza®) [SMC2209]. 08 November 2019 2019. (<https://scottishmedicines.org.uk/medicines-advice/olaparib-lynparza-full-smc2209/>).

179. National Centre for Pharmacoeconomics Ireland. Olaparib (Lynparza®) in combination with bevacizumab (1L maintenance HRD positive ovarian cancer). HTA ID: 21011. 27 January 2023 2023. (<https://www.ncpe.ie/olaparib-lynparza-in-combination-with-bevacizumab-1l-maintenance-hrd-positive-ovarian-cancer-hta-id-21011/>).

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

180. National Centre for Pharmacoeconomics Ireland. Niraparib (Zejula®) for 1L maintenance OVCA. HTA ID: 21004. 26 September 2022 2022. (<https://www.ncpe.ie/niraparib-zejula-1l-maintenance-ovca-hta-id-21004/>).
181. National Centre for Pharmacoeconomics Ireland. Olaparib (Lynparza®) (1L maintenance of BRCA-mutated advanced OVCA). 30 March 2020 2020. (<https://www.ncpe.ie/olaparib-lynparza-1l-maintenance-of-brca-mutated-advanced-ovca/>).
182. Pharmaceutical Benefits Advisory Committee. Olaparib: Tablet 100 mg, Tablet 150 mg; Lynparza® - Public Summary Document (PSD) July 2022 PBAC Meeting. July 2022 2022. (<https://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2022-07/Olaparib-Lynparza-PSD-july-2022>).
183. Pharmaceutical Benefits Advisory Committee. Olaparib: Tablet 100 mg, Tablet 150 mg; Lynparza® - Public Summary Document (PSD) November 2022 July 2023 PBAC Meetings. November 2022 2022. (<https://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2022-11/olaparib-lynparza-PSD-November-2022>).
184. Pharmaceutical Benefits Advisory Committee. Olaparib: Tablet 100 mg, Tablet 150 mg ; Lynparza® - Public Summary Document (PSD) November 2019 PBAC Meeting. November 2019 2019. (<https://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2019-11/olaparib-tablet-100-mg-tablet-150-mg-lynparza>).
185. Pharmaceutical Benefits Advisory Committee. Olaparib: Tablet 100 mg, Tablet 150 mg; Lynparza® - Public Summary Document (PSD) July 2020 PBAC Meeting. July 2020 2020. (<https://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2020-07/olaparib-tablet-100-mg-tablet-150-mg-lynparza>).
186. Pharmaceutical Benefits Advisory Committee. Niraparib: Capsule 100 mg; Zejula® - Public Summary Document (PSD) July 2021 PBAC Meeting. July 2021 2021. (<https://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2021-07/niraparib-capsule-100-mg-zejula>).
187. Pharmaceutical Benefits Advisory Committee. Niraparib: Capsule 100 mg; Zejula® - Public Summary Document (PSD) March 2022 PBAC Meeting. March 2022 2022. (<https://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2022-03/niraparib-capsule-100-mg-zejula>).
188. Canada's Drug Agency - L'Agence des Medicaments du Canada. Niraparib (Zejula) for first line Ovarian Cancer - Final Economic Guidance Report. 29 April 2021 2021. (<https://www.cda-amc.ca/niraparib-zejula-first-line-ovarian-cancer-details>).
189. Wu X, Liu J, Wang X, et al. LBA36 Efficacy and safety of senaparib as maintenance treatment in patients with newly diagnosed advanced ovarian cancer (FLAMES study): A randomized, double-blind, placebo-controlled, phase III trial. *Annals of Oncology* 2023;34:S1277-S1278. DOI: 10.1016/j.annonc.2023.10.030.
190. Lorusso D, Mouret-Reynier MA, Harter P, et al. Updated progression-free survival and final overall survival with maintenance olaparib plus bevacizumab according to clinical risk in patients with newly diagnosed advanced ovarian cancer in the phase III PAOLA-1/ENGOT-ov25 trial. *Int J Gynecol Cancer* 2024;34(4):550-558. (In eng). DOI: 10.1136/ijgc-2023-004995.
191. Chase DM, Marín MR, Backes F, et al. Impact of disease progression on health-related quality of life of advanced ovarian cancer patients - Pooled analysis from the PRIMA trial. *Gynecol Oncol* 2022;166(3):494-502. (In eng). DOI: 10.1016/j.ygyno.2022.06.028.

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

192. Friedlander M, Moore KN, Colombo N, et al. Patient-centred outcomes and effect of disease progression on health status in patients with newly diagnosed advanced ovarian cancer and a BRCA mutation receiving maintenance olaparib or placebo (SOLO1): a randomised, phase 3 trial. *Lancet Oncol* 2021;22(5):632-642. (In eng). DOI: 10.1016/s1470-2045(21)00098-x.
193. Gong H. 236P - Front-line maintenance therapy for platinum-sensitive ovarian cancer: What's next PARP inhibitors? *Annals of Oncology* 2019;30:ix81. DOI: <https://doi.org/10.1093/annonc/mdz426.012>.
194. Chase DM, Shukla S, de Courcy J, et al. VOCAL (Views of Ovarian Cancer patients-how maintenance therapy Affects their Lives) study: A lens into the financial and quality of life (QoL) impact of disease burden and ethnic disparities reported directly by the patient. *Journal of Clinical Oncology* 2022;40(28_suppl):274-274. DOI: 10.1200/JCO.2022.40.28_suppl.274.
195. Rose PG, Yao M, Chambers LM, Mei L, Le P. The Overtreatment and Cost Effectiveness of Primary versus Secondary Maintenance Therapy with Poly-Adenosine Ribose Phosphate Inhibitors (PARPi) for Epithelial Ovarian Cancer (EOC). *Gynecol Obstet (Sunnyvale)* 2021;11(9) (In eng).
196. Simmons D, Bhalla J, Stone R, Engstrom-Melnik J, McLaurin K. Clinical outcomes and cost associated with HRD biomarker guided first line maintenance therapy in advanced ovarian cancer. *Gynecologic Oncology* 2021;162:S111-S112. DOI: [https://doi.org/10.1016/S0090-8258\(21\)00854-4](https://doi.org/10.1016/S0090-8258(21)00854-4).
197. Hettle R, McLaurin K, Mihai A, et al. PCN107 COST COMPARISON OF ADVERSE EVENT MANAGEMENT WITH POLY (ADP-RIBOSE) POLYMERASE (PARP) INHIBITORS (PARPI) IN THE MAINTENANCE TREATMENT OF ADVANCED OVARIAN CANCER. *Value in Health* 2020;23:S42. DOI: 10.1016/j.jval.2020.04.1601.
198. Fan L, Zhang Y, Maguire P, et al. Cost comparison of adverse event management among breast and ovarian cancer patients treated with poly (ADP-ribose) polymerase inhibitors: analysis based on phase 3 clinical trials. *J Mark Access Health Policy* 2022;10(1):2078474. (In eng). DOI: 10.1080/20016689.2022.2078474.
199. Graybill WS, Vergote I, Pothuri B, et al. Use of individualized starting dose and niraparib hematologic adverse event management costs in ovarian cancer. *J Comp Eff Res* 2025;14(1):e240133. (In eng). DOI: 10.57264/ceer-2024-0133.
200. Mascialino B, Lahelma M, Salo K, et al. EE196 Has the Introduction of PARPi Changed Healthcare Resource Utilization (HCRU) and Medical Costs Among Patients With High-Grade Serous Ovarian Cancer (HGSOC) in the Real-Life Setting in Finland? *Value in Health* 2024;27(12):S92-S93. DOI: 10.1016/j.jval.2024.10.480.
201. Matsuo AL, Santi OS, Paloni E, Rocha ML, Andreghetto FM. Direct medical costs of maintenance therapy in Brazilian platinum-sensitive ovarian cancer patients of private healthcare system- retrospective analysis of an administrative database. *Value in Health ISPOR* 2017;20:4.
202. Bungey G, Brown L, De Boisvilliers S, et al. POSA262 The Use of Akaike Information Criterion and Bayesian Information Criterion Rules of Thumb in Nice Oncology Appraisals: A Targeted Review. *Value in Health* 2022;25(1):S171. DOI: 10.1016/j.jval.2021.11.829.
203. Burnham KP, Anderson DR. Multimodel Inference: Understanding AIC and BIC in Model Selection. *Sociological Methods & Research* 2004;33(2):261-304.

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

204. Burnham KP, Anderson DR, Huyvaert KP. AIC model selection and multimodel inference in behavioral ecology: some background, observations, and comparisons. *Behavioral Ecology and Sociobiology* 2011;65(1):23-35.
205. Kass RE, Raftery AE. Bayes Factors. *Journal of the American Statistical Association* 1995;90(430):773-795.
206. Office for National Statistics (ONS). Population estimates for the UK, England, Wales, Scotland and Northern Ireland: mid-2023. 8 October 2024 (<https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/bulletins/annualmidyearpopulationestimates/mid2023>).
207. Mai PL, Chatterjee N, Hartge P, et al. Potential excess mortality in BRCA1/2 mutation carriers beyond breast, ovarian, prostate, and pancreatic cancers, and melanoma. *PLoS One* 2009;4(3):e4812. (In eng). DOI: 10.1371/journal.pone.0004812.

5 Appendices

Appendix A: Summary of product characteristics (SmPC) and UK public assessment report

A1.1 SmPC



Zejula_SmPC.pdf

A1.2 UK public assessment report



Zejula_PAR.pdf

Appendix B: Identification, selection and synthesis of clinical evidence

B1.1 Identification and selection of relevant studies

An SLR was conducted in March 2024, with an update in February 2025, to identify evidence on the efficacy, safety and HRQoL of niraparib and relevant comparators in adults with advanced epithelial (FIGO stages III and IV) high-grade ovarian, fallopian tube, or primary peritoneal cancer, who have not progressed following first-line therapy, based on data from clinical trials and real-world evidence studies.²⁰ Studies were identified using a search strategy to search across relevant platforms (via the Ovid platform as well as conference proceedings and HTA websites). Inclusion and exclusion criteria were applied to studies to determine those most relevant for inclusion in this submission.²⁰

B.1.1.1 Search strategy

The 2024 SLR and the 2025 update were conducted based on the reporting standards of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), general methodological requirements outlined in the Cochrane Handbook for Systematic Reviews of Interventions and key HTA bodies, such as NICE.²⁰

The literature database searches included a combination of free-text and controlled vocabulary terms specific to each database.²⁰ The search strategy included terms for ovarian cancer which were combined with first-line and maintenance terms.²⁰ Terms specific to interventions of interest (e.g., PARPis, bevacizumab and monitoring) were added to focus the search strategy on relevant comparators of interest, which include those currently approved, recommended in clinical guidelines or a future comparator for PRIMA.²⁰

The SLR included full-text, peer-reviewed articles and evidence from pre-defined grey literature sources²⁰ The following databases were searched via the Ovid platform:²⁰

- MEDLINE and MEDLINE In-process
- Embase

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

- EBM Reviews: Cochrane Central Register of Controlled Trials (CENTRAL)
- NHS EED (via CRD)
- NHS HTA (via CRD)

Relevant abstracts from conference proceedings not indexed in Embase were manually searched using the conference website (2020-current):²⁰

- European Society of Gynaecological Oncology (ESGO)
- American Society of Clinical Oncology (ASCO)
- European Society for Medical Oncology (ESMO): annual meeting; Asia congress; gynaecological cancers congress and Targeted Anticancer Therapies
- Asian Society of Gynaecologic Oncology (ASGO)
- Society of Gynaecologic Oncology (SGO)
- National Cancer Research Institute (NCRI)
- European Association for Cancer Research (EACR)
- The Professional Society for Health Economics and Outcomes Research (ISPOR): annual meeting; Europe annual; Asia Pacific
- International Gynaecologic Cancer Society (IGCS)
- British Gynaecological Cancer Society (BGCS)

To identify any clinical data not otherwise available in peer-reviewed journals or conference abstracts, a search of prior HTA submissions was conducted, including:²⁰

- NICE
- Scottish Medicines Consortium (SMC)
- National Centre for Pharmacoeconomics (NCPE)
- Canadian Agency for Drugs and Technologies in Health (CADTH)/pan-Canadian Oncology Drug Review (pCODR)
- Pharmaceutical Benefits Advisory Committee (PBAC)

The original SLR was conducted in 2024, as such a date limit was applied to the 2025 update search strategy to restrict records published prior to January 2024.²⁰

Search strategies for electronic databases are presented in Table 68 to Table 72. Grey literature search strategies for conference and HTA websites are provided in Table 73 to Table 77, and Table 78 to Table 81, respectively.

Table 68. Ovid Embase search strategy (last search date: 06 February 2025)

#	Search terms	Search hits	
		25 Mar 2024	06 Feb 2025
1	exp ovary cancer/	185,463	162,768
2	(ovar* adj5 (cancer* or tumor* or tumor* or malignan* or neoplas* or carcinoma*)).mp.	209,421	217,130
3	(ovar* cancer* or fallopian tube cancer*).ti,ab. or exp peritoneum cancer/or (periton* cancer* or ((ovar* or fallopian or fallopian tube* or periton* or granulosa or krukensberg* or oviduct* or uterine tube*) adj3 (neoplas* or cancer* or tumor* or tumor* or carcino* or malignan* or adenocarcino* or metast* or mesothelioma*)) or dysgerminoma* or gynandroblastoma*).ti,ab.	191,335	199,259
4	or/1-3	249,825	258,977
5	((new* or first) adj2 diagnos*).mp,af,tw.	276,949	291,751
6	(untreat* or (no adj2 prior) or naive or treatment-naive or treatmentnaive or (chemo* adj naive) or chemonaive).mp,af,tw.	497,582	516,446
7	(first line or first-line or firstline or 1st-line or 1st line or 1stline or 1L or 1-L or "1 L" or 1st-L or 1stL or 1st L or frontline or front-line or front line or initial treatment* or initial therap* or upfront treatment* or upfront therap*).mp,af,tw.	220,216	338,540
8	((((maintenance or maintain or intermittent or continuous or continue* or consolidat*) adj2 (chemotherap* or strateg* or therap* or treatment*)) or "stop-and-go").ti,ab.	141,689	147,856
9	or/5-8	1,163,749	1,218,698
10	4 and 9	16,445	17,579
11	exp PARP inhibitor/or exp niraparib/or exp olaparib/or exp rucaparib/or exp veliparib/or exp talazoparib/or exp pazopanib/or exp bevacizumab/or exp monitoring/	1,183,988	1,300,660

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

#	Search terms	Search hits	
		25 Mar 2024	06 Feb 2025
12	(PARP inhibitor* or "poly ADP-ribose polymerase inhibitor" or niraparib or zejula or MK4827 or MK 4827 or olaparib or lynparza or AZD 2281 or AZD2281 or rucaparib or rubraca or veliparib or talazoparib or pazopanib or vortient or bevacizumab or avastin or altuzan or surveillance or monitoring).ti,ab.	1,265,194	1,337,966
13	11 or 12	1,961,318	2,124,895
14	10 and 13	4,229	4,784
15	Randomized Controlled Trial/or "Randomized Controlled Trial (topic)"/or Controlled Clinical Trial/or "Controlled Clinical Trial (topic)"/	1,283,845	1,328,856
16	Randomization/	99,102	99,550
17	Double Blind Procedure/or Single Blind Procedure/	268,896	281,881
18	Placebo/	410,691	420,818
19	Control Group/	110,758	109,386
20	(random* or sham or placebo*).ti,ab,hw,kf.	374,874	2,765,448
21	((singl* or doubl* or tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf.	1,791,373	387,412
22	(control* adj3 (study or studies or trial* or group*)).ti,ab,kf.	113,857	1,873,882
23	allocated.ti,ab,hw.	81,172	119,546
24	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf.	19,556	96,606
25	((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf.	296	21,223
26	(pragmatic study or pragmatic studies).ti,ab,hw,kf.	8,820	1,074
27	((pragmatic or practical) adj3 trial*).ti,ab,hw,kf.	274,803	10,169
28	(phase adj3 (II*1 or III*1 or IV*1 or 2*1 or 3*1 or 4*1 or two or three or four) adj3 (study or studies or trial*)).ti,hw,kf.	365,129	291,489
29	observational study/	622,818	410,969
30	cross-sectional study/	1,137,822	688,795
31	cohort analysis/	208,361	1,270,127
32	longitudinal study/	910,708	229,073
33	prospective study/	1,590,282	943,224
34	retrospective study/	2,163,482	1,733,992
35	follow up/	185,463	2,287,054
36	exp case control study/	233,440	245,256
37	quasi experimental study/	12,302	13,407

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

#	Search terms	Search hits	
		25 Mar 2024	06 Feb 2025
38	(observational adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.	37,922	407,377
39	cohort*.ti,ab,kf.	1,560,730	1,683,584
40	(prospective adj7 (study or studies or design or analysis or analyses)).ti,ab,kf.	849,937	895,436
41	((follow up or followup) adj7 (study or studies or design or analysis or analyses)).ti,ab,kf.	281,753	295,544
42	((longitudinal or longterm or (long adj term)) adj7 (study or studies or design or analysis or analyses or data)).ti,ab,kf.	518,039	548,300
43	(retrospective adj7 (study or studies or design or analysis or analyses or data or review)).ti,ab,kf.	1,220,187	1,316,318
44	((case adj control) or (case adj comparison) or (case adj controlled)).ti,ab,kf.	221,059	230,362
45	(case-referent adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.	709	698
46	(population adj3 (study or studies or analysis or analyses)).ti,ab,kf.	370,512	392,232
47	(descriptive adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.	179,066	193,771
48	((multidimensional or (multi adj dimensional)) adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.	6,117	6,538
49	(cross adj sectional adj7 (study or studies or design or research or analysis or analyses or survey or findings)).ti,ab,kf.	618,316	673,304
50	((natural adj experiment) or (natural adj experiments)).ti,ab,kf.	3,861	4,154
51	(quasi adj (experiment or experiments or experimental)).ti,ab,kf.	27,181	29,381
52	((non experiment or nonexperiment or non experimental or nonexperimental) adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.	2,467	2,578
53	(prevalence adj3 (study or studies or analysis or analyses)).ti,ab,kf.	75,821	80,607
54	((uncontrolled or non randomi#ed or nonrandomi#ed or epidemiologic* or noninterventional or non interventional or pragmatic) adj1 (study or studies)).ti,ab,kf.	151,585	155,706
55	(registry or register or registries or database* or claims or single center or single centre or multicenter or multi center or multicentre or multi centre or natural history or survey or record* or chart review or real world).ti,ab,kf.	4,680,088	4,955,455

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

#	Search terms	Search hits	
		25 Mar 2024	06 Feb 2025
56	or/15-55	11,650,085	12,261,506
57	14 and 56	3,062	3,508
58	case report/	2,979,144	3,048,235
59	(case report or comment).ti.	462,106	487,623
60	(book or chapter or conference review or editorial or erratum or letter or note or short or short survey or survey or tombstone).pt.	3,858,066	3,933,598
61	review.pt,sh. not (systematic review or systemic review or metaanalysis or meta analysis or meta-analysis).mp.	3,001,235	3,079,387
62	(animal* not human*).sh,hw.	4,935,869	5,002,642
63	(mouse or mice).ti.	631,224	697,262
64	conference abstract.pt.	5,088,203	5,360,035
65	limit 64 to yr="1974 - 2019"	3,860,074	3,884,354
66	or/58-63,65	17,715,948	18,022,979
67	57 not 66	1,874	2,285
68	limit 67 to yr="2024-current"		379

Table 69. Ovid Medline search strategy (last search date: 06 February 2025)

#	Search Terms	Hits 25 Feb 2024	Hits 6 Feb 2025
1	exp Ovarian Neoplasms/	97,621	100414
2	(ovar* adj5 (cancer* or tumor* or tumour* or malignan* or neoplas* or carcinoma*)).mp.	135,839	141087
3	(ovar* cancer* or fallopian tube cancer*).ti,ab. or exp Peritoneal Neoplasms/ or (periton* cancer* or ((ovar* or fallopian or fallopian tube* or periton* or granulosa or krukensberg* or oviduct* or uterine tube*) adj3 (neoplas* or cancer* or tumour* or tumor* or carcino* or malignan* or adenocarcino* or metast* or mesothelioma*)) or dysgerminoma* or gynandroblastoma*).ti,ab.	135,463	141145
4	or/1-3	163,745	169998
5	((new* or first) adj2 diagnos*).mp,af,tw.	121,258	128433
6	(untreat* or (no adj2 prior) or naive or treatment-naive or treatmentnaive or (chemo* adj naive) or chemonaive).mp,af,tw.	327,858	342447

#	Search Terms	Hits 25 Feb 2024	Hits 6 Feb 2025
7	(first line or first-line or firstline or 1st-line or 1st line or 1stline or 1L or 1-L or "1 L" or 1st-L or 1stL or 1st L or frontline or front-line or front line or initial treatment* or initial therap* or upfront treatment* or upfront therap*).mp,af,tw.	187,148	199906
8	((((maintenance or maintain or intermittent or continuous or continue* or consolidat*) adj2 (chemotherap* or strateg* or therap* or treatment*)) or "stop-and-go").ti,ab.	83,495	87566
9	or/5-8	690,015	726585
10	4 and 9	8,931	8895
11	exp "Poly(ADP-ribose) Polymerase Inhibitors"/ or exp Bevacizumab/	20,611	21808
12	(PARP inhibitor* or "poly ADP-ribose polymerase inhibitor" or niraparib or zejula or MK4827 or MK 4827 or olaparib or lynparza or AZD 2281 or AZD2281 or rucaparib or rubraca or veliparib or talazoparib or pazopanib or votrient or bevacizumab or avastin or altuzan or surveillance or monitoring).ti,ab.	905,849	971019
13	11 or 12	910,655	976012
14	10 and 13	1,477	1685
15	Randomized Controlled Trial/ or exp Randomized Controlled Trials as Topic/ or Controlled Clinical Trial/ or exp Controlled Clinical Trials as Topic/	869,945	902103
16	Random Allocation/	107,058	108097
17	Double-Blind Method/ or Single-Blind Method/	210,064	216141
18	Placebos/	35,934	36067
19	Control Groups/	2,116	2141
20	(Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Equivalence Trial or Clinical Trial Phase II or Clinical Trial Phase III or Clinical Trial Phase IV).pt.	732,940	755641
21	(random* or sham or placebo*).ti,ab,hw,kf.	1,891,058	1992980
22	((singl* or doubl* or tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf.	27,585	284284
23	(control* adj3 (study or studies or trial* or group*)).ti,ab,kf.	1,285,239	1361457
24	allocated.ti,ab,hw.	88,159	93467
25	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf.	47,326	50509
26	((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf.	13,156	14574

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

#	Search Terms	Hits 25 Feb 2024	Hits 6 Feb 2025
27	(pragmatic study or pragmatic studies).ti,ab,hw,kf.	641	694
28	((pragmatic or practical) adj3 trial*).ti,ab,hw,kf.	8,283	9135
29	(phase adj3 (II*1 or III*1 or IV*1 or 2*1 or 3*1 or 4*1 or two or three or four) adj3 (study or studies or trial*)).ti,hw,kf.	91,582	96529
30	observational study/	153,547	168660
31	observational studies as topic/	9,575	10382
32	clinical studies as topic/	824	866
33	controlled before-after studies/	752	776
34	cross-sectional studies/	496,531	531296
35	historically controlled study/	232	239
36	interrupted time series analysis/	2,014	2366
37	cohort studies/	339,124	353515
38	longitudinal studies/	170,337	180458
39	prospective studies/	683,018	709108
40	retrospective studies/	1,189,384	1262899
41	follow-up studies/	696,218	708458
42	case-control studies/	332,606	343856
43	single-case studies as topic/	100	143
44	(observational study or validation studies or clinical study).pt.	159,385	175171
45	(epidemiologic methods or epidemiologic studies).sh.	40,996	41153
46	(observational adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.	239,997	265450
47	cohort*.ti,ab,kf.	928,701	1018270
48	(prospective adj7 (study or studies or design or analysis or analyses)).ti,ab,kf.	560,039	593206
49	((follow up or followup) adj7 (study or studies or design or analysis or analyses)).ti,ab,kf.	177,716	187814
50	((longitudinal or longterm or (long adj term)) adj7 (study or studies or design or analysis or analyses or data)).ti,ab,kf.	366,768	393424
51	(retrospective adj7 (study or studies or design or analysis or analyses or data or review)).ti,ab,kf.	734,172	804751
52	((case adj control) or (case adj comparison) or (case adj controlled)).ti,ab,kf.	166,636	175123
53	(case-referent adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.	641	644
54	(population adj3 (study or studies or analysis or analyses)).ti,ab,kf.	246,180	261430

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

#	Search Terms	Hits 25 Feb 2024	Hits 6 Feb 2025
55	(descriptive adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.	118,321	129863
56	((multidimensional or (multi adj dimensional)) adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.	5,265	5722
57	(cross adj sectional adj7 (study or studies or design or research or analysis or analyses or survey or findings)).ti,ab,kf.	474,382	524766
58	((natural adj experiment) or (natural adj experiments)).ti,ab,kf.	3,619	3952
59	(quasi adj (experiment or experiments or experimental)).ti,ab,kf.	22,197	24626
60	((non experiment or nonexperiment or non experimental or nonexperimental) adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.	1,791	1899
61	(prevalence adj3 (study or studies or analysis or analyses)).ti,ab,kf.	52,542	56604
62	((uncontrolled or non randomi#ed or nonrandomi#ed or epidemiologic* or noninterventional or non interventional or pragmatic) adj1 (study or studies)).ti,ab,kf.	114,382	118798
63	(registry or register or registries or database* or claims or single center or single centre or multicenter or multi center or multicentre or multi centre or natural history or survey or record* or chart review or real world).ti,ab,kf.	3,278,587	3516286
64	or/15-63	8,153,209	8629082
65	14 and 64	801	936
66	case reports/	2,392,060	2460281
67	(case report or comment).ti.	380,130	409545
68	(address or autobiography or bibliography or biography or case reports or comment or congress or consensus development conference or consensus development conference nih or duplicate publication or editorial or festschrift or guideline or interview or lecture or legal case or legislation or letter or news or newspaper article or periodical index or personal narrative or portrait or practice guideline or published erratum or retracted publication or "retraction of publication" or study guide or technical report or video audio media or webcast).pt.	5,205,850	5382742
69	review.pt,sh. not (systematic review or systemic review or metaanalysis or meta analysis or meta-analysis).mp.	3,085,358	3202051

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

#	Search Terms	Hits 25 Feb 2024	Hits 6 Feb 2025
70	(animal* not human*).sh,hw.	5,161,469	5259160
71	(mouse or mice).ti.	583,747	601924
72	or/66-71	13,147,885	13538868
73	65 not 72	654	788
74	limit 73 to yr="2024 -Current"		168

Table 70. OVID Cochrane Central Register of Controlled Trials search strategy (last search date: February 6, 2025)

#	Search terms	Search hits	
		25 Mar 2024	06 Feb 025
1	exp Ovarian Neoplasms/	3,395	3,509
2	(ovar* adj5 (cancer* or tumor* or tumor* or malignan* or neoplas* or carcinoma*)).mp.	8,877	9,407
3	(ovar* cancer* or fallopian tube cancer*).ti,ab. or exp Peritoneal Neoplasms/or (periton* cancer* or ((ovar* or fallopian or fallopian tube* or periton* or granulosa or krukenberg* or oviduct* or uterine tube*) adj3 (neoplas* or cancer* or tumor* or tumor* or carcino* or malignan* or adenocarcino* or metast* or mesothelioma*)) or dysgerminoma* or gynandroblastoma*).ti,ab.	9,021	9,563
4	or/1-3	10,031	10,624
5	((new* or first) adj2 diagnos*).mp,af,tw.	19,099	20,582
6	(untreat* or (no adj2 prior) or naive or treatment-naive or treatmentnaive or (chemo* adj naive) or chemonaive).mp,af,tw.	49,309	52,314
7	(first line or first-line or firstline or 1st-line or 1st line or 1stline or 1L or 1-L or "1 L" or 1st-L or 1stL or 1st L or frontline or front-line or front line or initial treatment* or initial therap* or upfront treatment* or upfront therap*).mp,af,tw.	39,206	42,353
8	((((maintenance or maintain or intermittent or continuous or continue* or consolidat*) adj2 (chemotherap* or strateg* or therap* or treatment*)) or "stop-and-go").ti,ab.	30,965	32,863
9	or/5-8	122,273	130,344
10	4 and 9	2,329	2,517
11	exp "Poly(ADP-ribose) Polymerase Inhibitors"/or exp Bevacizumab/	3,230	3,373

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

#	Search terms	Search hits	
		25 Mar 2024	06 Feb 025
12	(PARP inhibitor* or "poly ADP-ribose polymerase inhibitor" or niraparib or zejula or MK4827 or MK 4827 or olaparib or lynparza or AZD 2281 or AZD2281 or rucaparib or rubraca or veliparib or talazoparib or pazopanib or votrient or bevacizumab or avastin or altuzan or surveillance or monitoring).ti,ab.	81,369	87,803
13	11 or 12	81,643	88,089
14	10 and 13	893	1,019
15	(case report or comment).ti.	1,997	2,171
16	(address or autobiography or bibliography or biography or case reports or comment or congress or consensus development conference or consensus development conference nih or duplicate publication or editorial or festschrift or guideline or interview or lecture or legal case or legislation or letter or news or newspaper article or periodical index or personal narrative or portrait or practice guideline or published erratum or retracted publication or "retraction of publication" or study guide or technical report or video audio media or webcast).pt.	19,915	20,135
17	(animal* not human*).sh,hw.	3,319	3,379
18	(mouse or mice).ti.	427	452
19	or/15-18	25,151	25,652
20	14 not 19	891	1,017
21	Limit 20 to yr="2024 -Current"		96

Table 71. National Health Service Economic Evaluations Database (via CRD; last search date: 06 February 2025)

#	Search terms	Search hits	
		22 Feb 2024	06 Feb 2025
Any field	((ovar* adj5 (cancer* or tumor* or tumor* or malignan* or neoplas* or carcinoma*))) OR ((ovar* cancer* or fallopian tube cancer* or periton* cancer* or dysgerminoma* or gynandroblastoma*)) OR (((ovar* or fallopian or fallopian tube* or periton* or granulosa or krukenberg* or oviduct* or uterine tube*) adj3 (neoplas* or cancer* or tumor* or tumor* or carcino* or malignan* or adenocarcino* or metast* or mesothelioma*)))	-	-
-	AND	-	
Any field	(new* or first or untreat* or (no adj2 prior) or naive or treatment-naive or treatmentnaive or (chemo* adj naive) or chemonaive) OR (first line or first-line or firstline or 1st-line or 1st line or 1stline or 1L or 1-L or 1 L or 1st-L or 1stL or 1st L or frontline or front-line or front line or initial treatment* or initial therap* or upfront treatment* or upfront therap* or maintenance or maintain or intermittent or continuous or continue* or consolidat* or stop-and-go)	53	
Publication limit	2024-2025		0

Table 72. INAHTA search strategy (last search date: 06 February 2025)

#	Search terms	Search hits	
		22 Feb 2024	06 Feb 2025
Any field	((ovar* adj5 (cancer* or tumor* or tumor* or malignan* or neoplas* or carcinoma*))) OR ((ovar* cancer* or fallopian tube cancer* or periton* cancer* or dysgerminoma* or gynandroblastoma*)) OR (((ovar* or fallopian or fallopian tube* or periton* or granulosa or krukenberg* or oviduct* or uterine tube*) adj3 (neoplas* or cancer* or tumor* or tumor* or carcino* or malignan* or adenocarcino* or metast* or mesothelioma*)))	-	-
-	AND	-	
Any field	(new* or first or untreat* or (no adj2 prior) or naive or treatment-naive or treatmentnaive or (chemo* adj naive) or chemonative) OR (first line or first-line or firstline or 1st-line or 1st line or 1stline or 1L or 1-L or 1 L or 1st-L or 1stL or 1st L or frontline or front-line or front line or initial treatment* or initial therap* or upfront treatment* or upfront therap* or maintenance or maintain or intermittent or continuous or continue* or consolidat* or stop-and-go)	53	
Publication limit	2024-2025		10

Table 73. European Association for Cancer Research congress

Conference year	Search strategy	Hits
European Association for Cancer Research 2024 Searched: February 10, 2025	Ovarian Cancer	214
	Fallopian tube cancer	2
	Peritoneal cancer	34
European Association for Cancer Research 2022* Searched: March 25, 2024	Ovarian cancer	55
	Fallopian tube cancer	0
	Peritoneal cancer	1
European Association for Cancer Research 2021 Searched: March 25, 2024	Ovarian cancer	76
	Fallopian tube cancer	0
	Peritoneal cancer	0

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Table 74. The Professional Society for Health Economics and Outcomes Research Asia congress (search date: 25 March 2024)

Conference	Search strategy	Hits
ISPOR Asia 2022	Ovarian cancer	0
	Fallopian tube cancer	0
	Peritoneal cancer	0

ISPOR = International Society for Pharmacoeconomics and Outcomes Research

Table 75. ESMO Gynaecological Cancer Congress (abstracts only; search date: 25 March 2024)

Conference	Search strategy	Hits
ESMO Asia Congress Searched: February 14, 2025	Ovarian cancer	10
	Fallopian tube cancer	0
	Peritoneal cancer	1
ESMO Gynaecological Cancer 2024 Searched: February 10, 2025	Ovarian cancer	31
	Fallopian tube cancer	28
	Peritoneal cancer	28
ESMO Gynaecological Cancer 2022 Searched: March 25, 2024	Ovarian cancer	27
	Fallopian tube cancer	2
	Peritoneal cancer	3

ESMO = European Society for Medical Oncology

Table 76. National Cancer Research Institute congress (search date: 25 March 2024)

Conference	Search strategy	Hits
National Cancer Research Institute 2021	Ovarian cancer	9
	Fallopian tube cancer	0
	Peritoneal cancer	1
National Cancer Research Institute 2020	Ovarian cancer	9
	Fallopian tube cancer	0
	Peritoneal cancer	4

Table 77. British Gynaecological Cancer Society (search date: 10 February 2025)

Conference	Search strategy	Hits
British Gynaecological Cancer Society	Ovarian cancer	156
	Fallopian tube cancer	0
	Peritoneal cancer	2

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Table 78. NICE search strategy (search date: 25 March 2024)

HTA body	Search strategy	Hits
NICE	Ovarian cancer	12
	Fallopian tube cancer	7
	Peritoneal cancer	7
	Olaparib	6
	Rucaparib	1
	Bevacizumab	15

HTA = health technology assessment; NICE = National Institute for Health and Care Excellence

Table 79. CDA search strategy (search date: 25 March 2024)

HTA body	Search strategy	Hits
CDA	Ovarian cancer	5
	Fallopian tube cancer	0
	Peritoneal cancer	0

CDA = Canada's Drug Agency; HTA = health technology assessment;

Table 80. Scottish Medicines Consortium search strategy (search date: 25 March 2024)

HTA body	Search strategy	Hits
Scottish Medicines Consortium	Ovarian cancer	14
	Fallopian tube cancer	12
	Peritoneal cancer	12

HTA = health technology assessment

Table 81. National Centre for Pharmacoeconomics search strategy (search date: 25 March 2024)

HTA body	Search strategy	Hits
National Centre for Pharmacoeconomics	Ovarian cancer	5
	Fallopian tube cancer	5
	Peritoneal cancer	5

HTA = health technology assessment;

B.1.1.2 Study selection

The selection of studies was guided by the population, intervention, comparison, outcome and study design (PICOS) criteria presented in Table 82.²⁰

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Table 82. PICO selection criteria

	Inclusion	Exclusion
Population	- Adult women with advanced (stage III) or metastatic (stage IV) OC^a who had a response (CR or PR) to first-line therapy - Subgroups of interest, including, but not limited to: - Bevacizumab use in first-line setting - High-risk^b - BRCAm or <i>BRC</i>Awt - HRd - HRp - HRun - High-risk subgroups: HR+<i>BRC</i>Am, HR+HRd, HR+HRd+<i>BRC</i>Awt, HR+HRp - HRd subgroups: HRd+<i>BRC</i>Awt, HRd+<i>BRC</i>Am - Receipt of neoadjuvant chemotherapy - Depth of response to first-line therapy e.g., CR subgroup or PR subgroup	- Patients with early disease stages (stage I or II) - Patients with stable disease or who progressed during or following first-line treatment (i.e., second- or later-line settings) - Any other indication
Interventions	- Systemic pharmacological treatment currently approved or under investigation for managing the disease as maintenance therapy, including^c: - Bevacizumab - Single PARPi (e.g., niraparib alone) - Single PARPi + bevacizumab - Single PARPi + immunotherapy	- Radiotherapy - Surgery - Studies where the cohort or treatment group received >1 PARPi (e.g. either niraparib or olaparib or rucaparib)
Comparators	No restrictions	NA
Outcomes	Clinical efficacy, including, but not limited to, for example: OS	Any other outcome (data relevant to the other SLRs will be flagged to ensure all relevant information is identified)

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

	Inclusion	Exclusion
	• PFS (IRC/INV) • PFS2 (IRC/INV) • ORR (IRC/INV) • DCR • TTD • SD • PD • RFS • PFI • TTNT • TFST • TSST Safety, including, but not limited to, for example: • Treatment discontinuation • Dose reduction/interruption • Total AEs^d • Total SAEs^d • Total grade 3/4 AEs^d • Grade ≥3 AEs^d ○ hypertension ○ fatigue ○ thrombocytopenia ○ nausea ○ anaemia ○ neutropenia • HRQoL and PROs, including, but not limited to: ○ EQ-5D (VAS and HUI) ○ EORTC QLQ-C30 ○ EORTC QLQ-OV28 ○ FACT-O ○ FOSI	• Studies in patients receiving 1L treatment followed by a maintenance phase, but with no outcomes specific for the maintenance phase will be excluded.
Study design	• Clinical trials: RCTs, non-RCTs, single-arm trials • RWE studies (e.g., observational studies or patient registries) • SLRs/NMAs (included for hand-searching of relevant studies only and excluded from the final review)	• Non-SLRs (i.e., targeted reviews) • Non-human studies • Pharmacodynamic studies • Preclinical studies / phase I trials • Case reports • Case studies • Commentaries, editorials, and letters

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

	Inclusion	Exclusion
		Consensus reports
Time frame	- Full text: no time limit 2025 update: 2024-February 2025 - Conference proceedings: since 2020 2025 update: since 2024	- Conference proceedings published prior to 2020 2025 update: prior to 2024
Language	English	Non-English language studies will be flagged for consideration in local market submissions

AE = adverse event; CR = complete response; DCR = disease control rate; EQ-5D = European Quality of Life 5 Dimensions scale questionnaire; FACT-O = Functional Assessment of Cancer Therapy – Ovarian; FOSI = Functional Assessment of Cancer Therapy Ovarian Cancer Symptom Index; HRD = homologous recombination deficiency; HRp = homologous recombination proficiency; HRR = homologous recombination repair; HRQoL = health-related quality of life; INV = investigator; IRC = Independent Review Committee; NA = not applicable; NMA = network meta-analysis; OC = ovarian cancer; ORR = objective response rate; OS = overall survival; PARPi = poly (ADP-ribose) polymerase inhibitor; PD = progressive disease; PFI = progression-free interval; PFS = progression free survival; PR = partial response; PRO = patient reported outcomes; RCT = randomized controlled trials; RFS = recurrence-free survival; RWE = real-world evidence; SAE = serious adverse event; SD = stable disease; SLR = systematic literature review; TFST = time-to first subsequent therapy; TSST = time-to second subsequent therapy; TTD = time to discontinuation; TTNT = time-to next treatment; VAS = visual analogue scale
^a OC is collectively defined as tumours of the ovary, peritoneum, and fallopian tube.

^b The definition of high risk was recorded in the data extraction file.

^c These treatments can be administered as monotherapy or as part of a combination therapy. Note that studies reporting outcomes where the intervention is >1 PARPi (e.g., the cohort of patients received either niraparib or olaparib) will not be included.

^d Including treatment-emergent and treatment-related adverse events

The screening was conducted in two phases using PICO criteria (as specified in Table 82): a) title/abstract screening, and b) full-text screening. At each phase, all records were screened by two independent reviewers, with conflicts resolved by a third independent reviewer.²⁰ Following the article selection process, a preliminary list of included and excluded studies (with reasons for exclusion at the full-text screening level) was generated.²⁰

B.1.1.3 Data extraction and quality assessment

Data from the included studies was extracted into standardised data extraction templates developed in Microsoft Excel[®] with separate tabs to capture publication, study, patient, and treatment characteristics, as well as outcome data of interest.²⁰ The data was extracted by one reviewer and a second reviewer assessed the entries to ensure consistency and accuracy.²⁰

A quality assessment of the primary, full-text studies was conducted using the Cochrane Risk of Bias Assessment Tool 2.0 for RCTs,¹³³ as recommended by HTA Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

bodies, such as NICE. RWE studies and single-arm trials were assessed using the Risk of Bias in Non-Randomised Studies – of Interventions (ROBINS-I) tool.¹³⁴ Conference abstracts were not quality assessed, given the limited information provided.

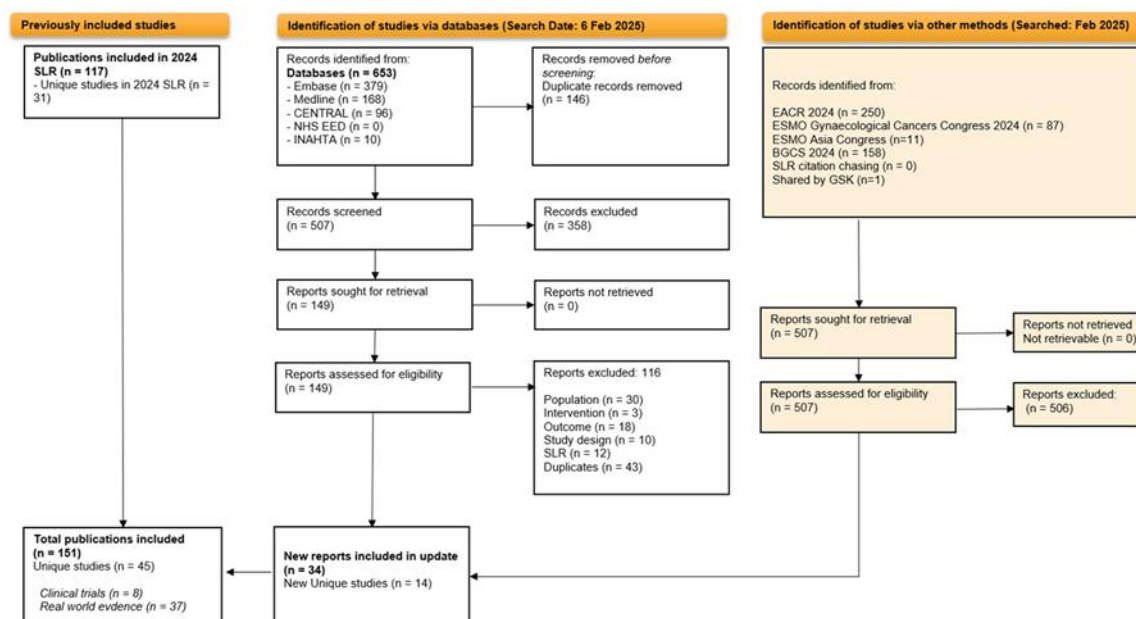
B.1.1.4 Results

Overview of search results

The original SLR was conducted in March 2024 and resulted in the inclusion of 117 publications representing 31 unique studies.²⁰ An update was conducted in February 2025 and yielded 653 records.²⁰ Of 507 unique records screened at the title and abstract level that remained after removing 146 duplicates, 149 were deemed eligible for full-text screening, while the others were excluded.²⁰ After the full-text review, a total of 33 records were included for synthesis from the database searches, and 1 record was additionally included from grey literature searches.²⁰ Therefore, a total of 34 records for 14 unique studies were included in the 2025 SLR update.²⁰

Accounting for the original SLR and subsequent updates, a total of 151 publications were included, representing 45 unique studies, including 8 clinical trials and 37 RWE studies.²⁰ Figure 30 shows the PRISMA diagram for the 2024 SLR and 2025 SLR update.

Figure 30. PRISMA flow diagram



BGCS = British Gynaecological Cancer Society; CENTRAL = Cochrane Central Register of Controlled Trials; EACR = European Association for Cancer Research; ESMO = European Society for Medical Oncology; INAHTA = International Network of Agencies for Health Technology Assessment; NHS EED = National Health Service Economic Evaluations Database; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR = systematic literature review

Included RCTs and RWE studies with their related publications are listed in Table 83 and Table 84, respectively.²⁰

Table 83. Included clinical trials – Primary/secondary publications and trial characteristics

Study name, NCT	Study design	Intervention	Primary publication	Secondary publication(s)	
ATHENA-MONO ATHENA-COMBO (NCT03522246)	Phase 3, double-blind RCT	Rucaparib + placebo vs placebo (ATHENA-MONO) Rucaparib + nivolumab vs rucaparib + placebo (ATHENA-COMBO)	Monk 2022 Monk 2024	Fujiwara 2022 Monk 2022 Oaknin 2022 O'Malley 2022	Kristeleit 2024 O'Malley 2024 Kristeleit 2024
FLAMES (NCT04169997)	Phase 3, double-blind RCT	Senaparib vs placebo	Wu 2024	Wu 2023 Wu 2023	
Oda 2024 (jRCT 2080223978)	Phase 2, single-arm trial ^a	Olaparib	Oda 2024	NA	
OVARIO (NCT03326193)	Phase 2, open-label, single-arm trial	Niraparib + bevacizumab	Hardesty 2022	Hardesty 2022 Hardesty 2021	
PAOLA-1 (NCT02477644)	Phase 3, double-blind RCT	Olaparib + bevacizumab vs bevacizumab	Lorusso 2024	Boidot 2023 Buisson 2023 Callens 2023 Callens 2023 Colombo 2020 Fujiwara 2021 Fujiwara 2020 González-Martín 2023 González-Martín 2022 Grimm 2020 Harter 2022	Lorusso 2023 Lorusso 2020 Loverix 2022 Martin 2023 Marchetti 2023 Montégut 2021 Nagao 2022 Pautier 2021 Pujade-Lauraine 2023 Pujade-Lauraine 2021 Ray-Coquard 2019

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Study name, NCT	Study design	Intervention	Primary publication	Secondary publication(s)	
				Harter 2020 Harter 2025 Hietanen 2021 Joly 2022 Kurtz 2022 Labidi-Galy 2023 Labidi-Galy 2022 Leman 2023	Ray-Coquard 2023 Ray-Coquard 2022 Sabatier 2023 Sabatier 2021 Schouten 2023 Schouten 2024 Montégut 2024
PRIMA (NCT02655016)	Phase 3, double-blind RCT	Niraparib vs placebo	Monk 2024	Barretina-Ginesta 2021 Barretina-Ginesta 2022 Braicu 2020 Chase 2021 Chase 2022 NCT02655016 EU clinical trials register Freyer 2020 González-Martín 2019 González-Martín 2022 González-Martín 2023 Gonzalez-Martín 2024 Graybill 2020 Graybill 2024 Han 2020 Haslund 2024	Herzog 2022 Herzog 2023 Martin 2023 Mirza 2023 Mirza 2020 Monk 2020 O'Cearbhaill 2021 O'Cearbhaill 2022 Pothuri 2024 Pothuri 2020 Valabrega 2024 Valabrega 2024 Valabrega 2020 Vulsteke 2024 Vulsteke 2024

Study name, NCT	Study design	Intervention	Primary publication	Secondary publication(s)	
PRIME (NCT03709316)	Phase 3, double-blind RCT	Niraparib vs placebo	Li 2023	Li 2022 Pan 2023 Wang 2022	Yin 2022 Zhu 2023
SOLO-1 (NCT01844986)	Phase 3, double-blind RCT	Olaparib vs placebo	DiSilvestro 2022	Banerjee 2021 Bradley 2021 NCT01844986 Colombo 2021 Colombo 2020	DiSilvestro 2020 Friedlander 2021 Friedlander 2020 Moore 2018 Wu 2021

Abbreviations: EU = European Union; NA = not applicable; NCT = National Clinical Trial; RCT = randomized controlled trial

^a Patients (n=32) were initially randomly assigned, in a 2:1 ratio, to receive either olaparib or placebo. However, when randomization became ethically difficult after approval of olaparib for germline BRCAm patients in the 1L setting in 2019, the study switched to a single-arm design and enrolled an additional n=26 patients for olaparib.

Table 84. Included RWE studies - Publications and study characteristics

Study, author, year	Study design	Maintenance therapies [n]	Study location	Data availability
Retrospective studies				
Adeji 2024	Retrospective Medicare and Optum's Clinformatics Data Mart database	Bevacizumab [1144]	US	OS
Apostol 2023	Retrospective	Niraparib [124]	Italy	PFS
CHAR1ZMA Salani 2025 Backes 2023 Coleman 2023 Salani 2024 Backes 2025	Retrospective Flatiron Health database	Niraparib [560]	US	PFS, TTD, TTNT, safety

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Study, author, year	Study design	Maintenance therapies [n]	Study location	Data availability
Bruno 2024	Retrospective	Niraparib [124]	Italy	PFS, safety
AR1ZE Chase 2025 Chase 2024	Retrospective Flatiron Health database	Niraparib [496]	US	PFS, TTNT
Chen 2024	Retrospective	Olaparib [104] Niraparib [60]	China	PFS, safety
PRED1CT Chase 2024	Retrospective Flatiron Health database	Niraparib [526]	US	TTNT
Giudice 2024	Retrospective	PARPi, bevacizumab [84]	Italy	OS, PFS
Graves 2025 Graves 2024	Retrospective	Bevacizumab [78]	USA	PFS
Ha 2024	Retrospective	Niraparib [64] Olaparib [27]	South Korea	Safety
Han 2024	Retrospective Korean National Health Insurance Service	Niraparib [118] Olaparib [104]	South Korea	Safety
Hannaway 2023	Retrospective	Niraparib [83]	Canada	PFS, safety
Hashimoto 2023	Retrospective	Niraparib [45]	Japan	Safety
Khaja 2024	Retrospective	Niraparib [19]	UK	OS, PFS
Kim 2024	Retrospective	Olaparib [80] Niraparib [31]	South Korea	OS, PFS, TFST, safety
Kumar 2024	Retrospective	Olaparib [27] Rucaparib [19]	India	PFS
Lee 2024	Retrospective	Bevacizumab [42] PARPi [98]	South Korea	PFS
Li 2022	Retrospective	Niraparib [93]	China	PFS

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Study, author, year	Study design	Maintenance therapies [n]	Study location	Data availability
NCT05153603 Li 2024 Li 2023	Retrospective	Olaparib [50]	China	PFS, OS, TFST, safety
OVAL-1 Lorusso 2022 Lorusso 2022	Retrospective	Olaparib [324]	France, Italy, and UK	Safety
Luk 2024	Retrospective	Olaparib [21]	Hong Kong	OS, PFS, safety
Nakamura 2024	Retrospective	Niraparib [60] Olaparib [30] Olaparib + bevacizumab [27]	Japan	PFS, safety
Piedimonte 2024	Retrospective	Niraparib [52]	Canada	PFS
Roy 2023	Retrospective	Olaparib or rucaparib ± bevacizumab [41]	India	PFS, safety
Shin 2021	Retrospective	Niraparib [35]	South Korea	Safety
Szamreta 2024	Retrospective Forian claims database	Olaparib [1,068]	US	PFS
SW1TCH Rimel 2024	Retrospective Flatiron Health database	Niraparib [93]	US	TTD, TTNT, safety
COMB1NE Thaker 2024 Thaker 2024	Retrospective Flatiron Health database	Niraparib + bevacizumab [59]	US	TTD, TTNT, safety
Veljovich 2024	Retrospective Flatiron Health database	Olaparib [69] Olaparib + bevacizumab [28]	US	TFST, TTD
Wenxin 2023	Retrospective	Niraparib [102]	China	PFS, safety

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Study, author, year	Study design	Maintenance therapies [n]	Study location	Data availability
NCT05734911 Zhao 2023	Retrospective	Niraparib [199]	China	PFS, TTD, safety
Zheng 2021	Retrospective	Olaparib [84]	China	PFS
Prospective studies				
Bellier 2023 Bellier 2020	Prospective	Olaparib [201]	France	Safety
de la Motte Rouge 2022	Prospective	Niraparib [67]	France	Safety
Jeong 2024	Prospective	Niraparib [53]	South Korea	Safety
RENI-1 Zuo 2024 Zheng 2024	Prospective	Niraparib [227]	China	PFS, safety
Ambispective studies				
MONITOR-UK Hasson 2024	Ambispective	Niraparib [165]	UK	PFS, safety

HRQoL = health-related quality of life; NR = not reported; OS = overall survival; PARPi = poly ADP-ribose polymerase; PFS = progression-free survival; RWE = real world evidence; TTD = time to discontinuation; TFST = time to first subsequent treatment; TTNT = time to next treatment; UK = United Kingdom; US = United States

Complete reference lists for included studies and excluded studies

Table 85 and Table 86 provide a list of studies that were included or excluded during eligibility review for data extraction, respectively.^{20,135}

Table 85. List of included clinical studies

SLR search	Study ID	Primary/ secondary publication	Citation
Original SLR (2024)	1a	Primary	Monk, B. J., Parkinson, C., Lim, M. C., O'malley, D. M., Oaknin, A., Wilson, M. K., & Kristeleit, R. S. (2022). A randomized, phase III trial to evaluate rucaparib monotherapy as maintenance treatment in patients with newly diagnosed ovarian cancer (ATHENA-MONO/GOG-3020/ENGOT-ov45). <i>Journal of Clinical Oncology</i> , 40(34), 3952-3964.
Original SLR (2024)	1a	Secondary	Fujiwara, K., Kristeleit, R., Ghamande, S., Lim, M. C., Parkinson, C., Morgan, M., Wilson, M. K., Oaknin, A., Buscema, J., Bessette, P., Lorusso, D., Ueland, F., Safra, T., Barlin, J. N., Marme, F., Herzog, T. J., McNeish, I. A., Goble, S., Hume, S., Monk, B. J. Rucaparib maintenance treatment in patients (pts) with newly diagnosed ovarian cancer (OC): Defining benefit according to disease risk subgroups within the phase III ATHENA-MONO study. <i>Annals of Oncology</i> . 2022. 33:S1505-S1506
Original SLR (2024)	1a	Secondary	Monk, B. J., Parkinson, C., Lim, M. C., O'Malley, D. M., Oaknin, A., Wilson, M. K., Coleman, R. L., Lorusso, D., Oza, A. M., Ghamande, S. A., Christopoulou, A., Prendergast, E., Demirkiran, F., Littell, R. D., Chudecka-Glaz, A. M., Morgan, M. A., Goble, S. M., Hume, S., Fujiwara, K., Kristeleit, R.. ATHENA-MONO (GOG-3020/ENGOT-ov45): A randomized, double-blind, phase 3 trial evaluating rucaparib monotherapy versus placebo as maintenance treatment following response to first-line platinum-based chemotherapy in ovarian cancer. <i>Journal of Clinical Oncology</i> . 2022. 40:#pages#
Original SLR (2024)	1a	Secondary	Oaknin, A., Kristeleit, R. S., Mahdi, H. S., Lim, M. C., De Vivo, R., Salinas, E. A., Wilson, M. K., Liontos, M., Santin, A. D., Provencher, D. M., Demirkiran, F., Willmott, L. J., Chudecka-Glaz, A. M., Herzog, T. J., Beiner, M. E., Copeland, L. J., McNeish, I. A., Lin, K. K., Monk, B. J.. PATIENTS WITH NEWLY DIAGNOSED OVARIAN CANCER TREATED WITH MAINTENANCE RUCAPARIB: EXPLORATORY BIOMARKER ANALYSIS FROM THE PHASE 3 ATHENA-MONO STUDY (GOG-3020/ ENGOT-OV45; NCT03522246). <i>International Journal of Gynecological Cancer</i> . 2022. 32:A472

SLR search	Study ID	Primary/ secondary publication	Citation
Original SLR (2024)	1a	Secondary	O'Malley, D.,Christopoulou, A.,Lim, M. C.,Diaz, J.,Demirkiran, F.,Wilson, M.,Jewell, A.,Drochytsek, V.,Bessette, P.,Morris, R.,Van Gorp, T.,Van Le, L.,Lindahl, G.,Eskander, R.,Collins, D.,Goble, S.,Hume, S.,Fujiwara, K.,Monk, B.,Kristeleit, R.. EFFICACY ANALYSIS BY DISEASE RISK SUBGROUP FOR THE PHASE 3 ATHENA-MONO STUDY (GOG- 3020/ENGOT-OV45) EVALUATING RUCAPARIB MAINTENANCE TREATMENT IN PATIENTS WITH NEWLY DIAGNOSED OVARIAN CANCER. International Journal of Gynecological Cancer. 2022. 32:A16
Original SLR (2024)	1a	Secondary	Interim post-progression data and updated survival in patients with newly-diagnosed advanced ovarian cancer in ATHENA-MONO
SLR update (2025)	1a	Secondary	O'Malley, D. M.,Monk, B. J.,Lim, M. C.,Pradera, J. F.,Buscema, J.,Wilson, M. K.,De Vivo, R.,Herzog, T. J.,Zagouri, F.,Oza, A. M.,Mikheeva, O. N.,Diaz, J. P.,Lisyanskaya, A. S.,Morris, R.,Bruchim, I.,Craib, M.,Connor, C.,Shih, D.,Fujiwara, K.,Kristeleit, R.. Final safety results from ATHENA-MONO (GOG-3020/ENGOT-ov45), a randomized, placebo-controlled, double-blind, phase 3 trial evaluating rucaparib monotherapy as maintenance treatment in patients with newly diagnosed ovarian cancer. J Clin Oncol. 2024;42(16):#Pages#.
SLR update (2025)	1a	Secondary	Kristeleit, R.,O'Malley, D.,Lim, M. C.,McNeish, I.,Herzog, T. J.,Wilson, M.,Fehm, T. N.,Coleman, R. L.,Van Gorp, T.,Oza, A. M.,Mikheeva, O.,Buscema, J.,Lisyanskaya, A. S.,Lindahl, G.,Gao, B.,Lorusso, D.,Morgan, M.,Shih, D.,Fujiwara, K.,Monk, B. J.. 49MO Updated progression-free survival (PFS) in patients (pts) with newly diagnosed advanced ovarian cancer (OC) treated with rucaparib (RUC) in ATHENA-MONO. ESMO open. 2024;9():#Pages#.
SLR update (2025)	1b	Secondary	Monk, B. J.,Oaknin, A.,O'Malley, D. M.,Wilson, M.,Lorusso, D.,Westin, S.,Oza, A. M.,Zagouri, F.,Herzog, T. J.,Mikheeva, O.,Parkinson, C.,Coleman, R. L.,Lim, M. C.,Chudecka-Glaz, A. M.,Eskander, R. N.,Bruchim, I.,Ghamande, S.,Despain, D.,Fujiwara, K.,Kristeleit, R.. LBA30 ATHENA-COMBO, a phase III, randomized trial comparing rucaparib (RUCA) + nivolumab (NIVO) combination therapy vs RUCA monotherapy as maintenance treatment in patients (pts) with newly diagnosed ovarian cancer (OC). Ann Oncol. 2024;35():S1223.

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

SLR search	Study ID	Primary/ secondary publication	Citation
Original SLR (2024)	2	Secondary	A Phase III, Randomised, Double Blind, Placebo Controlled, Multicentre Study of Olaparib Maintenance Monotherapy in Patients With BRCA Mutated Advanced (FIGO Stage III-IV) Ovarian Cancer Following First Line Platinum Based Chemotherapy https://clinicaltrials.gov/ct2/show/NCT01844986
Original SLR (2024)	2	Primary	DiSilvestro, P., Banerjee, S., Colombo, N., Scambia, G., Kim, B. G., Oaknin, A., Friedlander, M., Lisyanskaya, A., Floquet, A., Leary, A., Sonke, G. S., Gourley, C., Oza, A., Gonzalez-Martin, A., Aghajanian, C., Bradley, W., Mathews, C., Liu, J., McNamara, J., . . . Moore, K. N. (2022). Overall Survival With Maintenance Olaparib at a 7-Year Follow-Up in Patients With Newly Diagnosed Advanced Ovarian Cancer and a BRCA Mutation: The SOLO1/GOG 3004 Trial. <i>Journal of clinical oncology</i> , 41(3), 609-617.
Original SLR (2024)	2	Secondary	Banerjee, S., Moore, K. N., Colombo, N., Scambia, G., Kim, B. G., Oaknin, A., ... & DiSilvestro, P. (2021). Maintenance olaparib for patients with newly diagnosed advanced ovarian cancer and a BRCA mutation (SOLO1/GOG 3004): 5-year follow-up of a randomised, double-blind, placebo-controlled, phase 3 trial. <i>The Lancet Oncology</i> , 22(12), 1721-1731.
Original SLR (2024)	2	Secondary	Colombo, N., Moore, K., Scambia, G., Oaknin, A., Friedlander, M., Lisyanskaya, A., ... & DiSilvestro, P. (2021). Tolerability of maintenance olaparib in newly diagnosed patients with advanced ovarian cancer and a BRCA mutation in the randomized phase III SOLO1 trial. <i>Gynecologic oncology</i> , 163(1), 41-49.
Original SLR (2024)	2	Secondary	Friedlander, M., Moore, K. N., Colombo, N., Scambia, G., Kim, B. G., Oaknin, A., ... & DiSilvestro, P. (2021). Patient-centred outcomes and effect of disease progression on health status in patients with newly diagnosed advanced ovarian cancer and a BRCA mutation receiving maintenance olaparib or placebo (SOLO1): a randomised, phase 3 trial. <i>The Lancet Oncology</i> , 22(5), 632-642.
Original SLR (2024)	2	Secondary	Wu, L., Zhu, J., Yin, R., Wu, X., Lou, G., Wang, J., ... & Zhang, J. (2021). Olaparib maintenance therapy in patients with newly diagnosed advanced ovarian cancer and a BRCA1 and/or BRCA2 mutation: SOLO1 China cohort. <i>Gynecologic Oncology</i> , 160(1), 175-181.

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

SLR search	Study ID	Primary/ secondary publication	Citation
Original SLR (2024)	2	Secondary	DiSilvestro, P., Colombo, N., Scambia, G., Kim, B. G., Oaknin, A., Friedlander, M., ... & Moore, K. N. (2020). Efficacy of maintenance olaparib for patients with newly diagnosed advanced ovarian cancer with a BRCA mutation: subgroup analysis findings from the SOLO1 trial. <i>Journal of Clinical Oncology</i> , 38(30), 3528-3537.
Original SLR (2024)	2	Secondary	Moore, K., Colombo, N., Scambia, G., Kim, B. G., Oaknin, A., Friedlander, M., ... & DiSilvestro, P. (2018). Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer. <i>New England Journal of Medicine</i> , 379(26), 2495-2505.
Original SLR (2024)	2	Secondary	Friedlander, M. L., Moore, K., Colombo, N., Scambia, G., Kim, B. G., Oaknin, A., ... & Disilvestro, P. (2020). 234O Maintenance olaparib for patients (pts) with newly diagnosed, advanced ovarian cancer (OC) and a BRCA mutation (BRCAm): 5-year (y) follow-up (f/u) from SOLO1. <i>Annals of Oncology</i> , 31, S1334.
Original SLR (2024)	2	Secondary	Colombo, N., Bradley, W., Moore, K., González-Martín, A., Scambia, G., Oaknin, A., ... & Disilvestro, P. (2020). 392 Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer and a BRCA mutation: subgroup analysis by risk in the phase III SOLO1 study. <i>International Journal of Gynecologic Cancer</i> 2020, 30, A76-A77.
Original SLR (2024)	2	Secondary	Bradley, W., Moore, K., Colombo, N., Scambia, G., Kim, B. G., Oaknin, A., ... & DiSilvestro, P. (2021). Maintenance olaparib for patients with newly diagnosed, advanced ovarian cancer and a BRCA mutation: 5-year follow-up from SOLO1. <i>Gynecologic Oncology</i> , 162, S25-S26.
Original SLR (2024)	3	Secondary	Boidot, R., Blum, M. G. B., Wissler, M. P., Gottin, C., Ruzicka, J., Duforet-Frebourg, N., ... & Pujade-Lauraine, E. (2023). 39MO Clinical evaluation of a low-coverage whole-genome test for homologous recombination deficiency detection in ovarian cancer. <i>ESMO Open</i> , 8(1).
Original SLR (2024)	3	Secondary	Harter, P., Petran, D., Scambia, G., Ortega, E., Tsibulak, I., Nagao, S., ... & Ray-Coquard, I. (2020). 18 Efficacy of maintenance olaparib plus bevacizumab by biomarker status in clinical higher-and lower-risk patients with newly diagnosed, advanced ovarian cancer in the PAOLA-1 trial. <i>International Journal of Gynecological Cancer</i> , 30(Suppl 3), A13-A14.

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

SLR search	Study ID	Primary/ secondary publication	Citation
Original SLR (2024)	3	Secondary	Schouten, P. C., Schmidt, S., Becker, K., Thiele, H., Nurnberg, P., Richters, L. K., ... & Schmutzler, R. K. (2023). Ovarian carcinoma patients with a tumor BRCA-like genomic copy number aberration profile benefit from maintenance olaparib/bevacizumab therapy in the PAOLA-1 randomized controlled trial. medRxiv, 2023-05.
Original SLR (2024)	3	Secondary	Randomized, Double-Blind, Phase III Trial of Olaparib vs Placebo added to Bevacizumab in Maintenance in Patients with Advanced Ovarian, Fallopian Tube, or Peritoneal Cancer after treatment with standard First-Line Treatment, Combining Platinum-Taxane Chemotherapy and concurrent Bevacizumab.
Original SLR (2024)	3	Secondary	Marchetti, C., Fagotti, A., Cassani, C., Incorvaia, L., Perri, M. T., Sassu, C. M., ... & Lorusso, D. (2023). 42P Efficacy of maintenance with PARPi in advanced ovarian cancer according to the location of BRCA mutation. ESMO Open, 8(1), 100822.
Original SLR (2024)	3	Primary	Lorusso, D., Mouret-Reynier, M. A., Harter, P., Cropet, C., Caballero, C., Wolfrum-Ristau, P., ... & Ray-Coquard, I. (2024). Updated progression-free survival and final overall survival with maintenance olaparib plus bevacizumab according to clinical risk in patients with newly diagnosed advanced ovarian cancer in the phase III PAOLA-1/ENGOT-ov25 trial. International Journal of Gynecologic Cancer, 34(4).
Original SLR (2024)	3	Secondary	Leman, R., Muller, E., Legros, A., Goardon, N., Chentli, I., Atkinson, A., ... & Vaur, D. (2023). Validation of the clinical use of GIScar, an academic-developed genomic instability score predicting sensitivity to maintenance olaparib for ovarian cancer. Clinical Cancer Research, 29(21), 4419-4429.
Original SLR (2024)	3	Secondary	Ray-Coquard, I., Leary, A., Pignata, S., Cropet, C., González-Martín, A., Marth, C., ... & Harter, P. (2023). Olaparib plus bevacizumab first-line maintenance in ovarian cancer: final overall survival results from the PAOLA-1/ENGOT-ov25 trial. Annals of Oncology, 34(8), 681-692.
Original SLR (2024)	3	Secondary	Pujade-Lauraine, E., Brown, J., Barnicle, A., Wessen, J., Lao-Sirieix, P., Criscione, S. W., ... & Ray-Coquard, I. (2023). Homologous Recombination Repair Gene Mutations to Predict Olaparib Plus Bevacizumab Efficacy in the First-Line Ovarian Cancer PAOLA-1/ENGOT-ov25 Trial. JCO Precision Oncology, 7, e2200258.

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

SLR search	Study ID	Primary/ secondary publication	Citation
Original SLR (2024)	3	Secondary	Sabatier, R., Rousseau, F., Joly, F., Cropet, C., Montégut, C., Frindte, J., ... & Ray-Coquard, I. (2023). Efficacy and safety of maintenance olaparib and bevacizumab in ovarian cancer patients aged $\geq$ 65 years from the PAOLA-1/ENGOT-ov25 trial. <i>European Journal of Cancer</i> , 181, 42-52.
Original SLR (2024)	3	Secondary	Labidi-Galy, S. I., Rodrigues, M., Sandoval, J. L., Kurtz, J. E., Heitz, F., Mosconi, A. M., ... & Ray-Coquard, I. L. (2023). Association of location of BRCA1 and BRCA2 mutations with benefit from olaparib and bevacizumab maintenance in high-grade ovarian cancer: phase III PAOLA-1/ENGOT-ov25 trial subgroup exploratory analysis. <i>Annals of Oncology</i> , 34(2), 152-162.
Original SLR (2024)	3	Secondary	González-Martín, A., Desauw, C., Heitz, F., Cropet, C., Gargiulo, P., Berger, R., ... & Ray-Coquard, I. (2022). Maintenance olaparib plus bevacizumab in patients with newly diagnosed advanced high-grade ovarian cancer: Main analysis of second progression-free survival in the phase III PAOLA-1/ENGOT-ov25 trial. <i>European Journal of Cancer</i> , 174, 221-231.
Original SLR (2024)	3	Secondary	Harter, P., Mouret-Reynier, M. A., Pignata, S., Cropet, C., González-Martín, A., Bogner, G., ... & Ray-Coquard, I. (2022). Efficacy of maintenance olaparib plus bevacizumab according to clinical risk in patients with newly diagnosed, advanced ovarian cancer in the phase III PAOLA-1/ENGOT-ov25 trial. <i>Gynecologic Oncology</i> , 164(2), 254-264.
Original SLR (2024)	3	Secondary	Ray-Coquard I, Pautier P, Pignata S, Pérol D, González-Martín A, Berger R, Fujiwara K, Vergote I, Colombo N, Mäenpää J, Selle F, Sehouli J, Lorusso D, Guerra Alía EM, Reinthaller A, Nagao S, Lefeuvre-Plesse C, Canzler U, Scambia G, Lortholary A, Marmé F, Combe P, de Gregorio N, Rodrigues M, Buderath P, Dubot C, Burges A, You B, Pujade-Lauraine E, Harter P; PAOLA-1 Investigators. Olaparib plus Bevacizumab as First-Line Maintenance in Ovarian Cancer. <i>N Engl J Med</i> . 2019 Dec 19;381(25):2416-2428. doi: 10.1056/NEJMoa1911361. PMID: 31851799.

SLR search	Study ID	Primary/ secondary publication	Citation
Original SLR (2024)	3	Secondary	Callens, C., Rodrigues, M. J., Briaux, A., Browaeys, E., Eeckhoutte, A., Pujade-Lauraine, E., ... & Popova, T. (2023). 38MO Validation study of the ShallowHRDv2 assay for homologous recombination deficiency (HRD) detection in high-grade ovarian carcinomas (HGOc) in the first-line setting, from the phase III PAOLA-1/ENGOT-ov25 trial. ESMO Open, 8(1).
Original SLR (2024)	3	Secondary	Fujiwara, K., Fujiwara, H., Yoshida, H., Satoh, T., Yonemori, K., Nagao, S., ... & Ray-Coquard, I. (2021). Olaparib plus bevacizumab as maintenance therapy in patients with newly diagnosed, advanced ovarian cancer: Japan subset from the PAOLA-1/ENGOT-ov25 trial. Journal of gynecologic oncology, 32(5).
Original SLR (2024)	3	Secondary	Nagao, S., Harter, P., Leary, A., Cropet, C., Pignata, S., Fujiwara, K., ... & Ray-Coquard, I. (2022). 176O Final overall survival (OS) results from the phase III PAOLA-1/ENGOT-ov25 trial evaluating maintenance olaparib (ola) plus bevacizumab (bev) in patients (pts) with newly diagnosed advanced ovarian cancer (AOC). Annals of Oncology, 33, S1503-S1504.
Original SLR (2024)	3	Secondary	Buisson, A., Lamkhioued, M., Constantoulakis, P., Oikonomak, K., Harter, P., Pignata, S., ... & Ray-Coquard, I. (2023). Retrospective blind assessment of SOPHiA DDMTM Dx HRD solution for evaluation of olaparib maintenance treatment efficacy in ovarian cancer patients from the randomized, phase III PAOLA-1 trial in: 35th European Congress of Pathology – Abstracts. Virchows Arch 483 (Suppl 1), S55-S56.
Original SLR (2024)	3	Secondary	Martin, A. G., Medioni, J., Harter, P., Cropet, C., Cinieri, S., Denison, U., ... & Ray-Coquard, I. L. (2023). 36MO Maintenance olaparib plus bevacizumab (bev) in patients (pts) with newly diagnosed advanced ovarian cancer (OC): 5-year (y) progression-free survival (PFS) by molecular subgroup in the PAOLA-1/ENGOT-ov25 trial. ESMO Open, 8(1).
Original SLR (2024)	3	Secondary	Lorusso, D., Mouret-Reynier, M. A., Harter, P., Cropet, C., Diaz, C. C., Petru, E., ... & Ray-Coquard, I. L. (2023). 32O 5-year (y) overall survival (OS) with maintenance olaparib (ola) plus bevacizumab (bev) by clinical risk in patients (pts) with newly diagnosed advanced ovarian cancer (AOC) in the phase III PAOLA-1/ENGOT-ov25 trial. ESMO Open, 8(1).

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

SLR search	Study ID	Primary/ secondary publication	Citation
Original SLR (2024)	3	Secondary	Colombo, N., Gantzer, J., Ataseven, B., Cropet, C., Scambia, G., Herrero, A., ... & Ray-Coquard, I. L. (2020). 812MO maintenance olaparib+ bevacizumab (bev) in patients (PTS) with newly diagnosed advanced high-grade ovarian cancer (HGOC): RECIST and/or CA-125 objective response rate (Orr) in the phase III PAOLA-1 trial. <i>Annals of Oncology</i> , 31, S614.
Original SLR (2024)	3	Secondary	Grimm, C., Cropet, C., & Ray-Coquard, I. (2020). Maintenance olaparib plus bevacizumab (bev) after platinum-based chemotherapy plus bev in patients (pts) with newly diagnosed advanced high-grade ovarian cancer (HGOC): Efficacy by timing of surgery and residual tumor status in the Phase III PAOLA-1 trial. <i>Gynecologic Oncology</i> , 159, 19.
Original SLR (2024)	3	Secondary	Hietanen, S., Pautier, P., Harter, P., Cropet, C., Cinieri, S., Caballero, C., ... & Ray-Coquard, I. (2021). RECIST/CA-125 progression-free survival and the role of CA-125 surveillance in the phase III PAOLA-1/ENGOT-ov25 trial evaluating maintenance olaparib plus bevacizumab in patients with newly diagnosed advanced high-grade ovarian carcinoma. <i>Gynecologic Oncology</i> , 162, S71.
Original SLR (2024)	3	Secondary	Sabatier, R., Rousseau, F., Joly, F., Cropet, C., Montegut, C., Frindte, J., ... & Ray-Coquard, I. L. (2021). 739P Efficacy and safety of maintenance olaparib and bevacizumab (bev) in ovarian cancer (OC) patients (pts) aged ≥ 65 years (y) from the PAOLA-1/ENGOT-ov25 first-line trial. <i>Annals of Oncology</i> , 32, S737-S738.
Original SLR (2024)	3	Secondary	Montégut, C., Falandry, C., Cinieri, S., Montane, L., Rousseau, F., Joly, F., ... & Sabatier, R. (2021). 167 Safety and quality of life of first-line maintenance olaparib plus bevacizumab in older patients with advanced ovarian cancer in the PAOLA-1 trial.
Original SLR (2024)	3	Secondary	Loverix, L., Vergote, I., Busschaert, P., Vanderstichele, A., Boeckx, B., Venken, T., ... & Van Gorp, T. (2022). Predictive value of the Leuven HRD test compared with Myriad myChoice PLUS on 468 ovarian cancer samples from the PAOLA-1/ENGOT-ov25 trial (LBA 6). <i>Gynecologic Oncology</i> , 166, S51-S52.

SLR search	Study ID	Primary/ secondary publication	Citation
Original SLR (2024)	3	Secondary	Kurtz, J. E., Anota, A., Cropet, C., Priou, F., Harter, P., Pignata, S., ... & Ray-Coquard, I. L. (2022). Quality of life in patients with advanced high-grade ovarian cancer (HGOc) receiving maintenance therapies after first-line (1L) chemotherapy in the randomized phase III PAOLA-1/ENGOT-ov25 trial (NCT02477644).
Original SLR (2024)	3	Secondary	Joly, F., Chabaud, S., Cropet, C., Anota, A., Demarchi, M., Atasevan, B., ... & Ray-Coquard, I. L. (2022). Time without symptoms or toxicity (TWiST) in patients with newly diagnosed advanced ovarian cancer receiving maintenance olaparib or placebo plus bevacizumab: Analysis of PAOLA-1/ENGOT-ov25 phase III trial. <i>Journal of Clinical Oncology</i> , 40(16).
Original SLR (2024)	3	Secondary	Labidi-Galy, S. I., Rodrigues, M., Sandoval, J. L., Kurtz, J. E., Heitz, F., Mosconi, A. M., ... & Ray-Coquard, I. (2022). Efficacy of maintenance olaparib plus bevacizumab in patients with newly diagnosed advanced ovarian cancer according to BRCA mutation genotype in the phase III PAOLA-1/ENGOT-ov25 trial. <i>J Clin Oncol</i> , 40, 5571.
Original SLR (2024)	3	Secondary	Pujade-Lauraine, E., Brown, J., Barnicle, A., Rowe, P., Lao-Sirieix, P., Criscione, S., ... & Ray-Coquard, I. (2021). Homologous recombination repair mutation gene panels (excluding BRCA) are not predictive of maintenance olaparib plus bevacizumab efficacy in the first-line PAOLA-1/ENGOT-ov25 trial. <i>Gynecologic Oncology</i> , 162, S26-S27.
Original SLR (2024)	3	Secondary	Pautier, P., Harter, P., Pisano, C., Cropet, C., Hernando Polo, S., Berger, R., ... & Ray-Coquard, I. L. (2021). Progression-free survival (PFS) and second PFS (PFS2) by disease stage in patients (pts) with homologous recombination deficiency (HRD)-positive newly diagnosed advanced ovarian cancer receiving bevacizumab (bev) with olaparib/placebo maintenance in the phase III PAOLA-1/ENGOT-ov25 trial. <i>Journal of Clinical Oncology</i> 39, no. 15_suppl, 5514-5514.
Original SLR (2024)	3	Secondary	Fujiwara, K., Fujiwara, H., Yoshida, H., Satoh, T., Yonemori, K., Nagao, S., ... & Ray-Coquard, I. L. (2020). 236O Olaparib (ola) plus bevacizumab (bev) as maintenance (mx) therapy in patients (pts) with newly diagnosed advanced ovarian carcinoma (OC): Japan subset of the PAOLA-1 trial. <i>Annals of Oncology</i> , 31, S1335-S1336.

SLR search	Study ID	Primary/ secondary publication	Citation
Original SLR (2024)	3	Secondary	Martín, A. G., Tazi, Y., Heitz, F., Montane, L., Gargiulo, P., Berger, R., ... & Ray-Coquard, I. L. (2020). LBA33 maintenance olaparib plus bevacizumab (bev) in patients (PTS) with newly diagnosed advanced high-grade ovarian carcinoma (HGOC): final analysis of second progression-free survival (Pfs2) in the phase III PAOLA-1/ENGOT-ov25 trial. <i>Annals of Oncology</i> , 31, S1163-S1164.
Original SLR (2024)	3	Secondary	Lorusso, D., Lotz, J. P., Harter, P., Cropet, C., Rubio Pérez, M. J., Schauer, C., ... & Ray-Coquard, I. L. (2020). Maintenance olaparib plus bevacizumab (bev) after platinum-based chemotherapy plus bev in patients (pts) with newly diagnosed advanced high-grade ovarian cancer (HGOC): Efficacy by BRCA1 or BRCA2 mutation in the phase III PAOLA-1 trial. <i>Journal of Clinical Oncology</i> 38, no. 15_suppl 6039-6039.
Original SLR (2024)	3	Secondary	Callens, C., Rodrigues, M., Briaux, A., Frouin, E., Eeckhoutte, A., Pujade-Lauraine, E., ... & Popova, T. (2023). Shallow whole genome sequencing approach to detect Homologous Recombination Deficiency in the PAOLA-1/ENGOT-OV25 phase-III trial. <i>Oncogene</i> , 42(48), 3556-3563.
SLR update (2025)	3	Secondary	Harter, P.,Marth, C.,Mouret-Reynier, M. A.,Cropet, C.,Lorusso, D.,Guerra-Alia, E. M.,Matsumoto, T.,Vergote, I.,Colombo, N.,Maenpaa, J.,Lebreton, C.,de Gregorio, N.,Mosconi, A. M.,Rubio-Perez, M. J.,Bourgeois, H.,Fasching, P. A.,Cecere, S. C.,Hardy-Bessard, A. C.,Denschlag, D.,de Percin, S.,Hanker, L.,Favier, L.,Bauerschlag, D.,Desauw, C.,Hillemanns, P.,Largillier, R.,Sehouli, J.,Grenier, J.,Pujade-Lauraine, E.,Ray-Coquard, I. Efficacy of subsequent therapies in patients with advanced ovarian cancer who relapse after first-line olaparib maintenance: results of the PAOLA-1/ENGOT-ov25 trial. <i>Annals of oncology : official journal of the European Society for Medical Oncology</i>
SLR update (2025)	3	Secondary	Schouten, P. C.,Schmidt, S.,Becker, K.,Thiele, H.,Nurnberg, P.,Richters, L.,Ernst, C.,Treilleux, I.,Medioni, J.,Heitz, F.,Pisano, C.,Garcia, Y.,Petru, E.,Hietanen, S.,Colombo, N.,Vergote, I.,Nagao, S.,Linn, S. C.,Pujade-Lauraine, E.,Ray-Coquard, I.,Harter, P.,Hahnen, E.,Schmutzler, R. K.. Olaparib Addition to Maintenance Bevacizumab Therapy in Ovarian Carcinoma with BRCA -Like Genomic Aberrations. <i>JAMA network open</i> . 2024;#Volume#():E245552.

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

SLR search	Study ID	Primary/ secondary publication	Citation
SLR update (2025)	3	Secondary	Montegut, C.,Falandry, C.,Cinieri, S.,Cropet, C.,Montane, L.,Rousseau, F.,Joly, F.,Moubarak, M.,Mosconi, A. M.,Guerra-Alia, E. M.,Schauer, C.,Fujiwara, H.,Vergote, I.,Parma, G.,Lindahl, G.,Anota, A.,Canzler, U.,Marme, F.,Pujade-Lauraine, E.,Ray-Coquard, I.,Sabatier, R.. Safety and quality of life with maintenance olaparib plus bevacizumab in older patients with ovarian cancer: subgroup analysis of PAOLA-1/ENGOT-ov25. Oncologist. 2024;#Volume#():#Pages#.
Original SLR (2024)	4	Secondary	Barretina-Ginesta, M. P.,Monk, B. J.,Han, S.,Pothuri, B.,Auranen, A.,Chase, D.,Lorusso, D.,Anderson, C.,Abadie-Lacourtoisie, S.,Cloven, N.,Braicu, E. I.,Amit, A.,Redondo, A.,Shah, R.,Kebede, N.,Hawkes, C.,Gupta, D.,Woodward, T.,O'Malley, D. M.,Gonzalez Martin, A. J.. Quality-adjusted time without symptom or toxicity (QA-TWiST) and quality-adjusted progression-free survival (QA-PFS) of first-line (1L) maintenance niraparib in patients with advanced ovarian cancer (OC): Results from the PRIMA trial. Annals of Oncology. 2021. 32:S736-S737
Original SLR (2024)	4	Secondary	Barretina-Ginesta, M. P.,Monk, B. J.,Han, S.,Pothuri, B.,Auranen, A.,Chase, D. M.,Lorusso, D.,Anderson, C.,Abadie-Lacourtoisie, S.,Cloven, N.,Braicu, E. I.,Amit, A.,Redondo, A.,Shah, R.,Kebede, N.,Hawkes, C.,Gupta, D.,Woodward, T.,O'Malley, D. M.,Gonzalez-Martin, A.. Quality-adjusted time without symptoms of disease or toxicity and quality-adjusted progression-free survival with niraparib maintenance in first-line ovarian cancer in the PRIMA trial. Therapeutic Advances in Medical Oncology. 2022. 14:#pages#
Original SLR (2024)	4	Secondary	Braicu, E. I.,Pothuri, B.,Perez-Fidalgo, J. A.,O'Malley, D.,Honhon, B.,Graybill, W.,Fabbro, M.,Dahlstrand, H.,Gupta, D.,Monk, B. J.. Efficacy of niraparib therapy in patients with newly diagnosed advanced ovarian cancer by brcawt status: Prima/engot-OV26/GOG-3012 study. International Journal of Gynecological Cancer. 2020. 30:A70-A71

SLR search	Study ID	Primary/ secondary publication	Citation
Original SLR (2024)	4	Secondary	Chase, D. M.,Romeo Marin, M.,Backes, F.,Han, S.,Graybill, W.,Lund, B.,Pothuri, B.,Mangili, G.,O'Malley, D.,Berton, D.,Willmott, L.,Baumann, K.,Coleman, R.,Safra, T.,Heinzelmann-Schwarz, V.,Lorusso, D.,Karl, F.,Woodward, T.,Monk, B. J.,Gonzalez-Martin, A.. Impact of disease progression on healthrelated quality of life of advanced ovarian cancer (AOC) patients-pooled analysis from the prima trial. International Journal of Gynecological Cancer. 2021. 31:A284
Original SLR (2024)	4	Secondary	Chase, D. M.,Marin, M. R.,Backes, F.,Han, S.,Graybill, W.,Mirza, M. R.,Pothuri, B.,Mangili, G.,O'Malley, D. M.,Berton, D.,Willmott, L.,Baumann, K.,Coleman, R. L.,Safra, T.,Heinzelmann-Schwarz, V.,Lorusso, D.,Karl, F. M.,Woodward, T.,Monk, B. J.,Gonzalez-Martin, A.. Impact of disease progression on health-related quality of life of advanced ovarian cancer patients - Pooled analysis from the PRIMA trial. Gynecologic Oncology. 2022. 166:494-502
Original SLR (2024)	4	Secondary	Freyer, G.,Pothuri, B.,Han, S.,Chase, D.,Monk, B.,Heitz, F.,Burger, R.,Gaba, L.,Van Le, L.,Guerra, E.,Bender, D.,Korach, J.,Cloven, N.,Churruca, C.,Follana, P.,DiSilvestro, P.,Baurain, J. F.,Jardon, K.,Pisano, C.,Peen, U.,Maenpaa, J.,Hoskins, P.,Bacque, E.,Li, Y.,Eliaison, L.,Gonzalez-Martin, A.. Safety and patient-reported outcomes in patients receiving niraparib in the prima/ENGOTOV26/ GOG-3012 trial. International Journal of Gynecological Cancer. 2020. 30:A12-A13
Original SLR (2024)	4	Secondary	González-Martín A, Pothuri B, Vergote I, DePont Christensen R, Graybill W, Mirza MR, McCormick C, Lorusso D, Hoskins P, Freyer G, Baumann K, Jardon K, Redondo A, Moore RG, Vulsteke C, O'Cearbhaill RE, Lund B, Backes F, Barretina-Ginesta P, Haggerty AF, Rubio-Pérez MJ, Shahin MS, Mangili G, Bradley WH, Bruchim I, Sun K, Malinowska IA, Li Y, Gupta D, Monk BJ; PRIMA/ENGOT-OV26/GOG-3012 Investigators. Niraparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. N Engl J Med. 2019 Dec 19;381(25):2391-2402. doi: 10.1056/NEJMoa1910962. Epub 2019 Sep 28. PMID: 31562799.

SLR search	Study ID	Primary/ secondary publication	Citation
Original SLR (2024)	4	Secondary	Gonzalez Martin, A. J.,Pothuri, B.,Vergote, I. B.,Graybill, W.,Mirza, M. R.,McCormick, C.,Lorusso, D.,Freyer, G.,Backes, F.,Baumann, K. H.,Redondo Sanchez, A.,Moore, R. G.,Vulsteke, C.,O'Cearbhaill, R. E.,Malinowska, I.,Shtessel, L.,Compton, N.,Monk, B. J.. PRIMA/ENGOT-OV26/GOG-3012 study: Updated long-term PFS and safety. Annals of Oncology. 2022. 33:S789
Original SLR (2024)	4	Secondary	González-Martín, A., Pothuri, B., Vergote, I., Graybill, W., Lorusso, D., McCormick, C. C., ... & Monk, B. J. (2023). Progression-free survival and safety at 3.5 years of follow-up: results from the randomised phase 3 PRIMA/ENGOT-OV26/GOG-3012 trial of niraparib maintenance treatment in patients with newly diagnosed ovarian cancer. European Journal of Cancer, 189, 112908.
SLR update (2025)	4	Secondary	Gonzalez-Martin, A.,Pothuri, B.,Barretina Ginesta, M. P.,Graybill, W. S.,Vergote, I. B.,McCormick, C.,Mirza, M. R.,Moore, R. G.,Lorusso, D.,O'Cearbhaill, R. E.,Freyer, G.,O'Malley, D. M.,Heitz, F.,Shahin, M. S.,Bruchim, I.,Bradley, W. H.,Compton, N.,Malinowska, I.,Redondo, A.,Monk, B. J.. LBA29 Final overall survival (OS) in patients (pts) with newly diagnosed advanced ovarian cancer (aOC) treated with niraparib (nir) first-line (1L) maintenance: results from PRIMA/ENGOT-OV26/GOG-3012. Ann Oncol. 2024;35():S1222.
Original SLR (2024)	4	Secondary	W. Graybill, M. Mirza, A. González-Martín, D. O'Malley, L. Gaba, O.W.S. Yap, E. Guerra, P.G. Rose, J. Baurain, S. Ghamande, H. Denys, E. Prendergast, C. Pisano, P. Follana, E.I. Braicu, P.M. Calvert, J. Korach, Y. Li, D. Gupta, B.J. Monk, 13 Efficacy on individualized starting dose (ISD) and fixed starting dose (FSD) of niraparib per investigator-assessment (IA) in newly diagnosed advanced ovarian cancer (OC), International Journal of Gynecological Cancer, Volume 30, Supplement 3, 2020, Page A10, ISSN 1048-891X, https://doi.org/10.1136/ijgc-2020-IGCS.13 . (https://www.sciencedirect.com/science/article/pii/S1048891X2409145X)

SLR search	Study ID	Primary/ secondary publication	Citation
SLR update (2025)	4	Secondary	Graybill, W. S.,Pardo Burdalo, B.,O'Malley, D. M.,Vergote, I.,Monk, B. J.,Auranen, A.,Copeland, L. J.,Sabbatini, R.,Herzog, T. J.,Follana, P.,Pothuri, B.,Braicu, E. I.,McCormick, C.,Yubero, A.,Moore, R. G.,Vuylsteke, P.,Raaschou-Jensen, N.,York, W.,Hartman, J.,Gonzalez-Martin, A.. Predictors of long-term progression-free survival in patients with ovarian cancer treated with niraparib in the PRIMA/ENGOT-OV26/GOG-3012 study. Int J Gynecol Cancer. 2024;34(7):1041 EP - 1050.
Original SLR (2024)	4	Secondary	Han, S. N.,Monk, B. J.,Gonzalez-Martin, A.. Time to first subsequent therapy (TFST) and progression-free survival 2 (PFS2) from the phase 3 randomized, double-blind PRIMA/ENGOT-OV26/GOG-3012 study in patients with newly diagnosed ovarian cancer. Gynecologic Oncology. 2020. 159:18-19
SLR update (2025)	4	Secondary	Haslund, C. A.,Willmott, L. J.,Perez, M. J. R.,Cloven, N.,Van den Bulck, H. F. M.,Moore, R. G.,Pisano, C.,O'Cearbhaill, R. E.,Selle, F.,Pothuri, B.,Harter, P.,Ghamande, S.,Bruchim, I.,Disilvestro, P.,Ginesta, M. P. B.,Koliadi, A.,Malinowska, I.,York, W.,Gonzalez-Martin, A.,Monk, B. J.. 51P Efficacy and safety by time to maintenance therapy treatment initiation in PRIMA/ENGOT-OV26/GOG-3012. ESMO open. 2024;9():#Pages#.
Original SLR (2024)	4	Secondary	Herzog, Thomas et al.. EP224/#531 Optimization of assessment of disease progression between blinded central independent review and investigator assessment in the PRIMA/ENGOT-ov26/GOG-3012 trial. International Journal of Gynecological Cancer, Volume 32, A140 - A141
Original SLR (2024)	4	Secondary	Herzog, T. J., Wahab, S. A., Mirza, M. R., Pothuri, B., Vergote, I., Graybill, W. S., ... & Monk, B. J. (2023). Optimizing disease progression assessment using blinded central independent review and comparing it with investigator assessment in the PRIMA/ENGOT-ov26/GOG-3012 trial: challenges and solutions. International Journal of Gynecologic Cancer, 33(11).
Original SLR (2024)	4	Secondary	Martin, A. G., Pothuri, B., Vergote, I. B., Graybill, W., Mirza, M. R., McCormick, C., ... & Monk, B. J. (2023). 330 PRIMA/ENGOT-OV26/GOG-3012 study: long-term conditional PFS. ESMO Open, 8(1).

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

SLR search	Study ID	Primary/ secondary publication	Citation
Original SLR (2024)	4	Secondary	Mirza, M. R., Martin, A. G., Graybill, W., O'Malley, D. M., Gaba, L., Yap, O. W. S., Guerra, E. M., Rose, P. G., Baurain, J. F., Ghamande, S. A., Denys, H., Prendergast, E., Pisano, C., Follana, P., Baumann, K., Calvert, P., Korach, J., Li, Y., Gupta, D., Monk, B. J.. Evaluation of an individualized starting-dose of niraparib in the PRIMA/ENGOT-OV26/GOG-3012 study. <i>Journal of Clinical Oncology</i> . 2020. 38:#pages#
Original SLR (2024)	4	Secondary	Mirza, M. R., González-Martín, A., Graybill, W. S., O'Malley, D. M., Gaba, L., Stephanie Yap, O. W., ... & Monk, B. J. (2023). Prospective evaluation of the tolerability and efficacy of niraparib dosing based on baseline body weight and platelet count: Results from the PRIMA/ENGOT-OV26/GOG-3012 trial. <i>Cancer</i> , 129(12), 1846-1855.
Original SLR (2024)	4	Secondary	Monk, B. J., Martin, A. G.. Efficacy of niraparib therapy in patients with newly diagnosed advanced ovarian cancer by BRCA and homologous recombination status: PRIMA/ENGOT-OV26/GOG-3012 study. <i>Gynecologic Oncology</i> . 2020. 159:18
SLR update (2025)	4	Primary	Monk, B. J., Barretina-Ginesta, M. P., Pothuri, B., Vergote, I., Graybill, W., Mirza, M. R., McCormick, C. C., Lorusso, D., Moore, R. G., Freyer, G., O'Cearbhaill, R. E., Heitz, F., O'Malley, D. M., Redondo, A., Shahin, M. S., Vulsteke, C., Bradley, W. H., Haslund, C. A., Chase, D. M., Pisano, C., Holman, L. L., eacute,, rez, M. J. R., DiSilvestro, P., Gaba, L., Herzog, T. J., Bruchim, I., Compton, N., Shtessel, L., Malinowska, I. A., Gonz,, aacute,, lez, Mart, iacute,, n, A.. Niraparib first-line maintenance therapy in patients with newly diagnosed advanced ovarian cancer: final overall survival results from the PRIMA/ENGOT-OV26/GOG-3012 trial. <i>Annals of oncology : official journal of the European Society for Medical Oncology</i> . 2024;35(11):981.
Original SLR (2024)	4	Secondary	A Study of Niraparib Maintenance Treatment in Patients With Advanced Ovarian Cancer Following Response on Front-Line Platinum-Based Chemotherapy. A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study of Niraparib Maintenance Treatment in Patients With Advanced Ovarian Cancer Following Response on Front-Line Platinum-Based Chemotherapy. https://clinicaltrials.gov/ct2/show/NCT02655016

SLR search	Study ID	Primary/ secondary publication	Citation
Original SLR (2024)	4	Secondary	A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study of Niraparib Maintenance Treatment in Patients with Advanced Ovarian Cancer Following Response on Front-Line Platinum-Based Chemotherapy. https://www.clinicaltrialsregister.eu/ctr-search/trial/2015-000952-11/results
Original SLR (2024)	4	Secondary	O'Cearbhaill, R.,Perez-Fidalgo, J. A.,Monk, B. J.,Vulsteke, C.,McCormick, C.,Hietanen, S.,Moore, R. G.,Artioli, G.,Shahin, M. S.,Selle, F.,Bradley, W. H.,Baumann, K.,O'Malley, D.,Tusquets, I.,Slomovitz, B. M.,Levy, T.,Joly, F.,Malinowska, I.,Gupta, D.,Gonzalez-Martin, A.. Efficacy of niraparib by timing of surgery and residual disease: A post-hoc analysis of patients in the prima/engot-ov26/gog-3012 study. International Journal of Gynecological Cancer. 2021. 31:A203-A204
Original SLR (2024)	4	Secondary	O'Cearbhaill, R. E.,Perez-Fidalgo, J. A.,Monk, B. J.,Tusquets, I.,McCormick, C.,Fuentes, J.,Moore, R. G.,Vulsteke, C.,Shahin, M. S.,Forget, F.,Bradley, W. H.,Hietanen, S.,O'Malley, D. M.,Dorum, A.,Slomovitz, B. M.,Baumann, K.,Selle, F.,Calvert, P. M.,Artioli, G.,Levy, T.,Kumar, A.,Malinowska, I. A.,Li, Y.,Gupta, D.,Gonzalez-Martin, A.. Efficacy of niraparib by time of surgery and postoperative residual disease status: A post hoc analysis of patients in the PRIMA/ENGOT-OV26/GOG-3012 study. Gynecologic Oncology. 2022. 166:36-43
Original SLR (2024)	4	Secondary	Pothuri, B.,Han, S.,Chase, D.,Heitz, F.,Burger, R.,Gaba, L.,Van Le, L.,Guerra, E.,Bender, D.,Korach, J.,Cloven, N. G.,Follana, P.,Baurain, J. F.,Pisano, C.,Peen, U.,Maenpaa, J.,Bacque, E.,Li, Y.,Martin, A. G.,Monk, B. J.. Patient-reported outcomes (PROs) in patients (pts) receiving niraparib in the PRIMA/ENGOT-OV26/GOG-3012 trial. Annals of Oncology. 2020. 31:S612-S613
Original SLR (2024)	4	Secondary	Pothuri, B., Han, S., Chase, D. M., Heitz, F., Burger, R. A., Gaba, L., ... & González-Martín, A. (2024). Health-related quality of life in patients with newly diagnosed advanced ovarian cancer treated with niraparib vs placebo: Results from the phase 3 randomized PRIMA/ENGOT-OV26/GOG-3012 trial. Gynecologic oncology, 184, 168-177.

SLR search	Study ID	Primary/ secondary publication	Citation
Original SLR (2024)	4	Secondary	Valabrega, G., Pothuri, B., Oaknin, A., Graybill, W., Sánchez, A. B., McCormick, C., ... & Martín, A. G. (2020). 819P Efficacy and safety of niraparib in older patients (pts) with advanced ovarian cancer (OC): Results from the PRIMA/ENGOT-OV26/GOG-3012 trial. <i>Annals of Oncology</i> , 31, S619.
Original SLR (2024)	4	Secondary	Valabrega, G., et al. 2024. Examining health-related quality-of-life outcomes in older patients with advanced ovarian cancer treated with niraparib first-line maintenance therapy in context with efficacy and safety findings: results from the PRIMA/ENGOT-OV26/GOG-3012 Trial
SLR update (2025)	4	Secondary	Valabrega, G., Pothuri, B., Oaknin, A., Graybill, W. S., Sánchez, A. B., McCormick, C., Baurain, J. F., Tinker, A. V., Denys, H., O'Cearbhaill, R. E., Hietanen, S., Moore, R. G., Knudsen, A., Oslash, de La Motte Rouge, T., Heitz, F., Levy, T., York, W., Gupta, D., Monk, B. J., González, M., Martínez, A. Efficacy and safety of niraparib in patients aged 65 years and older with advanced ovarian cancer: results from the PRIMA/ENGOT-OV26/GOG-3012 trial. <i>Gynecol Oncol.</i> 2024;187():128.
Original SLR (2024)	4	Secondary	Vulsteke, C. et al., 2024. Tolerability of the niraparib individualised starting dose in the PRIMA/ENGOT-OV26/GOG-3012 trial of niraparib first-line maintenance therapy
SLR update (2025)	4	Secondary	Vulsteke, C., Chambers, S. K., Rez, M. J. R., Chan, J. K., Raaschou-Jensen, N., Zhuo, Y., Lorusso, D., Herzog, T. J., de la Motte Rouge, T., Thomes Pepin, J. A., Braicu, E. I., Chen, L. M., Levy, T., Barter, J. F., Pilar Barretina-Ginesta, M., Joosens, E., York, W., Malinowska, I. A., González, M., Martínez, A., Monk, B. J.. Tolerability of the niraparib individualized starting dose in the PRIMA/ENGOT-OV26/GOG-3012 trial of niraparib first-line maintenance therapy. <i>European journal of cancer (Oxford, England: . 2024;208():114157.</i>
Original SLR (2024)	5	Secondary	Wang, J., Wu, L., Zhu, J., Yin, R., Pan, L., Kong, B., Zheng, H., Liu, J., Wu, X., Wang, L., Huang, Y., Wang, K., Zou, D., Zhao, H., Wang, C., Lu, W., Lin, A., Zhen, X., Hang, W., Hou, J.. IMPACT OF INITIATION TIMING OF NIRAPARIB MAINTENANCE TREATMENT IN NEWLY DIAGNOSED ADVANCED OVARIAN CANCER. <i>International journal of gynecological cancer.</i> 2022. 32:A174

SLR search	Study ID	Primary/ secondary publication	Citation
Original SLR (2024)	5	Primary	Li, N., Zhu, J., Yin, R., Wang, J., Pan, L., Kong, B., ... & Wu, L. (2023). Treatment with niraparib maintenance therapy in patients with newly diagnosed advanced ovarian cancer: a phase 3 randomized clinical trial. JAMA oncology, 9(9), 1230-1237.
Original SLR (2024)	5	Secondary	Li, N.,Zhu, J.,Yin, R.,Wang, J.,Pan, L.,Kong, B.,Zheng, H.,Liu, J.,Wu, X.,Wang, L.,Huang, Y.,Wang, K.,Zou, D.,Zhao, H.,Wang, C.,Lu, W.,Lin, A.,Lou, G.,Li, G.,Qu, P.,Yang, H.,Zhen, X.,Hang, W.,Hou, J.,Wu, L.. Efficacy and safety of niraparib as maintenance treatment in patients with newly diagnosed advanced ovarian cancer using an individualized starting dose (PRIME Study): A randomized, double-blind, placebo-controlled, phase 3 trial (LBA 5). Gynecologic Oncology. 2022. 166:S50-S51
Original SLR (2024)	5	Secondary	Zhu, J., Wu, L., Yin, R., Wang, J., Pan, L., Kong, B., ... & Hou, J. (2023). Impact of dose modifications due to treatment-emergent adverse events (TEAEs) on the efficacy of niraparib maintenance treatment with an individualized starting dose in patients (Pts) with newly diagnosed advanced ovarian cancer (aOC)(1266). Gynecologic Oncology, 176, S168-S169.
Original SLR (2024)	5	Secondary	Pan, L., Wu, L., Zhu, J., Yin, R., Wang, J., Kong, B., ... & Hou, J. (2023). 37MO Niraparib maintenance therapy in patients with newly diagnosed advanced ovarian cancer: A post hoc analysis on efficacy by surgical timing and residual disease status in the phase III PRIME trial. ESMO Open, 8(1).
Original SLR (2024)	5	Secondary	Yin, R.,Li, N.,Wu, L.,Wang, J.,Zhu, J.,Pan, L.,Kong, B.,Zheng, H.,Liu, J.,Wu, X.,Wang, L.,Huang, Y.,Wang, K.,Zou, D.,Zhao, H.,Wang, C.,Lu, W.,Zhen, X.,Hang, W.,Hou, J.. Efficacy of niraparib maintenance therapy in patients with newly diagnosed advanced ovarian cancer in phase 3 PRIME study: A subgroup analysis by response to first-line platinum-based chemotherapy. Journal of Clinical Oncology. 2022. 40:#pages#
Original SLR (2024)	6	Secondary	Hardesty, M., Krivak, T., Wright, G., Hamilton, E., Fleming, E., Belotte, J., ... & Richardson, D. (2021). Phase II OVARIO study of niraparib+ bevacizumab therapy in advanced ovarian cancer following front-line platinum-based chemotherapy with bevacizumab. Gynecologic Oncology, 162, S17.

SLR search	Study ID	Primary/ secondary publication	Citation
Original SLR (2024)	6	Primary	Hardesty, M. M., Krivak, T. C., Wright, G. S., Hamilton, E., Fleming, E. L., Belotte, J., ... & Richardson, D. L. (2022). OVARIO phase II trial of combination niraparib plus bevacizumab maintenance therapy in advanced ovarian cancer following first-line platinum-based chemotherapy with bevacizumab. <i>Gynecologic oncology</i> , 166(2), 219-229.
Original SLR (2024)	6	Secondary	Hardesty, M., Krivak, T., Wright, G., Hamilton, E., Fleming, E., Belotte, J., ... & Richardson, D. (2022). OVARIO, A Phase 2 Study of Niraparib+ Bevacizumab in Advanced Ovarian Cancer Following Front-Line Platinum-Based Chemotherapy with Bevacizumab: Updated Analysis (039). <i>Gynecologic Oncology</i> , 166, S27-S28.
Original SLR (2024)	7	Secondary	Wu, X., Liu, J., Wang, X., Wang, J., Wang, L., Zhu, J., ... & Pan, H. (2023). PO012LBA/# 1511 Flames: randomized phase 3 trial of maintenance senaparib in patients with newly diagnosed advanced ovarian cancer. <i>International Journal of Gynecologic Cancer</i> , 33, A10-A11.
Original SLR (2024)	7	Secondary	Wu, X., Liu, J., Wang, X., Wang, J., Wang, L., Zhu, J., ... & Lou, G. (2023). LBA36 Efficacy and safety of senaparib as maintenance treatment in patients with newly diagnosed advanced ovarian cancer (FLAMES study): A randomized, double-blind, placebo-controlled, phase III trial. <i>Annals of Oncology</i> , 34, S1277-S1278.
SLR update (2025)	7	Primary	Wu, X.,Liu, J.,Wang, J.,Wang, L.,Lin, Z.,Wang, X.,Zhu, J.,Kong, B.,Fei, J.,Tang, Y.,Xia, B.,Liang, Z.,Wang, K.,Huang, Y.,Zheng, H.,Lin, A.,Jiang, K.,Wang, W.,Wang, X.,Lou, G.,Pan, H.,Yao, S.,Li, G.,Hao, M.,Cai, Y.,Chen, X.,Yang, Z.,Chen, Y.,Wen, H.,Qu, P.,Xu, C.,Hsieh, C. Y.,Flames Investigators. Senaparib as first-line maintenance therapy in advanced ovarian cancer: a randomized phase 3 trial. <i>Nat Med</i> . 2024;30(6):1612.
SLR update (2025)	8	Primary	Oda, K.,Shintani, D.,Mori, M.,Matsumura, N.,Kato, K.,Nagao, S.,Kagabu, M.,Takenaka, M.,Yoshihara, K.,Konno, Y.,Hamanishi, J.,Nishijima, A.,Sato, S.,Ueda, K.,Kashiwabara, K.,Aoki, T.,Nishimura, K.,Tatsuno, K.,Aburatani, H.,Hasegawa, K.. A phase II study of the efficacy of olaparib maintenance monotherapy for patients with HRD-positive, newly diagnosed, advanced, high-grade ovarian cancer, evaluated by whole-exome sequencing (MSBM-OL). <i>Ann Oncol</i> . 2024;35(Supplement 2):S585.

SLR search	Study ID	Primary/ secondary publication	Citation
Original SLR (2024)	9	Primary	Hannaway, N., Kassaris, S., Davies, J., Smrke, A., Tinker, A., & Drew, Y. (2023). EP244/# 277 Examining real-world treatment benefits of first-line maintenance niraparib in non-BRCA mutant high grade serous ovarian cancers. International Journal of Gynecologic Cancer, 33, A178.
Original SLR (2024)	10	Primary	de la Motte Rouge, T., Selle, F., Kfoury, M., Fumet, J. D., Frenel, J. S., Wasserman, J., ... & Pautier, P. (2022). 2022-RA-1134-ESGO First real-life data on niraparib maintenance in newly-diagnosed advanced ovarian cancer: a descriptive analysis of the Temporary Authorisation for Use (ATU) cohort. International Journal of Gynecologic Cancer, 32, A303-A304.
Original SLR (2024)	11	Primary	Wenxin, L., Wang, K., Zhang, L., Ma, Y., Wu, H., Chen, Y., ... & Fu, X. (2023). 315P Real-world experience of niraparib as maintenance therapy in newly diagnosed advanced ovarian cancer: A single-center retrospective study. Annals of Oncology, 34, S1594.
Original SLR (2024)	12	Primary	Li, J., Wu, X., Shou, H., Zheng, F., Huang, X., Liu, F., ... & Zhang, L. (2022). Real-world outcomes of niraparib treatment in patients with ovarian cancer: The first observational multicenter study in China. Journal of Clinical Oncology, 40(16 Suppl).
Original SLR (2024)	13	Primary	Zhao, M., Qiu, S., Wu, X., Miao, P., Jiang, Z., Zhu, T., ... & Shen, Y. (2023). Efficacy and Safety of Niraparib as First-Line Maintenance Treatment for Patients with Advanced Ovarian Cancer: Real-World Data from a Multicenter Study in China. Targeted Oncology, 18(6), 869-883.
Original SLR (2024)	14	Primary	Shin, W., Noh, J. J., Baek, S. H., Kim, B. G., Lim, M. C., & Park, S. Y. (2021). Real-world experience of niraparib in newly-diagnosed epithelial ovarian cancer. Anticancer Research, 41(9), 4603-4607.
Original SLR (2024)	15	Primary	Apostol, A. I., Sassu, C. M., Lardino, S., Boccia, S. M., Corrado, G., Palluzzi, E., ... & Marchetti, C. (2023). # 709 The effects of niraparib dose reduction on long-term outcomes in ovarian cancer patients: a large retrospective, observational study. International Journal of Gynecologic Cancer, 33, A23.

SLR search	Study ID	Primary/ secondary publication	Citation
Original SLR (2024)	16	Secondary	Lorusso, D., Gourley, C., Garbay, D., Asselain, B. J. R., Raspagliesi, F., Zamagni, C., ... & Miller, R. (2022). 2022-RA-944-ESGO Real-world safety, baseline characteristics and first-year therapy management in patients with BRCA1/BRCA2-mutated advanced ovarian cancer treated with olaparib tablets in the first-line maintenance setting: first analysis of the pan-European OVAL-1 study.
Original SLR (2024)	16	Primary	Lorusso, D.M.P., Villanucci, A.M., Scalone, S.M.,...& Padrone, C. (2022). OLAPARIB FIRST-LINE (1L) MAINTENANCE THERAPY IN BRCA1/BRCA2-MUTATED (BRCAM) ADVANCED OVARIAN CANCER (OC) PATIENTS (PTS): REAL-WORLD SAFETY PROFILE OF FIRST YEAR TREATMENT IN ITALY (PART OF THE OVAL-1 STUDY). Tumori, 108(4 Supplement), 87-88.
Original SLR (2024)	17	Primary	Kim, J. H., Kim, S. I., Park, E. Y., Kim, E. T., Kim, H., Kim, S., ... & Lim, M. C. (2024). Comparison of survival outcomes between olaparib and niraparib maintenance therapy in BRCA-mutated, newly diagnosed advanced ovarian cancer. Gynecologic Oncology, 181, 33-39.
Original SLR (2024)	18	Secondary	Li, J., Youguo, C., Mian, H., Chen, X., Wen, H., Kang, Y., ... & Lin, Z. (2023). 316P First evidence of olaparib maintenance therapy in patients with newly diagnosed BRCA wild-type ovarian cancer: A real-world multicenter study. Annals of Oncology, 34, S1594-S1595.
SLR update (2025)	18	Primary	Li, J.,Chen, Y.,He, M.,Chen, X.,Wen, H.,Kang, Y.,Liu, K.,Lou, G.,Wang, X.,Wen, Q.,Wang, L.,Lin, Z.. First evidence of olaparib maintenance therapy in patients with newly diagnosed homologous recombination deficient positive/BRCA wild-type ovarian cancer: real-world multicenter study. Front Med. 2024;#Volume#():#Pages#.
Original SLR (2024)	19	Primary	Bellier, C., Gladiëff, L., Le Du, F., Berton, D., Bonnard, C., Suau, D., ... & Kfoury, M. (2023). Olaparib First-Line Maintenance Monotherapy in BRCA-Mutated Epithelial Ovarian Cancer: Descriptive Analysis of the First French Real-World Data Study. Drugs-Real World Outcomes, 10(2), 207-213.

SLR search	Study ID	Primary/ secondary publication	Citation
Original SLR (2024)	19	Secondary	Bellier, C., Gladieff, L., Le Du, F., Tixidre, C. G., Berton-Rigaud, D., Bonnard, C., ... & Kfoury, M. (2020). 827P First real-life data on olaparib in 1st line (1stL) maintenance BRCA1/2 mutated epithelial ovarian cancer (EOC) in France: Descriptive analysis of 201 patients (pts) enrolled in the cohort temporary authorization for use (ATUc). Annals of Oncology, 31, S623-S624.
Original SLR (2024)	20	Primary	Zheng, H., Gao, Y., Guo, H., Li, L., Li, Q., Cui, H., ... & Bai, W. (2021). Real-world experience of olaparib treatment in patients with ovarian cancer: a Chinese multicenter study. Molecular Cancer Therapeutics, 20(9), 1735-1742.
SLR update (2025)	21	Secondary	Backes, F. J., Calderón Boyle, T. A., Lim, J., Hartman, J., Schilder, J. M., Hurteau, J. A., Perhanidis, J., Golembesky, A., & Salani, R. (2025). Real-world duration of first-line maintenance niraparib monotherapy in patients with epithelial ovarian cancer in the United States: the CHAR1ZMA study. International journal of gynecological cancer : official journal of the International Gynecological Cancer Society, 35(2), 100044. https://doi.org/10.1016/j.ijgc.2024.100044
Original SLR (2024)	21	Secondary	Backes, F., Boyle, T., Perhanidis, J., Lim, J., Hartman, J., Schilder, J. M., ... & Salani, R. (2023). 789P Real-world (RW) duration of treatment in first-line maintenance (1Lm) niraparib monotherapy in epithelial ovarian cancer (EOC): CHAR1ZMA study. Annals of Oncology, 34, S530.
Original SLR (2024)	21	Secondary	Coleman, R. L., Salani, R., Boyle, T., Perhanidis, J., Lim, J., Kalilani, L., ... & Backes, F. (2023). 43P Time to next treatment (TTNT) of first-line maintenance (1Lm) niraparib monotherapy in epithelial ovarian cancer (EOC) patients (pts) in the CHAR1ZMA study. ESMO Open, 8(1), 100823.
Original SLR (2024)	21	Secondary	Real-world progression-free survival in patients with homologous recombination-deficient epithelial ovarian cancer who received niraparib first-line maintenance therapy in the CHAR1ZMA Study

SLR search	Study ID	Primary/ secondary publication	Citation
SLR update (2025)	21	Primary	Salani R, Calderón Boyle TA, Lim J, Schilder JM, Hurteau JA, Perhanidis J, Golembesky A, Backes FJ. Real-world outcomes of first-line maintenance niraparib monotherapy in patients with epithelial ovarian cancer. <i>Future Oncol.</i> 2025 Jan;21(2):213-219. doi: 10.1080/14796694.2024.2441654. Epub 2025 Jan 17. PMID: 39819260; PMCID: PMC11792861.
Original SLR (2024)	22	Primary	Chen, J., Zhang, M., Li, K., Duan, Y., Zeng, J., Li, Q., ... & Yin, R. (2024). PARP inhibitor maintenance treatment for newly diagnosed ovarian cancer patients: a real-world study from China. <i>Frontiers in Oncology</i> , 14.
SLR update (2025)	23	Primary	Veljovich, D. S., Penson, R. T., Birrer, M. J., Luo, L., Pyrh, N., Pack, S., lu, C., Hada, M.. Real-world biomarker testing, treatment patterns and outcomes in a US cohort of patients with advanced ovarian cancer. <i>J Clin Oncol.</i> 2024;42(16 Supplement):#Pages#.
Original SLR (2024)	24	Secondary	Characteristics and real-world outcomes of patients with epithelial ovarian cancer who received niraparib plus bevacizumab first-line maintenance therapy in the COMB1NE Study
SLR update (2025)	24	Primary	Thaker, P. H., Boyle, T. A. C., Burns, S., Lim, J., Hartman, J., Kalilani, L. V., Schilder, J. M., Hurteau, J. A., Golembesky, A. K.. Characteristics and real-world outcomes of patients with epithelial ovarian cancer who received niraparib plus bevacizumab first-line maintenance therapy in the COMB1NE study. <i>Int J Gynecol Cancer.</i> 2024;34(12):1924
SLR update (2025)	25	Primary	Chase, D. M., Hanna, M., Lim, J. T., Boyle, T. A. C., Guinter, M., Richey, M., Patel, K., Schilder, J. M., Hurteau, J. A., Golembesky, A. K.. Niraparib as First-Line Maintenance Therapy in Patients with Stage III Ovarian Cancer and No Visible Residual Disease: AR1ZE Real-World Study. <i>Oncology and Therapy.</i> 2025;#Volume#():e104.
Original SLR (2024)	25	Secondary	The potential impact of excluding patients with stage III epithelial ovarian cancer and no postoperative visible residual disease from the PRIMA/ENGOT-OV26/GOG-3012 Trial: The AR1ZE real-world study of niraparib first-line maintenance therapy
Original SLR (2024)	26	Primary	Real-world time-to-event outcomes in patients with ovarian cancer receiving olaparib maintenance therapy in the United States

SLR search	Study ID	Primary/ secondary publication	Citation
Original SLR (2024)	27	Primary	Real world outcomes of first line maintenance Niraparib in advanced high grade serous ovarian cancers - A single centre experience
Original SLR (2024)	28	Primary	Roy, S., Ghosh, J., Bhattacharjee, A., Ganguly, S., Biswas, B., Patel, Y. S., ... & Chakraborti, B. (2023). 287MO Real-world experience with maintenance PARP inhibitor plus minus bevacizumab in newly diagnosed advanced ovarian cancer with germline BRCA mutations or homologous recombination deficiency (HRD) positive. Annals of Oncology, 34, S1585.
SLR update (2025)	29	Secondary	Zheng, Z.,Zuo, J.,Wang, K.,Zhumei, C.,Li, Q.,Xiaodong, C.,Sun, L. X.,Hui, Z.,Zhang, J.,Wang, S.,Cao, D.,Chen, L.,Zhao, H.,Duan, W.,Zheng, M.,Shou, H.,Li, J.,Wang, Y.,Wu, L.. RENI-1 efficacy and safety of niraparib as first-line maintenance therapy in newly diagnosed ovarian cancer: A prospective, multicenter real-world study, updated in 24-month follow-up. Ann Oncol. 2024;35(Supplement 4):S1549.
Original SLR (2024)	29	Primary	RENI-1: a prospective, multicenter real-world study of niraparib as first-line maintenance therapy in newly diagnosed advanced ovarian cancer
Original SLR (2024)	30	Primary	Efficacy of bevacizumab versus PARP inhibitors as maintenance therapy after first-line platinum-based chemotherapy for homologous recombination proficient, advanced high-grade ovarian cancer patients: a retrospective study
Original SLR (2024)	31	Primary	Tolerability and the use of low-dose olaparib as maintenance therapy in Asian women with advanced primary epithelial ovarian cancer
Original SLR (2024)	32	Primary	Real world clinical outcomes of niraparib first line maintenance therapy in patients with BRCA wildtype advanced ovarian cancer
Original SLR (2024)	33	Primary	Hashimoto, K., Kawakami, K., Yokokawa, T., Shibata, N., Soejima, A., Sugisaki, T., ... & Yamaguchi, M. (2023). Serum Creatinine Elevation as a Risk Factor for Niraparib-induced Hematologic Toxicity. Anticancer Research, 43(10), 4533-4541.
SLR update (2025)	34	Primary	Rimel, B.,Boyle, T. A. C.,Burns, S.,Lim, J.,Hartman, J.,Kalilani, L.,Schilder, J. M.,Hurteau, J. A.,Golembesky, A.. Real-World First-Line Maintenance Niraparib Monotherapy Use Following Chemotherapy Plus Bevacizumab: The SW1TCH Study. Oncology and Therapy. 2024;12(3):465 EP - 475.

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

SLR search	Study ID	Primary/ secondary publication	Citation
SLR update (2025)	35	Primary	Chase, D. M.,Shukla, S.,Moore, J.,Boyle, T. A. C.,Lim, J.,Perhanidis, J.,Hurteau, J. A.,Schilder, J. M. 2024. Patient Characteristics Associated with Time to Next Treatment in Patients with Ovarian Cancer Treated with Niraparib: The PRED1CT Real-World Study Oncology and Therapy, Oncol Ther;12(3):599–607.
SLR update (2025)	36	Primary	Kumar, Y. S.,Panda, S. S.,Moharana, L.,Samantaray, L.,Saju, S. V.,Rathnam, K. K.,Raju, H. S.,Sehrawat, A.,Sundriyal, D.,Kingsley, P. A.,Priya, K. B.,Kayal, S.,Dubashi, B.,Philips, A. O.,Cyriac, S. L.,Natarajan, S.,Mohanty, S. S.,Ganesan, P.. Real-world data of PARP inhibitors in first-line maintenance for BRCA mutated or HRD positive advanced ovarian cancer: A multicenter retrospective study from India. Ann Oncol. 2024;35(Supplement 4):S1552.
SLR update (2025)	37	Primary	Nakamura, K.,Matsuoka, H.,Yorimitsu, M.,Ogawa, M.,Kanemori, M.,Sueoka, K.,Kozai, A.,Nakamura, H.,Haruma, T.,Shiroyama, Y.,Hayata, Y.,Sugii, H.,Ueda, A.,Kurihara, S.,Urayama, S.,Shimizu, M.,Masuyama, H.. Efficacy and safety of olaparib, olaparib plus bevacizumab and niraparib maintenance treatment in Japanese patients with platinum-sensitive advanced ovarian cancer. Jpn J Clin Oncol. 2024;54(1):31 EP - 37.
SLR update (2025)	38	Primary	Bruno, M.,Apostol, A. I.,Boccia, S. M.,Sassu, C. M.,Lardino, S.,Culcasi, C.,Lorusso, D.,Scambia, G.,Fagotti, A.,Marchetti, C.. Effects of niraparib dose reduction on short-term outcomes in ovarian cancer patients. Int J Gynecol Cancer. 2024;34(10):1596 EP - 1603.
SLR update (2025)	39	Primary	Han, G. H.,Kim, H. R.,Yun, H.,Kim, J. H.,Cho, H.. Comparison of Adverse Events Between PARP Inhibitors in Patients with Epithelial Ovarian Cancer: A Nationwide Propensity Score Matched Cohort Study. Target Oncol. 2024;19(2):251 EP - 262.
SLR update (2025)	40	Primary	Ha, H. I.,Yoon, H. J.,Song, C.,Kim, E. T.,Suh, D. S.,Kim, K. H.,Na, Y. J.,Song, Y. J.. Clinical Outcomes of Poly(ADP-Ribose) Polymerase Inhibitors as Maintenance Therapy in Patients with Ovarian Cancer in the Southeastern Region of Korea. Current Oncology. 2024;31(11):6711 EP - 6722.

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

SLR search	Study ID	Primary/ secondary publication	Citation
SLR update (2025)	41	Primary	Lee, Y. J.,Shin, Y. K.,Kim, N. R.,Kim, S. I.,Lee, Y. Y.,Park, J. Y.,Kim, J. W.,Cho, H. W.,Lee, J. Y.. Chemotherapy response score no longer predicts survival outcomes in high-grade serous ovarian cancer patients with BRCA mutation and/or maintenance therapy. J Gynecol Oncol. 2024;35(6):e73.
SLR update (2025)	42	Primary	Jeong, Young Wook,Kim, Dongkyu Eugene,Kim, Ji Hyun,Kim, Se Ik,Ha, Hyeong In,Park, Sang-Yoon,Lim, Myong Cheol. Time-Trend Analysis and Risk Factors for Niraparib-Induced Nausea and Vomiting in Ovarian Cancer: A Prospective Study. Cancer research and treatment. 2024;#Volume#():#Pages#.
SLR update (2025)	43	Primary	Graves, S.,Sullivan, M. W.,Adkoli, A.,Zhou, Q.,Iasonos, A.,Selenica, P.,Aghajanian, C.,Liu, Y. L.,Tew, W.,Sonoda, Y.,Ellenson, L. H.,Chi, D.,O'Cearbhaill, R. E.,Weigelt, B.,Grisham, R. N.. Association between genomic instability score and progression-free/overall survival in patients with newly diagnosed non-BRCA1/2 ovarian cancer. Gynecol Oncol. 2025;192():120 EP - 127.
SLR update (2025)	43	Secondary	Graves, S.,Sullivan, M.,Adkoli, A.,Zhou, Q.,Chi, D.,Ellenson, L.,O'Cearbhaill, R.,Weigelt, B.,Grisham, R.. Progression-free and overall survival in newly-diagnosed homologous recombination DNA-repair deficient ovarian cancer without a BRCA mutation. Gynecol Oncol. 2024;190(Supplement 1):S43 EP - S44.
SLR update (2025)	44	Primary	Adjei, N. N.,Haas, A.,Zhao, H.,Primm, K. M.,Giordano, S. H.,Sun, C. C.,Meyer, L. A.. Real-world trends in the use of maintenance therapy in ovarian cancer across the United States from 2017 to 2021. Gynecol Oncol. 2024;190():255 EP - 261.
SLR update (2025)	45	Primary	Hasson, S. P.,Bowen, R.,Ang, J. E.,McGrane, J.,Vazquez, I.,George, A.,Millar, J.,Walther, A.,Hudson, E.,King, E.,Miller, R.,Green, C.,Williams, S.,Agarwal, R.,Jackson, D. P.,Patel, N.,Brooks, R.,Connolly, S.,Tran, A.,Banerjee, S. 2024. 52P MONITOR-UK: An initial analysis of a multi-centre, observational study of maintenance niraparib in ovarian cancer ESMO Open, 9(Supplement 5): 103559.

Table 86. List of excluded clinical studies

Title	Author	Year	Exclusion reason
2025 SLR update			
Real-world TRAE association between niraparib and platinum-based chemotherapy	Wang, L	2024	Population
Real-world outcomes of PARP inhibitor maintenance in advanced ovarian cancer: a focus on disease patterns and treatment modalities at recurrence	Loverro, M	2025	Outcome
Comparison of survival outcomes and safety between early and late initiation of niraparib maintenance in newly diagnosed advanced epithelial ovarian cancer	Kim, S	2024	Duplicate
Germline BRCA1/2 status and chemotherapy response score in high-grade serous ovarian cancer: Genetics and Genomics	Morgan, R	2024	Population
Incidence, characteristics and outcome of therapy-related myeloid neoplasms in women with epithelial ovarian cancer after exposure to poly-ADPribose polymerase inhibitors: A cancer center experience	Verrou, E	2024	Outcome
Effectiveness of PARP Inhibitor Maintenance Therapy in Ovarian Cancer by BRCA1/2 and a Scar-Based HRD Signature in Real-World Practice	Richardson, D	2024	Outcome
Usefulness of Nutritional Assessment Indicators in Predicting Treatment Discontinuation Due to Adverse Events from PARP Inhibitors in Ovarian Cancer Patients	Tanaka, Y	2024	Outcome
Real-world BRCA1/2 and homologous recombination deficiency testing dynamics and time to treatment discontinuation on PARP inhibitor first-line maintenance among patients with epithelial ovarian cancer	Previs, R	2024	Outcome

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Title	Author	Year	Exclusion reason
Sleep disturbance and fatigue in patients with ovarian cancer during chemotherapy and surgery compared to PARPi maintenance therapy	Newell, A	2024	Outcome
Real-world clinical outcomes and prognostic factors of olaparib maintenance in Korean patients with primary or recurrent high-grade ovarian cancer with exploratory analysis of location of BRCA1 and BRCA2 mutations	Kim, J	2024	Outcome
PARPi response and outcome of ovarian cancer patients with BRCA1/2 germline mutation and a history of breast cancer	Yuan, H	2024	Outcome
Niraparib as maintenance therapy in Japan: a retrospective observational study using a Japanese claims database	Motohashi, T	2024	Outcome
PARP inhibitor maintenance treatment for newly diagnosed ovarian cancer patients: a real-world study from China	Chen, J	2024	Duplicate
Medical cannabis and its effect on oncological outcomes in patients with ovarian cancer treated with PARP inhibitors	Hasson, S	2024	Intervention
Adherence of PARP inhibitor for frontline maintenance therapy in primary epithelial ovarian cancer: a cross-sectional survey	Kim, J	2024	Duplicate
Prescribers and patients drive maintenance therapy patterns in a community oncology practice: National guidelines versus the real-world experience	Chase, D	2024	Outcome
Prognostic Role of CA-125 Elimination Rate Constant (KELIM) in Patients with Advanced Epithelial Ovarian Cancer Who Received PARP Inhibitors	Kim, J	2024	Outcome
Body composition and inflammation variables as the potential prognostic factors in epithelial ovarian cancer treated with Olaparib	Guo, X	2024	Population

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Title	Author	Year	Exclusion reason
Comparison of survival outcomes between olaparib and niraparib maintenance therapy in BRCA-mutated, newly diagnosed advanced ovarian cancer	Kim, J	2024	Duplicate
The power of hope: Views of Ovarian Cancer patients on how maintenance therapy Affects their Lives (VOCAL)	Chase, D	2024	Outcome
62P A multi-center real-world study of the efficacy and safety of PARP inhibitors in patients with ovarian cancer in Spain	Bayona, R	2024	Population
Progression-free survival and safety at 3.5 years of follow-up: results from the randomized phase 3 PRIMA/ENGOT-OV26/GOG-3012 trial of niraparib maintenance treatment in patients with newly diagnosed ovarian cancer - a plain language summary	Gonzalez-Martin, A	2024	Duplicate
Efficacy and safety of PARP inhibitor maintenance therapy for ovarian cancer: a meta-analysis and trial sequential analysis of randomized controlled trials	Sun, G	2024	SLR/NMA for citation chasing
Durvalumab plus paclitaxel/carboplatin plus bevacizumab followed by durvalumab, bevacizumab plus olaparib maintenance among patients with newly-diagnosed advanced ovarian cancer without a tumor BRCA1/BRCA2 mutation: updated results from DUO-O/ENGOT-OV46/GOG-3025 Trial	Harter, P	2024	Duplicate
Examining health-related quality of life outcomes among older patients with advanced ovarian cancer treated with niraparib first-line maintenance therapy in context with efficacy and safety findings: results from the PRIMA/ENGOT-OV26/GOG-3012 trial	Pothuri, B	2024	Duplicate
Interim post-progression data and updated survival in patients with newly diagnosed advanced ovarian cancer in ATHENA-MONO	Kristeleit, R	2024	Duplicate

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Title	Author	Year	Exclusion reason
Fuzuloparib as maintenance therapy among patients with advanced ovarian cancer after a response to first-line platinum-based chemotherapy: results from a randomized, placebo-controlled, phase III trial	Wu, L	2024	Duplicate
Utilization of PARP inhibitor maintenance therapy, with or without bevacizumab, in the treatment of patients with homologous recombination proficient, wild-type BRCA1/2 ovarian carcinoma	Weiss, A	2024	Outcome
Safety and tolerability of durvalumab (D) + carboplatin/paclitaxel (CP) + bevacizumab (B) followed by D, B + olaparib (O) maintenance (mtx) in patients (pts) with newly diagnosed advanced ovarian cancer (AOC) without a tumour BRCA1/BRCA2 mutation (non-tBRCAm) in the phase III DUO-O trial	Aghajanian, C	2024	Population
First-line bevacizumab plus chemotherapy in Chinese patients with stage III/IV epithelial ovarian cancer, fallopian tube cancer or primary peritoneal cancer: a phase III randomized controlled trial	Wu, X	2024	Population
Patterns of initial ovarian cancer recurrence on niraparib maintenance monotherapy in patients with no baseline evidence of disease after first-line chemotherapy: an ad hoc subgroup analysis of PRIMA/ENGOT-OV26/GOG-3012	Kamrava, M	2024	Outcome
Health-related quality of life in patients with newly diagnosed advanced ovarian cancer treated with niraparib vs placebo: results from the phase 3 randomized PRIMA/ENGOT-OV26/GOG-3012 trial	Pothuri, B	2024	Duplicate

Title	Author	Year	Exclusion reason
430 Durvalumab (D) + carboplatin/paclitaxel (CP) + bevacizumab (B) followed by D, B + olaparib (O) maintenance (mtx) for newly diagnosed advanced ovarian cancer (AOC) without a tumour BRCA1/BRCA2 mutation (non-tBRCaM): updated results from DUO-O	Trillsch, F	2024	Population
Predictors of long-term progression-free survival in patients with ovarian cancer treated with niraparib in the PRIMA/ENGOT-OV26/GOG-3012 study	Graybill, W	2024	Duplicate
Efficacy and safety of niraparib in patients aged 65 years and older with advanced ovarian cancer: results from the PRIMA/ENGOT-OV26/GOG-3012 trial	Valabrega, G	2024	Duplicate
Olaparib Addition to Maintenance Bevacizumab Therapy in Ovarian Carcinoma With BRCA-Like Genomic Aberrations	Schouten, P	2024	Duplicate
Updated progression-free survival and final overall survival with maintenance olaparib plus bevacizumab according to clinical risk in patients with newly diagnosed advanced ovarian cancer in the phase III PAOLA-1/ENGOT-ov25 trial	Lorusso, D	2024	Duplicate
Anlotinib or bevacizumab as first-line maintenance treatment for patients with HRD-negative advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer: a non-comparative, randomised, phase 2 Study		2024	Study design
A quality initiative focused on BRCA and HRD testing and use of first line maintenance in advanced ovarian cancer	Gart, M	2024	Outcome
Incorporating immune checkpoint inhibitors in epithelial ovarian cancer	Bogani, G	2025	SLR/NMA for citation chasing
Haematological toxicity of PARP inhibitors in advanced ovarian cancer: A systematic review and meta-analysis	Pio Maiorano, M	2025	SLR/NMA for citation chasing

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Title	Author	Year	Exclusion reason
Molecular Subgroups of HRD Positive Ovarian Cancer and Their Prognostic Significance	Kekeeva, T	2024	Population
RWD139 Characteristics of Ovarian Cancer Patients: A Real-World Perspective for 1st Line Maintenance Treatment Choice After 1st Line Platinum Based Induction Therapy Across EU4 & UK	Emeanuru, K	2024	Outcome
Prevalence and outcomes of germline pathogenic variants of homologous recombination repair genes in ovarian cancer	Miwa, M	2024	Population
Efficacy and safety of angiogenesis inhibitors combined with poly ADP ribose polymerase inhibitors in the maintenance treatment of advanced ovarian cancer: a meta-analysis	Huang, R	2024	SLR/NMA for citation chasing
Post-marketing study to evaluate the safety and efficacy of bevacizumab biosimilar in patients with advanced ovarian cancer	Mohapatra, P	2024	Population
Real-world safety of olaparib in ovarian cancer (OC): A retrospective, observational, database study in China	Li, N	2024	Population
Gut microbiome associated with PARP inhibitor efficacy in patients with ovarian cancer	Okazawa-Sakai, M	2024	Population
Outcomes of niraparib first-line maintenance among patients with BRCA wild-type advanced ovarian cancer in a real-world clinical setting	Kupets, R	2024	Duplicate
Predictors for PARP inhibitor hematologic toxicity in ovarian cancer: Are patients with chemotherapy-induced toxicity at an increased risk?	Salman, L	2024	Duplicate
Characteristics and real-world outcomes of patients with epithelial ovarian cancer who received niraparib + bevacizumab first-line maintenance therapy in the COMB1NE study	Thaker, P	2024	Duplicate

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Title	Author	Year	Exclusion reason
The potential impact of excluding patients with stage III epithelial ovarian cancer and no postoperative visible residual disease from the PRIMA/ENGOT-OV26/GOG-3012 trial: The AR1ZE real-world study of niraparib first-line maintenance therapy	Chase, D	2024	Duplicate
Efficacy and safety of niraparib as first-line maintenance treatment for patients with advanced ovarian cancer: Real-world data from a multicenter study in China	Shen, Y	2024	Duplicate
Real-world time-to-event outcomes among patients with ovarian cancer receiving olaparib maintenance therapy in the United States	Szamreta, E	2024	Duplicate
Real-world progression-free survival among patients with homologous recombination-deficient epithelial ovarian cancer who received niraparib first-line maintenance therapy in the CHAR1ZMA study	Salani, R	2024	Duplicate
The effect of antibiotics, proton pump inhibitors, H2-receptor antagonists, and steroids on survival among ovarian cancer patients receiving PARP inhibitor therapy	Kistenfeger, Q	2024	Population
Correlation between real-world progression-free survival and other outcomes among patients with ovarian cancer who received poly(ADP-ribose) polymerase inhibitors in the first-line maintenance setting	Kobayashi, M	2024	Duplicate
Efficacy of chemotherapy after progression during or following PARPi exposure in ovarian cancer	Xu-Vuillard, A	2024	Population
Niraparib Population Pharmacokinetics and Exposure-Response Relationships in Patients With Newly Diagnosed Advanced Ovarian Cancer	Monk, B	2024	Study design

Title	Author	Year	Exclusion reason
Anti-angiogenic therapy in first-line treatment of low-grade serous ovarian cancer: Exploratory meta-analysis of the prospective AGO-OVAR 11/12/16 studies	Czogalla, B	2024	Study design
Senaparib as first-line maintenance therapy in advanced ovarian cancer: a randomized phase 3 trial	Wu, X	2024	Duplicate
Study on the efficacy and toxicity of pamiparib combined with tamoxifen in the treatment of patients with epithelial ovarian cancer with biochemical recurrence during first-line PARPi maintenance therapy	Meng, Y	2024	Study design
A phase IV trial to confirm the efficacy of olaparib in combination with bevacizumab as maintenance frontline treatment of HRD-positive ovarian tumours (IOlanThe)	Tomao, F	2024	Study design
Efficacy of niraparib in patients with advanced ovarian cancer: A meta-analysis of randomized controlled trials	Marinho, A	2024	SLR/NMA for citation chasing
Real-World Safety of Niraparib for Maintenance Treatment of Ovarian Cancer in Canada	Guan, Q	2024	Population
Real-world data of poly (ADP-ribose) polymerase inhibitor response in Japanese patients with ovarian cancer	Uekusa, R	2024	Population
Association Between Hormonal Maintenance Therapy and Progression-Free Survival in Advanced Epithelial Ovarian Cancer Patients: A Retrospective Study	Sadeghi, A	2024	Intervention
Efficacy and safety of PARP inhibitors combined with antiangiogenic agents in the maintenance treatment of ovarian cancer: a systematic review and meta-analysis with trial sequential analysis of randomized controlled trials	Wei, Y	2024	SLR/NMA for citation chasing

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Title	Author	Year	Exclusion reason
Health-related quality of life in patients with newly diagnosed advanced ovarian cancer treated with niraparib vs placebo: Results from the phase 3 randomized PRIMA/ENGOT-OV26/GOG-3012 trial	Pothuri, B	2024	Duplicate
Determining the maximum tolerated dose of paclitaxel combined with fixed dose of cisplatin for hyperthermic intraperitoneal chemotherapy in ovarian cancer: A multicenter phase I trial	Wu, M	2024	Population
Endocrine therapy in advanced high-grade ovarian cancer: real-life data from a multicenter study and a review of the literature	Aubert, M	2024	Population
Increase in creatinine levels associated with niraparib maintenance therapy in ovarian cancer	Takahashi, Y	2024	Population
The impact of PARP inhibitors in the whole scenario of ovarian cancer management: A systematic review and network meta-analysis	Staropoli, N	2024	SLR/NMA for citation chasing
Clinical characteristics and treatment modalities in women with newly diagnosed advanced high-grade serous epithelial ovarian cancer in Taiwan	Hsu, H	2024	Population
Quality of life in ovarian cancer patients treated with bevacizumab: a meta-analysis	Wu, D	2024	SLR/NMA for citation chasing
Safety and efficacy of Rucaparib in the treatment of ovarian cancer and patients with BRCA mutation: a systematic review and meta-analysis of phase III randomized clinical trials	Mustafa, M	2024	SLR/NMA for citation chasing
Tailored Treatment Strategies in First Line Therapy for Ovarian Cancer Patients: A Critical Review of the Literature	Luvero, D	2024	SLR/NMA for citation chasing

Title	Author	Year	Exclusion reason
Does the choice of platinum doublet matter? A study to evaluate the impact of platinum doublet choice for treatment of platinum-sensitive ovarian cancer recurrence on the development of future PARP inhibitor and platinum resistance	Levine, M	2024	Population
PARP inhibitor era in ovarian cancer treatment: a systematic review and meta-analysis of randomized controlled trials	Baradacs, I	2024	SLR/NMA for citation chasing
Prior authorization for FDA-approved PARP inhibitors in ovarian cancer	Smith, A	2024	Outcome
A retrospective analysis of haematological side effects of olaparib in excess-weight and normal BMI patients with ovarian cancer	Stanislawiak-Rudowicz, J	2024	Population
72P Real-world data of treatment and outcome of patients with advanced ovarian cancer (AOC) in Germany: QS OVAR of the AGO Study Group	Harter, P	2024	Outcome
Safety assessments and clinical features of PARP inhibitors from real-world data of Japanese patients with ovarian cancer	Uekusa, R	2024	Population
First Interim Analysis of the SCOUT-1 Study (NOGGO ov54, NCT04830709): A Non-Interventional Study to evaluate Treatment Patterns and Longterm Outcome in Patients with Newly Diagnosed Advanced Ovarian Cancer	Pietzner, K	2024	Study design
The unconfounded effect of bevacizumab on advanced ovarian clear cell carcinoma: a systematic review, traditional metaanalysis, and network meta-analysis	Huang, F	2024	SLR/NMA for citation chasing
Tolerability of the niraparib individualized starting dose in the PRIMA/ENGOT-OV26/GOG-3012 trial of niraparib first-line maintenance therapy	Vulsteke, C	2024	Duplicate

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Title	Author	Year	Exclusion reason
63P A real-world comparison of the tolerability and toxicity of niraparib in older and younger women with high-grade serous ovarian carcinoma	Low, S	2024	Population
58P A multicenter, prospective, non-interventional drug intensive monitoring study of olaparib in real-world Chinese patients with ovarian cancer (DIM-OC)	Lin, Z	2024	Population
Rucaparib (Ovarialkarzinom; Erhaltungstherapie nach Erstlinientherapie)	Institut für Qualität und Wirtschaftlichkeit im, Gesundheitswesen	2024	Study design
Olaparib for maintenance treatment of BRCA mutation-positive advanced ovarian, fallopian tube or peritoneal cancer after response to first-line platinum-based chemotherapy. NICE technology appraisal guidance 962	National Institute for, Health,Care, Excellence	2024	Study design
Olaparib with bevacizumab for maintenance treatment of advanced high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer. NICE technology appraisal guidance 946	National Institute for, Health,Care, Excellence	2024	Study design
Olaparib-induced hyperglycemia in ovarian cancer patients - a case series analysis of a three-month therapy with a consideration of BMI	Stanislawiak-Rudowicz, J.	2025	Population
Comparison of survival outcomes and safety between early and late initiation of niraparib maintenance in newly diagnosed advanced epithelial ovarian cancer	Kim, S.	2025	Duplicate
Incidence, characteristics and outcome of therapy-related myeloid neoplasms in women with epithelial ovarian cancer after exposure to poly-ADPribose polymerase inhibitors: A cancer center experience	Verrou, E.	2024	Duplicate
Comparison of survival outcomes between olaparib and niraparib maintenance therapy in BRCA-mutated, newly diagnosed advanced ovarian cancer	Kim, J. H.	2024	Duplicate

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Title	Author	Year	Exclusion reason
Progesterone Enhances Niraparib Efficacy in Ovarian Cancer by Promoting Palmitoleic-Acid-Mediated Ferroptosis	Wu, N.	2024	Population
Usefulness of Nutritional Assessment Indicators in Predicting Treatment Discontinuation Due to Adverse Events from PARP Inhibitors in Ovarian Cancer Patients	Tanaka, Y.	2024	Duplicate
Efficacy of PARP inhibitors in advanced high-grade serous ovarian cancer according to BRCA domain mutations and mutation type	Buonaiuto, R.	2024	Population
Progression-free survival and safety at 3.5 years of follow-up: results from the randomized phase 3 PRIMA/ENGOT-OV26/GOG-3012 trial of niraparib maintenance treatment in patients with newly diagnosed ovarian cancer - a plain language summary	Gonzalez-Martin, A.	2024	Study design
Efficacy and safety of niraparib in patients aged 65 years and older with advanced ovarian cancer: Results from the PRIMA/ENGOT-OV26/GOG-3012 trial	Valabrega, G.	2024	Duplicate
The serum LDH level and KELIM scores are potential predictors of a benefit from bevacizumab first-line therapy for patients with advanced ovarian cancer	Liu, Y.	2025	Population
Characteristics and real-world outcomes of patients with epithelial ovarian cancer who received niraparib plus bevacizumab first-line maintenance therapy in the COMB1NE study	Thaker, P.	2024	Duplicate
Clinical Outcomes of Poly(ADP-Ribose) Polymerase Inhibitors as Maintenance Therapy in Patients with Ovarian Cancer in the Southeastern Region of Korea	Ha, H.	2024	Duplicate
Clinical characteristics and treatment modalities in women with newly diagnosed advanced high-grade serous epithelial ovarian cancer in Taiwan	Hsu, H.	2024	Duplicate

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Title	Author	Year	Exclusion reason
Prognostic factors and overall survival among patients with ovarian cancer in the pre-PARP inhibitor era: the OCRWE-Finland study	Lahelma, M.	2024	Intervention
Tolerability of the niraparib individualized starting dose in the PRIMA/ENGOT-OV26/GOG-3012 trial of niraparib first-line maintenance therapy	Vulsteke, C.	2024	Duplicate
Medical cannabis and its effect on oncological outcomes in patients with ovarian cancer treated with PARP inhibitors	Peleg H.	2024	Duplicate
Updated progression-free survival and final overall survival with maintenance olaparib plus bevacizumab according to clinical risk in patients with newly diagnosed advanced ovarian cancer in the phase III PAOLA-1/ENGOT-ov25 trial	Lorusso, D.	2024	Duplicate
Comparison of Adverse Events Between PARP Inhibitors in Patients with Epithelial Ovarian Cancer: A Nationwide Propensity Score Matched Cohort Study	Han, G.	2024	Duplicate
Adherence of PARP inhibitor for frontline maintenance therapy in primary epithelial ovarian cancer: a cross-sectional survey	Kim, J. H.	2024	Duplicate
Health-related quality of life in patients with newly diagnosed advanced ovarian cancer treated with niraparib vs placebo: Results from the phase 3 randomized PRIMA/ENGOT-OV26/GOG-3012 trial	Pothuri, B.	2024	Duplicate
Safety and efficacy of Rucaparib in the treatment of ovarian cancer and patients with BRCA mutation: a systematic review and meta-analysis of phase III randomized clinical trials	Mustafa, M.	2024	Duplicate
Prescribers and patients drive maintenance therapy patterns in a community oncology practice: National guidelines versus the real-world experience	Chase, D.	2024	Duplicate

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Title	Author	Year	Exclusion reason
Prognostic Role of CA-125 Elimination Rate Constant (KELIM) in Patients with Advanced Epithelial Ovarian Cancer Who Received PARP Inhibitors	Kim, J. H.	2024	Duplicate
Age Is a Risk Factor for Olaparib Dose Modification and Discontinuation in Patients With Ovarian Cancer	Inui, H.	2024	Population
PARP inhibitor maintenance treatment for newly diagnosed ovarian cancer patients: a real-world study from China	Chen, J.	2024	Duplicate
2024 SLR update			
Disease progression in patients with ovarian cancer who received first-line maintenance therapy or active surveillance, a US real-world analysis.	Chase, D.	2021	Intervention
Durvalumab with paclitaxel/carboplatin (PC) and bevacizumab (bev), followed by maintenance durvalumab, bev, and olaparib in patients (pts) with newly diagnosed advanced ovarian cancer (AOC) without a tumor BRCA1/2 mutation (non-tBRCAm): Results from the randomized, placebo (pbo)-controlled phase III DUO-O trial	Harter, P.	2023	Study design
Real-world outcomes following first-line treatment in patients with advanced ovarian cancer with multiple risk factors for disease progression who received maintenance therapy or active surveillance.	Chase, D.	2023	Intervention
Real-world Outcomes Associated With Poly (ADP-ribose) Polymerase Inhibitor Monotherapy Maintenance in Patients With Primary Advanced Ovarian Cancer.	Chan, J. K.	2023	Outcome
Efficacy and safety results from OCTAVIA, a single-arm phase II study evaluating front-line bevacizumab, carboplatin and weekly paclitaxel for ovarian cancer	Gonzalez-Martin, A.	2013	Study design

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Title	Author	Year	Exclusion reason
Real-world clinical outcomes of patients with de novo advanced high-grade epithelial ovarian cancer eligible to niraparib maintenance in France	Rodrigues, M.	2021	Outcome
Evaluating the real-world impact of first line PARP inhibitor maintenance therapy in patients with BRCA mutated ovarian tumors (1213)	Piedimonte, S.	2023	Outcome
Real-world analysis of survival outcomes and toxicities with PARPi use across indications.	Wield, A.	2021	Outcome
Real-world progression-free survival among patients with newly diagnosed advanced ovarian cancer: Does maintenance therapy work?	Liu, J.	2021	Outcome
Real-world trends of PARPi maintenance treatment uptake and progression-free survival (PFS) in patients (pts) with newly diagnosed advanced ovarian cancer (AOC) in the United States.	Chan, J. K.	2022	Outcome
The use of real-world evidence from the edinburgh ovarian cancer database to explore a data gap in the prima trial.	Hollis, R. L.	2022	Outcome
Adherence of PARP inhibitor for frontline maintenance therapy in primary epithelial ovarian cancer: a cross-sectional survey.	Kim, J. H.	2024	Outcome
HRD effects on first-line adjuvant chemotherapy and PARPi maintenance therapy in Chinese ovarian cancer patients.	Li, L.	2023	Outcome
Impact of veliparib, paclitaxel dosing regimen, and germline BRCA status on the primary treatment of serous ovarian cancer—an ancillary data analysis of the VELIA trial.	Aghajanian, C.	2022	Population
Veliparib with first-line chemotherapy and as maintenance therapy in ovarian cancer.	Coleman, R. L.	2019	Population

Title	Author	Year	Exclusion reason
Characterization of patients with BRCA mutated ovarian cancer who are eligible versus not eligible for PARP inhibitor maintenance therapy: exploratory analysis of the VELIA study	Swisher, E.	2021	Population
Response to Chemotherapy Post PARP Inhibitor in High-Grade Serous Ovarian Cancer Patients: Results from an Australian, Retrospective, Multi-Institute Cohort Study	Tharani Sivakumaran	2020	Population
Phase II OVARIO study of niraparib + bevacizumab therapy in advanced ovarian cancer following front-line platinum-based chemotherapy with bevacizumab.	Hardesty M.M.	2020	Outcome
Efficacy Of PARP inhibitors maintenance in older patients with newly diagnosed ovarian cancer: A meta-analysis.	Maiorano B.A.	2021	Study design
EPV187/#241 EFFICACY OF PARP INHIBITORS MAINTENANCE IN OLDER PATIENTS WITH OVARIAN CANCER: A META-ANALYSIS	B A Maiorano	2021	Study design
Treatment and outcome of patients with high-grade advanced ovarian cancer (AOC): Real-world data in Germany (QS Ovar of the AGO Study Group).	Mahner S.	2022	Population
TREATMENT AND OUTCOME OF PATIENTS WITH HIGH-GRADE ADVANCED OVARIAN CANCER (AOC) - REAL WORLD DATA OF THE GERMAN QUALITY ASSURANCE PROJECT (QS OVAR OF THE AGO STUDY GROUP).	Mahner S.	2022	Population
2022-RA-617-ESGO THE ROLE OF SYSTEMATIC PELVIC AND PARA-AORTIC LYMPHADENECTOMY IN THE MANAGEMENT OF PATIENTS WITH ADVANCED EPITHELIAL OVARIAN, TUBAL, AND PERITONEAL CANCER: A SYSTEMATIC REVIEW AND META-ANALYSIS	Alexander Tzanis	A 2022	Outcome

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Title	Author	Year	Exclusion reason
Real-world experience of poly (ADP-ribose) polymerase inhibitor use in a community oncology practice: The clinical and financial burden.	Eakin C.	2020	Population
Retrospective analysis of ovarian cancer patients treated with PARP inhibitors.	Liang C.	2021	Population
Risk factor for the failure of first-line PARP inhibitor maintenance therapy in patients with advanced ovarian cancer: Gynecologic oncology research investigators coLLborAtion study (GORILLA-3004) (1152).	Kim N.K.	2023	Outcome
A multi-center, phase II study of Olaparib maintenance therapy for high-grade ovarian cancer with positive biomarker by exome sequencing.	-	2018	Outcome
A Pan-Canadian Consensus Statement on First-Line PARP Inhibitor Maintenance for Advanced, High-Grade Serous and Endometrioid Tubal, Ovarian, and Primary Peritoneal Cancers	Anna V Tinker	2022	Study design
A real-world study on characteristics, treatments and outcomes in US patients with advanced stage ovarian cancer	Daniel C Beachler	2020	Population
A review of the current evidence for maintenance therapy in ovarian cancer.	Foster T.	2009	SLR/NMA for citation chasing
Adverse effects of olaparib in the treatment of ovarian cancer:a real-world study.	Wang H.	2023	Language (Non-English)
Adverse events in the placebo arm of maintenance therapy trials in advanced ovarian cancer: A systematic review and meta-analysis.	Simon S.	2022	SLR/NMA for citation chasing
Analysis of Efficacy-To-Safety Ratio of Angiogenesis-Inhibitors Based Therapies in Ovarian Cancer: A Systematic Review and Meta-Analysis	Dana Lucia Stănculeanu	2023	SLR/NMA for citation chasing

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Title	Author	Year	Exclusion reason
Anti-Angiogenesis Maintenance Therapy in Newly Diagnosed and Relapsed Ovarian Cancer: A Meta-analysis of Phase III Randomized Controlled Trials	Yizi Wang	2021	SLR/NMA for citation chasing
Antiangiogenesis therapy in ovarian cancer patients An updated meta-analysis for 15 randomized controlled trials	Yanyan Jiang	2018	Intervention
Assessing frequency and clinical outcomes of BRCA mutated ovarian cancer in Saudi women	Naela Agha	2022	Population
Assessment of Progression-Free Survival as a Surrogate End Point of Overall Survival in First-Line Treatment of Ovarian Cancer A Systematic Review and Meta-analysis	Xavier Paoletti	2020	SLR/NMA for citation chasing
Circulating T-cell receptor diversity as predictive biomarker for PARP inhibitors maintenance therapy in high grade serous ovarian cancer.	Shu T.	2023	Outcome
Efficacy and Prognostic Factors for PARP Inhibitors in Patients With Ovarian Cancer	Saveri Bhattacharya	2020	SLR/NMA for citation chasing
Efficacy and safety of PARP inhibitors for maintenance treatment of ovarian cancer, regardless of BRCA or HRD status: a comprehensive updated meta-analysis.	Li Y.	2023	SLR/NMA for citation chasing
Evaluation of an initial treatment with bevacizumab in combination with chemotherapy and then in combination with niraparib in maintenance in patients with advanced ovarian cancer after complete initial surgery.	-	2021	Outcome
ОПЫТ ПРИМЕНЕНИЯ ИНГИБИТОРА ПОЛИ (АДФ-РИБОЗО) ПОЛИМЕРАЗЫ ОЛАПАРИБА В ПОДДЕРЖИВАЮЩЕЙ ТЕРАПИИ BRCA-АССОЦИИРОВАННОГО РАКА ЯИЧНИКОВ	В Н Журман	2023	Language (Non-English)

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Title	Author	Year	Exclusion reason
Impact of postoperative residual disease on survival in epithelial ovarian cancer with consideration of recent frontline treatment advances: A systematic review and meta-analysis.	Kim J.H.	2023	SLR/NMA for citation chasing
Maintenance Therapy in Ovarian Cancer with Targeted Agents Improves PFS and OS: A Systematic Review and Meta-Analysis	Xinyu Qian	2015	SLR/NMA for citation chasing
Horizon Scanning in Oncology	Olaparib (Lynparza	2019	Study design
Olaparib Maintenance Monotherapy in Participants with BRCA Wild Type Ovarian Cancer Following Response to First-line Platinum-based Chemotherapy.	-	2021	Outcome
Olaparib Monotherapy in Patients with BRCA Mutated Ovarian Cancer following First Line Platinum Based Chemotherapy.	-	2013	Outcome
Optimal timing of interval debulking surgery for advanced epithelial ovarian cancer: A retrospective study from the ESME national cohort.	Thomas Q.D.	2022	Intervention
PARP Inhibitors as Frontline Treatment in Patients With Ovarian Cancer.	Wright	2020	Study design
PARP inhibitors in newly diagnosed or recurrent ovarian cancer maintenance therapy: evidence of efficacy and safety from randomized controlled trials	Khanh Ngoc	2023	SLR/NMA for citation chasing
PARP Inhibitors Rising as an Epoch-Making Strategy in First-Line Maintenance Therapy of Ovarian Cancer: A Systematic Review and Meta-Analysis.	Ying Z.	2022	SLR/NMA for citation chasing
Prognosis and conditional survival among women with newly diagnosed ovarian cancer.	Szamreta E.A.	2024	Population
Prognostic impact of adjuvant chemotherapy treatment intensity for ovarian cancer	Kristen D Starbuck	2018	Population

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Title	Author	Year	Exclusion reason
Prognostic value of CA125 kinetics, half-life, and nadir in the treatment of epithelial ovarian cancer: a systematic review and meta-analysis.	Kim J.H.	2023	SLR/NMA for citation chasing
Progression-free survival as a surrogate endpoint for overall survival in modern ovarian cancer trials: a meta-analysis.	Sjoquist K.M.	2018	SLR/NMA for citation chasing
Randomized, Double-Blind, Phase III Trial of Olaparib vs Placebo in Patients with Advanced FIGO Stage IIIB-IV High Grade Serous or Endometrioid Ovarian, Fallopian Tube, or Peritoneal Cancer treated with standard First-Line Treatment, Combining Platinum-Taxane Chemotherapy and Bevacizumab Concurrent with Chemotherapy and in Maintenance.	-	2015	Outcome
Real-world bevacizumab utilization and outcomes among women with ovarian cancer in Europe and the United States.	Monberg M.J.	2021	Outcome
Real-world clinical practice patterns and outcomes for advanced ovarian cancer in Spain (GEICO-42-R study)	Andrés Redondo	2021	Population
SOLO-1. Study Protocol	-	2013	Outcome
Study of Chemotherapy With Pembrolizumab (MK-3475) Followed by Maintenance With Olaparib (MK-7339) for the First-Line Treatment of Women With BRCA Non-mutated Advanced Epithelial Ovarian Cancer (EOC) (MK-7339-001/KEYLYNK-001/ENGOT-ov43/GOG-3036).	-	2018	Outcome
Survival outcomes in patients with BRCA mutated, variant of unknown significance, and wild type ovarian cancer treated with PARP inhibitors.	Musacchio L.	2023	Population
The effect of PARP inhibitors in homologous recombination proficient ovarian cancer: meta-analysis.	Skelin M.	2023	SLR/NMA for citation chasing

Title	Author	Year	Exclusion reason
Unresectable Ovarian Cancer Requires a Structured Plan of Action: A Prospective Cohort Study	Gatske M Nieuwenhuyz-De Boer	2023	Population
Veliparib in combination with carboplatin and paclitaxel and as continuation maintenance therapy in subjects with newly diagnosed, untreated Stage III or IV high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer.	-	2015	Outcome
Veliparib With Carboplatin and Paclitaxel and as Continuation Maintenance Therapy in Adults With Newly Diagnosed Stage III or IV, High-grade Serous, Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer.	-	2015	Population
Veliparib With Carboplatin and Paclitaxel and as Continuation Maintenance Therapy in Subjects With Newly Diagnosed Stage III or IV, High-grade Serous, Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer.	-	2015	Population
1L maintenance therapy in patients with newly diagnosed advanced or metastatic ovarian cancer in routine care in Germany: Results from the German registry platform-SMARAGD.	Juhasz-Boss I.	2023	Outcome
2041P The prevalence of hematologic adverse events (HAEs) and myelodysplastic syndrome/acute myeloid leukemia (MDS/AML) in patients (pts) with advanced high grade ovarian carcinoma (aHGOC) receiving PARP inhibitor (PARPi), with or without a germline BRCA pathogenic variant.	Valenza C.	2023	Population
51P Efficacy of PARP inhibitors in patients with advanced high grade serous ovarian cancer according to BRCA domain mutations.	Buonaiuto R.	2023	Outcome

Title	Author	Year	Exclusion reason
A novel clinically applicable biomarker for testing HRD status based on the mutational signatures: Results for the phase 2 trial of olaparib maintenance monotherapy in patients with primary high-grade ovarian carcinoma (2271).	Oda K.	2023	Population
ADOPTION OF NEW FIRST-LINE MAINTENANCE STRATEGIES AMONG PATIENTS WITH PRIMARY ADVANCED OVARIAN CANCER AFTER FOOD AND DRUG ADMINISTRATION APPROVAL.	Liu J.	2022	Outcome
Adverse events experienced by patients in the placebo arm of maintenance therapy trials in advanced ovarian cancer.	Simon S.	2021	Study design
5PSQ-067 ARE POLY (ADP-RIBOSE) POLYMERASE INHIBITORS WELL TOLERATED BY OUR PATIENTS? A SAFETY STUDY IN REAL-WORD PRACTICE 1	D Rubio Calvo	2022	Study design
BRCA GENETIC STATUS DOES IMPACT THE TOXICITY OF RARP INHIBITORS IN PATIENTS WITH EPITHELIAL OVARIAN CANCER.	Li H.	2022	Population
CO133 Systematic Literature Review (SLR) of Clinical Data from First-Line Treatment or First-Line Maintenance Therapy for Advanced or Metastatic Ovarian Cancer (2010-2023).	Kiss Z.	2023	Study design
Comparative efficacy of first-line maintenance PARP inhibitors (PARPI) in advanced ovarian cancer (OC): A network meta-analysis.	Hammoud D.	2020	SLR/NMA for citation chasing
Comparative tolerability and dose modifications of poly(ADP-ribose) polymerase inhibitors in ovarian cancer: a retrospective cohort study of US healthcare claims data.	Arend R.	2021	Population

Title	Author	Year	Exclusion reason
Comparison of the toxicity between olaparib and niraparib for the treatment of the patients with ovarian, fallopian, and peritoneal cancer : A single-institution retrospective analysis.	Shun E.	2023	Population
Contrasting clinical characteristics and treatment patterns in women with newly diagnosed advanced-stage ovarian cancer in Australia, South Korea and Taiwan.	Chou H.-H.	2020	Intervention
Correlation of BRCA and HRD status with clinical and survival outcomes in patients with advanced-stage ovarian cancer in the age of PARPi maintenance therapy (187).	Sims T.	2022	Outcome
First Interim Analysis of the SCOUT-1 Study (NOGGO ov54, NCT04830709): A Non-Interventional Study to evaluate Treatment Patterns and Longterm Outcome in Patients with Newly Diagnosed Advanced Ovarian Cancer.	Pietzner K.	2024	Outcome
FIRST-LINE MAINTENANCE AMONG ADVANCED OVARIAN CANCER PATIENTS IN THE US ONCOLOGY NETWORK: A REAL-WORLD RETROSPECTIVE COHORT STUDY.	Chase D.	2022	Outcome
Conclusion The PTC shows an excellent prognosis with a low SBR grade and a molecular profile luminal A and a low incidence of recurrence. IGCS20_1350 327 VENOUS THROMBOEMBOLISM IN PATIENTS RECEIVING NEOADJUVANT CHEMOTHERAPY FOR OVARIAN CANCER 1	K Black	2020	Population
MO71-4 Real-world treatment of niraparib as maintenance therapy in patients newly diagnosed advanced ovarian cancer in Japan.	Shimada M.	2023	Outcome

Title	Author	Year	Exclusion reason
ODALIE Study, a retrospective analysis of a real-life cohort of patients with de novo advanced high grade epithelial ovarian cancer treated with a first-line platinum-and taxane-based chemotherapy combined with bevacizumab	Sarah Lagarde	2022	Population
Outcomes based on treatment regimen in newly diagnosed ovarian, primary peritoneal and fallopian tube cancer receiving intravenous or intraperitoneal platinum-based chemotherapy in combination with veliparib and bevacizumab.	Washington C.R.	2020	Population
Outcomes of newly diagnosed stage II ovarian, primary peritoneal and fallopian tube cancer receiving intravenous or intraperitoneal platinum based chemotherapy in combination with veliparib and bevacizumab.	Washington C.R.	2020	Population
Ovarian Cancer Retrospective European (O'CaRE) observational study to assess burden of disease and time to next treatment in real-world clinical practice: Results from the United Kingdom (UK).	McGrane J.	2021	Outcome
Patient-reported quality of life during PARP-inhibitor treatment for high-grade serous ovarian cancer (468).	Philp L.	2022	Population
PCN249 Real World Treatment Patterns of Patients with Ovarian Cancer: Analysis of Targeted Therapies in the French National Claims Data.	Wu E.	2021	Outcome
Poly (adenosine diphosphate [ADP]-ribose) polymerase inhibitor first-line maintenance among patients with newly diagnosed advanced ovarian cancer in a real-world database (351).	Liu J.	2022	Outcome
2022-RA-1235-ESGO ADULT OVARIAN GRANULOSA CELL TUMORS: CLINICAL AND IMAGING FINDINGS CHARACTERISTICS OF A TUNISIAN POPULATION SAMPLE	Rahma Bouhmida	2022	Outcome

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Title	Author	Year	Exclusion reason
2022. International Journal of Gynecological Cancer. 32;Supplement 3: A154.		2022	Outcome
Real-world-data (RWD) on platinum (Pt) outcomes after PARP inhibitors (PARPi) progression in high grade serous ovarian cancer (HGSOC) patients (p).	Plaja Salarich A.	2020	Population
Real-world effectiveness of first-line maintenance olaparib in women with BRCAmutated advanced ovarian cancer: U.S. retrospective cohort study.	Eskander R.N.	2022	Outcome
2021. International Journal of Gynecological Cancer. 31;SUPPL 1: A204-A205.		2021	Outcome
RETROSPECTIVE ANALYSIS COMPARING THE SURVIVAL OUTCOME OF NIRAPARIB AND OLAPARIB IN ADVANCED OVARIAN CANCER PATIENTS.	Kim W.-J., Lee Y.Y., Noh J., Choi C.H., Kim T.-J., Lee J.-W., Kim B.G.	2023	Population
2023. Value in Health. 26;12 Supplement: S506.		2023	Population
Safety of veliparib in combination with chemotherapy and as maintenance in front-line ovarian cancer: results in BRCAm, hrd, and whole populations from the velia trial.	Swisher EM	2020	Population
Starting dose of niraparib as first-line maintenance among patients with newly diagnosed advanced ovarian cancer in a real- world database (352).	Liu J.	2022	Outcome
SYSTEMATIC LITERATURE REVIEW OF EFFICACY AND SAFETY OF FIRST-LINE MAINTENANCE THERAPY TRIALS IN ADVANCED OVARIAN CANCER 1	Holly Guy	2020	SLR/NMA for citation chasing
The correlation of homologous recombination deficiency status with and Olaparib efficacy in Chinese ovarian cancer patients.	Peng Y.	2022	Outcome

Title	Author	Year	Exclusion reason
2022-RA-956-ESGO TREATMENT PATTERNS AND OUTCOMES AFTER PROGRESSION ON POLY-ADP RIBOSE POLYMERASE INHIBITOR MAINTENANCE THERAPY 1	Giulia Tasca	2022	Outcome
Use of PARPi among patients with advanced ovarian cancer: Results from a real-world database.	Dawood S.	2021	Outcome
VOCAL (Views of Ovarian Cancer patients-how maintenance therapy Affects their Lives) study: A lens into the financial and quality of life (QoL) impact of disease burden and ethnic disparities reported directly by the patient.	Chase D.M.	2022	Outcome
Platine, Avastin and OLaparib in 1st Line.	-	2015	Outcome
Clinical characteristics and treatment modalities in women with newly diagnosed advanced high-grade serous epithelial ovarian cancer in Taiwan.	Hsu	2024	Outcome
Efficacy and safety of PARP inhibitors in elderly patients with advanced ovarian cancer: a systematic review and metaanalysis	Brigida Anna Maiorano	2022	SLR/NMA for citation chasing
Medical cannabis and its effect on oncological outcomes in patients with ovarian cancer treated with PARP inhibitors.	Peleg Hasson	2024	Intervention
PARP inhibitor era in ovarian cancer treatment: a systematic review and metaanalysis of randomized controlled trials	István Baradács	2024	SLR/NMA for citation chasing
Impact of Treatment Delay on the Prognosis of Patients with Ovarian Cancer: A Population-based Study Using the Surveillance, Epidemiology, and End Results Database.	Zhao	2024	Population
Quality of life in ovarian cancer patients treated with bevacizumab: a meta-analysis.	Wu	2024	SLR/NMA for citation chasing

Title	Author	Year	Exclusion reason
Increase in creatinine levels associated with niraparib maintenance therapy in ovarian cancer.	Takahashi	2024	Population
Comparison of poly (ADP-ribose) polymerase inhibitors (PARPis) as maintenance therapy for newly-diagnosed and platinum-sensitive recurrent ovarian cancer with BRCA mutational status: a systematic review and network meta-analysis.	Zhou	2024	SLR/NMA for citation chasing
Safety and efficacy of Rucaparib in the treatment of ovarian cancer and patients with BRCA mutation: a systematic review and meta-analysis of phase III randomized clinical trials.	Mustafa	2024	SLR/NMA for citation chasing
The power of hope: Views of Ovarian Cancer patients on how maintenance therapy Affects their Lives (VOCAL).	Chase	2024	Outcome
The impact of PARP inhibitors in the whole scenario of ovarian cancer management: A systematic review and network meta-analysis.	Staropoli	2024	SLR/NMA for citation chasing
Frequency of peripheral PD-1+regulatory T cells is associated with treatment responses to PARP inhibitor maintenance in patients with epithelial ovarian cancer.	Park	2023	Outcome
Impact of PARP inhibitor maintenance therapy in newly diagnosed advanced epithelial ovarian cancer: A meta-analysis.	Lee	2023	SLR/NMA for citation chasing
Risk factors for the failure of first-line PARP inhibitor maintenance therapy in patients with advanced ovarian cancer: Gynecologic Oncology Research Investigators Collaboration Study (GORILLA-3004).	Kim	2023	Outcome
Description of a Retrospective Cohort of Epithelial Ovarian Cancer Patients with Brain Metastases: Evaluation of the Role of PARP Inhibitors in this Setting.	Alizzi	2023	Population

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Title	Author	Year	Exclusion reason
Ovarian Real-World International Consortium (ORWIC): A multicentre, real-world analysis of epithelial ovarian cancer treatment and outcomes.	Cheeseman	2023	Population
Pharmacist-led olaparib follow-up service for ambulatory ovarian cancer patients: A prospective study in a tertiary specialized cancer hospital in China	Yanting Wang	2022	Outcome
Real-World Data on Newly Diagnosed BRCA-Mutated High-Grade Epithelial Ovarian Cancers: The French National Multicenter ESME Database.	Bini	2022	Outcome
Comparative Efficacy and Safety of Poly (ADP-Ribose) Polymerase Inhibitors in Patients With Ovarian Cancer: A Systematic Review and Network Meta-Analysis.	Luo	2022	SLR/NMA for citation chasing
Real-World Treatment Patterns, Survival, and Costs for Ovarian Cancer in Canada: A Retrospective Cohort Study Using Provincial Administrative Data.	Hurry	2021	Outcome
Population-adjusted indirect treatment comparison of maintenance PARP inhibitor with or without bevacizumab versus bevacizumab alone in women with newly diagnosed advanced ovarian cancer.	Hettle	2021	SLR/NMA for citation chasing
PARP Inhibitors in Patients With Newly Diagnosed Advanced Ovarian Cancer: A Meta-Analysis of Randomized Clinical Trials.	Wang	2020	SLR/NMA for citation chasing
Angiogenesis inhibitors for the treatment of epithelial ovarian cancer.	Gaitskell	2023	SLR/NMA for citation chasing
Comparison of PARPi efficacy according to homologous recombination deficiency biomarkers in patients with ovarian cancer: a systematic review and meta-analysis.	Batalini	2023	SLR/NMA for citation chasing

Title	Author	Year	Exclusion reason
Cytoreductive surgery for advanced epithelial ovarian cancer in the poly(ADP-ribose) polymerase inhibitors era-Is it time for a new paradigm shift? A systematic review and meta-analysis.	Peters	2023	SLR/NMA for citation chasing
Analysis of adverse events and quality of life in high-grade serous ovarian cancer patients with Olaparib maintenance therapy A single-center study in China	Yi Jiang	2023	Outcome
Real-world outcomes associated with use of front-line bevacizumab in ovarian cancer.	Ethier	2023	Population
Veliparib with frontline chemotherapy and as maintenance in Japanese women with ovarian cancer: a subanalysis of efficacy, safety, and antiemetic use in the phase 3 VELIA trial.	Mizuno	2023	Population
Contrasting clinical characteristics and treatment patterns in women with newly diagnosed advanced-stage epithelial ovarian cancer in Australia, South Korea and Taiwan.	Chou	2023	Outcome
CA-125 KELIM as a Potential Complementary Tool for Predicting Veliparib Benefit: An Exploratory Analysis From the VELIA/GOG-3005 Study	Benoit You	2023	Population
A Real World Perspective of PARP Inhibitor Use in Gynecological Cancer Patients.	Lee	2023	Outcome
The first Chinese National Union of Real-world Gynaecological Oncology Research and Patient Management Platform: A retrospective study.	Zeng	2022	Population
[Real-world clinical data analysis of PARPi as first-line maintenance therapy in newly diagnosed epithelial ovarian cancer patients].	Wang	2022	Language (Non-English)

Title	Author	Year	Exclusion reason
Maintenance therapy with a poly(ADP-ribose) polymerase inhibitor in patients with newly diagnosed advanced epithelial ovarian cancer: individual patient data and trial-level meta-analysis.	Gulia	2022	SLR/NMA for citation chasing
Real-life data on treatment and outcomes in advanced ovarian cancer: An observational, multinational cohort study (RESPONSE trial)	Christian Marth	2022	Population
Bevacizumab versus PARP-inhibitors in women with newly diagnosed ovarian cancer: a network meta-analysis	Young Ju Suh	2022	SLR/NMA for citation chasing
Treatment patterns after poly-ADP ribose polymerase (PARP) inhibitors in epithelial ovarian cancer patients	Sivakumaran T.	2022	Outcome
Poly(ADP-ribose) polymerase (PARP) inhibitors for the treatment of ovarian cancer (Review)	Cochrane Library	2022	SLR/NMA for citation chasing
Austria-based real-world data on bevacizumab in newly diagnosed epithelial ovarian cancer.	Tsibulak	2022	Population
Prospective non-interventional BELOVA/BGOG-ov16 study on safety of frontline bevacizumab in elderly patients with FIGO stage IV ovarian cancer: a study of the Belgian and Luxembourg Gynaecological Oncology Group.	Vergote	2022	Population
Patterns of use and outcomes of adjuvant bevacizumab therapy prior to regulatory approval in women with newly diagnosed ovarian cancer.	Gamble	2022	Population
Evaluation of patterns of progression on poly (ADP-ribose) polymerase inhibitor (PARPi) maintenance in ovarian cancer: a cross-sectional study	Cerda V.	2022	Outcome
Impact of homologous recombination status and responses with veliparib combined with first-line chemotherapy in ovarian cancer in the Phase 3 VELIA/GOG-3005 study.	Swisher	2022	Population

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Title	Author	Year	Exclusion reason
Prognostic significance of ethnicity and age in advanced stage epithelial ovarian cancer: An NRG oncology/gynecologic oncology group study.	duPont	2022	Population
Evaluation of maintenance treatment with PARP inhibitors in ovarian carcinoma patients responding to platinum therapy: Use of restricted mean survival time as an index of efficacy.	Cancanelli	2022	Study design
Utilization of Poly(ADP-Ribose) Polymerase Inhibitors in Ovarian Cancer: A Retrospective Cohort Study of US Healthcare Claims Data.	Arend	2022	Outcome
Population-adjusted indirect treatment comparison of the SOLO1 and PAOLA-1/ENGOT-ov25 trials evaluating maintenance olaparib or bevacizumab or the combination of both in newly diagnosed, advanced BRCA-mutated ovarian cancer.	Vergote	2021	SLR/NMA for citation chasing
Progression-free survival by investigator versus blinded independent central review in newly diagnosed patients with high-grade serous ovarian cancer: Analysis of the VELIA/GOG-3005 trial.	Aghajanian C.	2021	Population
Poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitors as maintenance therapy in women with newly diagnosed ovarian cancer: a systematic review and meta-analysis.	Cheng	2021	SLR/NMA for citation chasing
The efficacy and safety of niraparib for ovarian cancer: a single-center observational study from China	Jing Ni	2021	Outcome
Consolidation or maintenance systemic therapy for newly diagnosed stage II, III, or IV epithelial ovary, fallopian tube, or primary peritoneal carcinoma: A systematic review.	Hirte	2021	SLR/NMA for citation chasing
PARP inhibitors in breast and ovarian cancer with BRCA mutations: a meta-analysis of survival.	Shao	2021	SLR/NMA for citation chasing

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Title	Author	Year	Exclusion reason
The use of bevacizumab in the modern era of targeted therapy for ovarian cancer: A systematic review and meta-analysis.	Liu	2021	SLR/NMA for citation chasing
Myelodysplastic syndrome and acute myeloid leukaemia in patients treated with PARP inhibitors: a safety meta-analysis of randomised controlled trials and a retrospective study of the WHO pharmacovigilance database.	Morice	2021	SLR/NMA for citation chasing
PARP inhibitors as maintenance therapy in newly diagnosed advanced ovarian cancer: a meta-analysis.	Lin	2021	SLR/NMA for citation chasing
Poly (ADP-ribose) polymerase (PARP) inhibitor regimens for ovarian cancer in phase III randomized controlled trials: a network meta-analysis.	Gong	2020	Study design
Real world experience of poly (ADP-ribose) polymerase inhibitor use in a community oncology practice.	Eakin	2020	Population
Bevacizumab as maintenance treatment in BRCA mutated patients with advanced ovarian cancer: A large, retrospective, multicenter case-control study.	Lorusso	2020	Population
A phase I study of intravenous or intraperitoneal platinum based chemotherapy in combination with veliparib and bevacizumab in newly diagnosed ovarian, primary peritoneal and fallopian tube cancer.	Moore	2020	Population
Real-world treatment patterns in patients with advanced (stage III-IV) ovarian cancer in the USA and Europe.	Hall	2020	Outcome
Poly(ADP-ribose) polymerase inhibitors as maintenance treatment in patients with newly diagnosed advanced ovarian cancer: a meta-analysis.	Ibrahim	2020	SLR/NMA for citation chasing

Title	Author	Year	Exclusion reason
Efficacy and safety of PARP inhibitors as the maintenance therapy in ovarian cancer: a meta-analysis of nine randomized controlled trials	Fengping Shao	2020	SLR/NMA for citation chasing
Patient preferences for maintenance PARP inhibitor therapy in ovarian cancer treatment.	Havrilesky	2020	Population
Tolerability of Bevacizumab in elderly Ovarian cancer patients (TURBO study): a case-control study of a real-life experience.	Amadio	2020	Population
Bevacizumab combined with platinum-taxane chemotherapy as first-line treatment for advanced ovarian cancer: a prospective observational study of safety and efficacy in Japanese patients (JGOG3022 trial).	Komiyama	2019	Outcome
Olaparib in the therapy of advanced ovarian cancer: first real world experiences in safety and efficacy from China.	Ni	2019	Outcome
Comparison of PARPis with Angiogenesis Inhibitors and Chemotherapy for Maintenance in Ovarian Cancer: A Network Meta-Analysis.	Feng	2019	SLR/NMA for citation chasing
Overall survival results of AGO-OVAR16: A phase 3 study of maintenance pazopanib versus placebo in women who have not progressed after first-line chemotherapy for advanced ovarian cancer	I Vergote	2019	Intervention
Angiogenesis Inhibitors for the Treatment of Ovarian Cancer An Updated Systematic Review and Meta-analysis of Randomized Controlled Trials	Haihong Wang	2018	SLR/NMA for citation chasing
Quality of life in patients with advanced epithelial ovarian cancer (EOC) randomized to maintenance pazopanib or placebo after first-line chemotherapy in the AGO-OVAR 16 trial. Measuring what matters-patient-centered end points in trials of maintenance therapy.	Friedlander	2018	Intervention

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Title	Author	Year	Exclusion reason
Long-Term Responders on Olaparib Maintenance in High-Grade Serous Ovarian Cancer: Clinical and Molecular Characterization	Stephanie Lheureux	2017	Population
Bevacizumab combined with chemotherapy for ovarian cancer: an updated systematic review and meta-analysis of randomized controlled trials.	Wu	2017	SLR/NMA for citation chasing
Comparative efficacy of targeted maintenance therapy for newly diagnosed epithelial ovarian cancer: a network meta-analysis.	Xiaoyu Xu	2019	Population
Bevacizumab Dose Affects the Severity of Adverse Events in Gynecologic Malignancies.	Lee	2019	Population
BRCA1/2 mutations associated with progression-free survival in ovarian cancer patients in the AGO-OVAR 16 study.	Harter	2016	Intervention
Neoadjuvant Chemotherapy Followed by Maintenance Therapy With or Without Bevacizumab in Unresectable High-Grade Serous Ovarian Cancer: A Case-Control Study.	Petrillo	2015	Population
Poly(ADP-ribose) polymerase (PARP) inhibitors for the treatment of ovarian cancer.	Wiggans	2015	SLR/NMA for citation chasing
Addition of bevacizumab to chemotherapy in patients with ovarian cancer: a systematic review and meta-analysis of randomized trials.	Li	2015	SLR/NMA for citation chasing
Phase III trials of standard chemotherapy with or without bevacizumab for ovarian cancer: a meta-analysis.	Zhou	2013	Population
Phase II study of carboplatin, paclitaxel, and bevacizumab with maintenance bevacizumab as first-line chemotherapy for advanced mullerian tumors.	Penson	2010	Population

Title	Author	Year	Exclusion reason
Veliparib with carboplatin and paclitaxel in frontline high-grade serous ovarian cancer (HGSOC): Efficacy and safety of paclitaxel weekly and every 3 weeks in the VELIA study.	Okamoto A.	2020	Outcome
PFS by blinded independent central review (BICR) in the VELIA trial of veliparib (V) plus carboplatin/paclitaxel (CP) and as monotherapy in newly diagnosed patients (pts) with high-grade serous ovarian cancer (HGSC).	Aghajanian C.	2020	Population
Health-related quality of life (HRQoL) in patients (pts) with newly diagnosed stage III or IV ovarian cancer treated with veliparib (vel) + chemotherapy followed by vel maintenance (maint).	Cella D.	2020	Population
Exploring the relationship between homologous recombination score and progression-free survival in BRCA wildtype ovarian carcinoma: Analysis of veliparib plus carboplatin/paclitaxel in the velia study.	Swisher E.M.	2020	Population
SNP was detected by the PCR-RFLP followed by sequencing. BUB1 expression, BUB1mRNA and miRNA-495 were assessed using IHC & qRT-PCR	I Larionova	2022	Outcome
Risk of secondary hematologic malignancies in patients with ovarian cancer treated with PARP inhibitors: A combined metaanalysis of seven phase III randomized controlled trials.	Htut T.	2020	SLR/NMA for citation chasing
A comprehensive systematic review and network meta-analysis: the role of anti-angiogenic agents in advanced epithelial ovarian cancer.	Helali	2022	Population
BRCA/HRD genetic status does not increase toxicity to PARP inhibitors or next-line cytotoxic chemotherapy in women with epithelial ovarian cancer.	Wield A.	2022	Outcome

Title	Author	Year	Exclusion reason
Comparison of advanced ovarian cancer patients treated with or without bevacizumab in the US Community Oncology Clinics.	DeClue	2023	Population
Population-adjusted indirect treatment comparison (PAITC) of maintenance PARP inhibitor (PARPi) with or without bevacizumab versus bevacizumab in women with newly diagnosed ovarian cancer (OC).	Hettle R.	2020	Study design

B.1.1.5 Summary of trials used for indirect or mixed treatment comparisons

The clinical SLR identified eight relevant studies for 1L maintenance in aOC: SOLO-1, PAOLA-1, ATHENA-MONO, PRIME, PRIMA, FLAMES, OVARIO, Oda 2024 (Appendix B.1.1.4).²⁰ The Oda 2024 trial was excluded on the basis that it was a Phase 2 single-arm trial with limited sample size (N=32), while the FLAMES, OVARIO and PAOLA-1 trials were excluded as they assessed seneparib, niraparib plus bevacizumab and olaparib plus bevacizumab as interventions, respectively, which are not considered relevant comparators for niraparib.²⁰ The PARPi monotherapy treatment options (olaparib and rucaparib) which are considered relevant comparators for niraparib are listed in Section 1.2, along with the rationale for their relevance.

Methods and outcomes of studies included in indirect or mixed treatment comparisons

Four unique clinical trials were identified and included in the ITC feasibility assessment (FA). Only studies assessing PARPi monotherapy initiated during the maintenance phase were included in the assessment (Section 2.7, Figure 10). The primary focus was to determine the possibility of estimating relative effects for olaparib vs niraparib in the BRCAm and high-risk subgroup and rucaparib vs niraparib in the BRCAwt subgroup.

Effect Modifiers and Prognostic Factors

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

The process for selecting the most appropriate ITC approach involved identifying all treatment effect modifiers (EMs) and prognostic factors (PFs) and assessing if they were balanced across all study populations. The list of potential EMs/PFs was identified based on a review of HTA submissions, published ITCs, stratification factors in pivotal trials, and subgroup analyses for each trial. Note that several of these variables are highly correlated, including i) NACT and timing of surgery, ii) residual disease status and history of cytoreductive surgery, and iii) BRCa status and HRd status.^{28,136}

1. Age
2. FIGO stage
3. Prior bevacizumab use
4. Eastern Cooperative Oncology Group performance status (ECOG PS)
5. Response to first-line chemotherapy
6. Histology
7. BRCa status
8. CA-125 level
9. Tumour location
10. Receipt of neoadjuvant chemotherapy
11. Residual disease status
12. History of cytoreductive surgery
13. HRd status
14. Timing of surgery

Study Design

All four RCTs included in the ITC FA were generally similar in terms of study design (i.e., phase 3 and double-blind studies). Three out of four of the RCTs were conducted internationally, with the exception of the PRIME trial, which was exclusively conducted in China. There were some differences in the criteria for assessing response to first-line chemotherapy (complete response/partial response) using CA-125 levels across trials. PRIMA and PRIME included only patients who had CA-125 in the normal range or a >90% decrease in CA-125 during first-line treatment that was stable for at least 7 days and did not increase >15% from the completion of chemotherapy. In contrast, ATHENA-MONO and SOLO-1 enrolled patients who had CA-125 in the normal range. Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

or above the ULN, provided that a second measurement taken at least 7 days later did not show an increase of $\geq 15\%$ (Table 87).

Table 87. Summary of study designs

	PRIMA¹²	PRIME¹³	ATHENA-MONO¹⁴	SOLO-1¹⁵
Intervention	Niraparib	Niraparib	Rucaparib	Olaparib
Comparator	Placebo	Placebo	Placebo	Placebo
Study design	RCT (double-blind)	RCT (double-blind)	RCT (double-blind)	RCT (double-blind)
Trial phase	Phase III	Phase III	Phase III	Phase III
Number of patients	Niraparib: 487 Placebo: 246	Niraparib: 255 Placebo: 129	Rucaparib: 425 Placebo: 111	Olaparib: 260 Placebo: 131
Response to 1L chemotherapy	CR/PR ^a	CR/PR ^a	NED, CR/PR or GCIG CA-125 response ^b	CR/PR ^c
Country	181 centres in 20 countries (Europe, North America)	29 centres in China	200 centres in 24 countries (Asia, Australia/New Zealand, Europe, North America)	International 15 countries (Asia, Australia, Europe, North America, South America)
HRD/BRCA tests	Myriad's myChoice HRD test ^d Sponsor will accept BRCA results obtained according to local practice guidelines	gBRCAm ^e and HRD status determined by BGI Genomics HRD assay	FoundationOne CDx next-generation sequencing assay	Can be randomized based on known BRCAm test result Myriad's myChoice HRD test required for confirmation/determination
Assessment schedules	Assessed at screening, then every 12 weeks (+/- 1 week) until progression confirmed by BICR	Assessed at screening, then every 12 weeks (+/- 1 week) until progression confirmed by BICR	Assessed at screening, then every 12 weeks (+/- 1 week) for the first 3 years, and every 24 weeks thereafter until objective radiologic progressive disease	Assessed at baseline, then every 12 weeks (+/- 1 week) up to 3 years, and then every 24 weeks until objective radiological disease progression

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

	PRIMA¹²	PRIME¹³	ATHENA-MONO¹⁴	SOLO-1¹⁵
Maximum treatment duration	36 months. Patients benefitting from treatment per investigator assessment were eligible to continue receiving treatment beyond 3 years	Up to 36 months	Up to 24 months	Up to 24 months
PFS definition	Time from the date of randomization to the date of first documentation of progression or death, whichever occurs first	Same as PRIMA	Same as PRIMA	Same as PRIMA
PFS censoring rules	1. No baseline OR no post-baseline radiographic assessments = censor at randomization date 2. No progressive disease or death = censor at last evaluable assessment 3. Progressive disease or death occurred after two or more missed assessments = censor at last evaluable assessment prior to missed interval 4. Received subsequent anti-cancer therapy before progressive disease or death = censor at last	Similar to PRIMA ^f	Same as PRIMA	1-3. Same as PRIMA 4. Progression is always considered an event, regardless if a patient receives another anti-cancer therapy prior to progression.

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

	PRIMA¹²	PRIME¹³	ATHENA-MONO¹⁴	SOLO-1¹⁵
	evaluable assessment prior to treatment initiation			

Abbreviations: BICR = blinded independent central review; BRCA = breast cancer gene; BRCAm = BRCA mutation; CA-125 = cancer antigen 125; CR = complete response; GCIG = Gynaecologic Cancer InterGroup; gBRCAm = germline BRCA mutation; HRD = homologous recombination deficiency; HRDpos = homologous recombination deficiency positive; NED = no evidence of disease; NVRD = no visible residual disease; PFS = progression-free survival; PR = partial response; RECIST v1.1 = Response Evaluation Criteria in Solid Tumours version 1.1; RCT = randomised controlled trial; sBRCA = somatic BRCA mutation; ULN = upper limit of normal.

^aPRIMA and PRIME included only patients with CA-125 in the normal range or a decrease of more than 90% during first-line therapy, stable for at least 7 days (no increase > 15% from completion of chemotherapy).

^bATHENA-MONO included patients without evidence of disease progression radiologically or through rising CA125 (per GCIG guidelines) at any time during first-line treatment, which included patients with no evidence of measurable disease by RECIST v1.1 (if complete resection/NVRD at primary or interval cytoreductive surgery); or a PR or CR per RECIST v1.1 (if measurable disease was present after surgery and before chemotherapy); or a GCIG CA-125 response (if only non-measurable disease was present after surgery and before chemotherapy). Pretreatment CA-125 had to be within ULN, or, if greater than ULN, a second assessment must be performed at least 7 days after the first. If the second assessment is ≥15% more than the first, the patient was considered not eligible.

^cSOLO-1 included patients with a clinical CR, PR or clinical evidence of disease progression on the post-treatment scan or a rising CA-125 level, following completion of chemotherapy. Pretreatment CA-125 had to be within ULN or, if greater than ULN, a second assessment had to be performed at least 7 days after the first. If the second assessment was ≥15% more than the first, the patient was considered not eligible.

^dFor patients with a documented deleterious gBRCA or sBRCA mutation by local results, randomisation may occur before the HRD results are available; for stratification purposes, these patients will be considered as having HRDpos tumours.

^epatients were stratified by germline BRCAm status, whereas other trials did not differentiate between type (germline vs somatic) of BRCAm

^fIn PRIMA, PAOLA-1, SOLO-1, censor at randomisation unless death occurred within two visits of randomisation (25 weeks, allowing for a visit window). In PRIME, censor at randomisation if no post-baseline assessments unless death occurred before first scheduled visit.

HRD Status

BRCA and HRD testing was done at screening in PRIMA, PRIME, SOLO-1, and ATHENA-MONO. In PRIME, patients were stratified by germline BRCAm status, whereas other trials did not differentiate between the type (germline vs somatic) of BRCAm. Additionally, PRIME and ATHENA-MONO used a different HRD assay in comparison with the other trials (Table 88).

Table 88. Comparison of HRD Testing

Trial	HRD/BRCA Tests
PRIMA	Myriad's myChoice HRD test ^a Sponsor will accept BRCA results obtained according to local practice guidelines
PRIME	gBRCAm and HRD status determined by the BGI Genomics HRD assay

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

SOLO-1	Can be randomised based on the known BRCAm test result Myriad's myChoice HRD test required for confirmation/determination
ATHENA-MONO	FoundationOne CDx next-generation sequencing assay

Abbreviations: BGI = Beijing Genomics Institute; BRCA = breast cancer gene; BRCAm = BRCA mutation; CDx = companion diagnostic; gBRCAm = germline BRCA mutation; HRD = homologous recombination deficiency; HRDpos = homologous recombination deficiency positive; Myriad = Myriad Genetics; NGS = next-generation sequencing.

^a For patients with a documented deleterious gBRCA or sBRCA mutation by local results, randomisation may occur before the HRD results are available; for stratification purposes, these patients will be considered as having HRDpos tumours.

Subsequent Therapies

Only PRIMA explicitly reported that cross-over was not permitted; this was not reported for all other studies. Nevertheless, 14% of patients in the placebo arm received subsequent niraparib and 3% of niraparib patients were retreated with niraparib in a subsequent line. The percent of patients receiving subsequent PARPi varied across trials (i.e., PRIMA, SOLO-1, and ATHENA-MONO), subgroups, and treatment arms. These discrepancies would likely bias and diminish the reliability of indirect comparisons for OS and PFS2, as these outcomes directly depend on the effect of subsequent treatments. Additionally, there is no data available on subsequent treatments in PRIME, and thus it is not possible to know how it compares with PRIMA, ATHENA-MONO, and SOLO-1. Due to limited data (e.g., missing information on specific line / intended use of PARPi's [treatment vs maintenance], and specific PARPi treatments received), it would not be possible to properly adjust for differences in subsequent treatments across trials.

Table 89. Comparison of Subsequent Treatment Distributions

Subsequent PARPi	ITT		BRCAm	
	Active arm	PBO	Active arm	PBO
PRIMA				
Any subs. trt.	████	████	-	-
Any PARPi	57 (12%)	93 (38%)	29 (19%)	41 (58%)
PARPi as 2L	40 (8.2%)	75 (30.5%)	24 (16%)	33 (46.5%)
PARPi as 3L+	17 (3.5%)	18 (7.3%)	(3%)	8 (11%)
Other PARPi trials				

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Subsequent PARPi	ITT		BRCAm	
	Active arm	PBO	Active arm	PBO
SOLO-1¹⁵	-	-	Any subs: 46.9% Any PARPi: 14.6% 2L PARPi: 5.8% 3L+ PARPi: 8.9%	Any subs: 74% Any PARPi: 44.3% 2L PARPi: 24.4% 3L+ PARPi: 19.9%
ATHENA-MONO¹⁴	Any subs: 53.3% Any PARPi: 5.6%	Any subs: 53.3% Any PARPi: 23.4%	-	-

Abbreviations: 2L = second line; 3L+ = third line and beyond; ATHENA-MONO = a specific clinical trial; BRCAm = BRCA mutation; ITT = intention-to-treat; PARPi = PARP inhibitor; PBO = placebo; PRIMA = a specific clinical trial; SOLO-1 = a specific clinical trial; subs. trt. = subsequent treatment.

Treatment Characteristics

All four trials were placebo-controlled. There was consistency in the administration and frequency of the placebo arm. There are some differences in treatment duration across trials, with this being up to 36 months in niraparib trials (PRIMA, PRIME) compared to up to 24 months in ATHENA-MONO and SOLO-1. Additionally, in PRIMA, patients who were deemed to benefit from treatment by the investigator had the option to continue receiving treatment beyond 3 years, but this was not mandatory.

Table 90. Treatment Characteristics

Intervention	Comparator	Trial	Dosage	Route of Administration	Frequency of Administration	Cycle Length	Treatment Duration (as per trial)
Niraparib	Placebo	PRIMA ¹²	300 mg or 200 mg*	Oral	Once daily	28 days	For 36 months or until disease progression
Niraparib	Placebo	PRIME ¹³	300 mg or 200 mg*	Oral	Once daily	28 days	For 36 months or until disease progression
Rucaparib	Placebo	ATHENA-MONO ¹⁴	600 mg	Rucaparib & placebo: Oral Placebo: IV	Oral: twice daily IV: every 4 weeks [^]	28 days	For 24 months ⁺ or until disease progression. Treatment

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

							beyond disease progression permitted
Olaparib	Placebo	SOLO-1 ¹⁵	300 mg	Oral	Twice daily	Not reported	Up to 2 years or continuously until objective radiological disease progression [‡]

Abbreviations: IV = intravenous

*In patients weighing less than 77 kg, a platelet count of less than 150,000 /μL or both.

^Starting in cycle 2

†After initiation of placebo IV administration

‡ Patients with stable disease may continue treatment beyond 2 years

Inclusion/Exclusion Criteria

General similarities:

- All RCTs included in the ITC FA enrolled patients with high-grade serous or endometrioid ovarian cancer, including primary peritoneal and fallopian tube cancers, at FIGO stages III/IV.
- All RCTs required patients to have had a clinical complete or partial response following first-line chemotherapy.

Notable differences across trials:

- There was variability in surgical history requirements across trials: the PRIMA trial enrolled Stage III patients with visible residual disease after primary debulking surgery but excluded those with complete cytoreduction, whereas the ATHENA-MONO, SOLO-1 and PRIME trials included patients irrespective of residual disease status
- In ATHENA-MONO and SOLO-1, complete response was defined as the absence of measurable disease on post-treatment scans or investigator assessed complete response. While in PRIMA complete response was as per RECIST v1.1
- CA-125 criteria varied across the trials, patients enrolled in PRIMA were required to have either a normal CA-125 level or a >90% reduction in CA-125 following frontline platinum-based treatment
- In the PRIMA trial, it was required that all residual disease following chemotherapy be 2 cm or less, a criterion not specified in other trials

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

- SOLO-1 only recruited patients with BRCA mutations, while the other trials recruited patients regardless of BRCA mutation status.
- Prior use of bevacizumab was permitted in most trials (PRIMA, PRIME, ATHENA-MONO) and prohibited in the SOLO-1 trial.

The eligibility criteria for these trials exhibit considerable heterogeneity, underscoring substantial differences in the target populations that these trials aimed to study. The different eligibility criteria for BRCA mutation status, surgical history, and prior bevacizumab use could lead to substantial imbalances in baseline distributions, limiting the comparability of outcomes across the trials.

Clinical Risk Status

PRIMA enrolled patients at a high risk of disease progression, whereas the comparator studies enrolled a mix of low and high-risk patients. In particular, only PRIMA excluded Stage III patients with complete cytoreduction (no visible residual disease [VRD]) following primary debulking surgery (PDS)—who would have a lower risk of progression. As clinical risk is a key treatment effect modifier, it is necessary to restrict any ITCs based on PRIMA to the high-risk population for valid statistical inference. SOLO-1 reported outcomes in a comparable 'PRIMA-like' population (i.e., high-risk subgroups, Table 91).

It must be noted that outcomes in a comparable 'PRIMA-like' high-risk population were not reported in the ATHENA-MONO and PRIME studies.

Table 91. High and low-Risk Definitions

Definition	PRIMA	SOLO-1
Higher-risk	1) Patients with inoperable Stage III and IV disease; 2) All Stage IV patients with operable disease; 3) Patients with Stage III or IV disease treated with NACT and interval debulking surgery; 4) Patients with stage III disease who have VRD after PDS. <i>Stage III with complete cytoreduction (no VRD) following PDS not allowed</i>	Those with stage IV disease or those with stage III disease who had either residual disease following PDS or had undergone interval surgery ^a

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Lower-risk	N/A	Those with stage III disease who did not have residual disease following PDS

Abbreviations: NACT = neoadjuvant chemotherapy; PDS = primary debulking surgery; VRD = visible residual disease

^aStage III patients with inoperable disease and who did not undergo surgery were excluded from SOLO-1 study

Baseline Characteristics

Available baseline characteristics in the intent-to-treat (ITT) population and high-risk subgroups of interest for ITCs are summarised in this section.

Overall Population

For comparisons vs rucaparib (ATHENA-MONO), subgroup analyses for ATHENA-MONO have not been published in a PRIMA-like population (i.e., excluding the lower-risk stage III patients without VRD). Therefore, it was only possible to compare niraparib (based on data from PRIME rather than PRIMA) with rucaparib (ATHENA-MONO) in a broader population comprising a mix of both low and high-risk patients.

Patient-level data were not available for either rucaparib (ATHENA-MONO) or niraparib (PRIME), making only unadjusted ITCs (e.g., Bucher's method) possible. Baseline characteristics were compared to identify noteworthy imbalances in EMs that could distort a Bucher ITC. Substantial differences were found in the distributions of age, ECOG performance scores and responses to 1L chemotherapy across the trials, which may bias an ITC of ATHENA-MONO versus PRIME. Additionally, there were imbalances in CA-125 levels, primary tumour locations, histology, and proportion of patients with BRCA mutations (Table 92).

Table 92. Baseline Characteristics: Overall Population

	PRIME		ATHENA-MONO	
	Niraparib (n=255)	Placebo (n=129)	Rucaparib (n=427)	Placebo (n=111)
Age (years), median (range)	53 (32 - 77)	54 (33 - 77)	61 (30-83)	61 (31 – 80)
Race, n (%)				
White	NR	NR	328 (76.8)	87 (78.4)
Black	NR	NR	NR	NR
Asian	255 (100.0)	129 (100.0)	80 (18.7)	16 (14.4)
Other	NR	NR	11 (2.6)	6 (5.4)

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

FIGO stage, n (%)				
Stage III	182 (71.4)	94 (72.9)	323 (75.6)	78 (70.3)
Stage IV	73 (28.6)	35 (27.1)	104 (24.4)	33 (29.7)
ECOG PS, n (%)				
0	98 (38.4)	52 (40.3)	295 (69.1)	76 (68.5)
1	157 (61.6)	77 (58.7)	131 (30.7)	35 (31.5)
Primary tumour location, n (%)				
Ovary	229 (89.8)	117 (90.7)	336 (78.7)	85 (76.6)
Fallopian tube	19 (7.5)	9 (7)	50 (11.7)	18 (16.2)
Primary peritoneal	7 (2.7)	3 (2.3)	41 (9.6)	8 (7.2)
Histology, n (%)				
Serous	253 (99.2)	128 (99.2)	384 (89.9)	106 (95.5)
Endometrioid	2 (0.8)	0 (0.0)	13 (3.0)	1 (0.9)
Clear cell	NR	NR	13 (3.0)	2 (1.8)
Mixed	NR	NR	10 (2.3)	1 (0.9)
Other	0 (0.0)	1 (0.8)	7 (1.6)	1 (0.9)
BRCA mutation, n (%)				
Yes	85 (33.3)	40 (31.0)	91 (21.3)	24 (21.6)
No	NR	NR	336 (78.8)	87 (78.4)
Prior bevacizumab use, n (%)				
Yes	NR	NR	84 (19.7)	12 (10.8)
No	NR	NR	NR	NR
Response to 1L chemotherapy, n (%)				
Complete response	212 (83.1)	103 (79.8)	73 (17.1)	11 (9.9)
Partial response	43 (16.9)	26 (20.2)	76 (17.8)	22 (19.8)
No evidence of disease	NR	NR	224 (52.5)	64 (57.7)
CA-125 level, n (%)				
≤ULN	252 (98.8)	128 (99.2)	371 (86.9)	100 (90.1)
>ULN	3 (1.2)	1 (0.8)	56 (13.1)	11 (9.9)
Receipt of NACT, n (%)				
Yes	NR	NR	218 (51.1)	57 (51.4)
No	NR	NR	NR	NR
Timing of surgery, n (%)				
PCS/PDS or upfront	NR	NR	209 (48.9)	54 (48.6)
ICS/IDS	NR	NR	218 (51.1)	57 (51.4)

Abbreviations: 1L = first-line; ECOG-PS = Eastern Cooperative Oncology Group-performance status; FIGO = International Federation of Gynecology and Obstetrics; ICS = interval cytoreductive surgery; IDS = interval debulking surgery; ITT = intent-to-treat; PCS = primary cytoreductive surgery; PDS = primary debulking surgery; NR = not reported; ULN = upper limit of normal

HRd, HRd/BRCAwT, BRCaM, and HRp Subgroups

In the absence of BRCAwT data for rucaparib (from ATHENA-MONO trial), ITC analyses vs niraparib (based on the PRIME trial) were conducted for the ITT population and any subgroup for which data were available. Comparisons were conducted in the HRd, HRd/BRCAwT, BRCaM, and HRp subgroups. Baseline patient Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

characteristics were not available for these subgroups in ATHENA-MONO and/or PRIME, making a comparison of EMs across study populations not possible.

BRCAm and High-Risk Subgroup

The ITC of interest for the BRCAm and high-risk subgroup is between olaparib (SOLO-1) vs niraparib (PRIMA). Patient-level data are available for the PRIMA trial, and aggregate data are available for SOLO-1. However, although the possibility of conducting an anchored STC was explored, it was deemed inappropriate and unreliable due to counter-intuitive associations between PFS and both ECOG and age. These counter-intuitive associations may be explained by the fact that we have focused on a small subset of the data (i.e., BRCAm for PRIMA and high-risk for SOLO-1), because associations in the ITT population were either reversed or null. It should be noted that BRCA mutation status was not a stratification factor in PRIMA.

Table 93. Baseline Characteristics: BRCAm and High-risk Subgroup

	PRIMA		SOLO-1	
	Niraparib ████████	Placebo ████████	Olaparib (n=146)	Placebo (n=73)
Age (years), Median (Range)	██████	████████	54 (29–82)	54 (35–84)
Race, n (%)				
White	████████	████████	NR	NR
Black	██████	██████	NR	NR
Asian	██████	██████	NR	NR
Other	██████	██████	NR	NR
FIGO stage, n (%)				
Stage III	████████	████████	106 (72.6)	47 (64.3)
Stage IV	████████	████████	40 (27.4)	26 (35.6)
ECOG PS, n (%)				
0	████████	████████	107 (73.3)	54 (74.0)
1	████████	████████	39 (26.7)	19 (26.0)
Primary tumour location, n (%)				

	PRIMA		SOLO-1	
	Niraparib ████████	Placebo ████████	Olaparib (n=146)	Placebo (n=73)
Ovary	████████	████████	NR	NR
Fallopian tube	████████	████████	NR	NR
Primary peritoneal	██████	██████	NR	NR
Histology, n (%)				
Serous	NR	NR	NR	NR
Endometrioid	NR	NR	NR	NR
Clear cell	NR	NR	NR	NR
Mixed	NR	NR	NR	NR
Other	NR	NR	NR	NR
BRCA mutation, n (%)				
Yes	████████	████████	260 (100.0)	131 (100.0)
No	██████	██████	0 (0.0)	0 (0.0)
Prior bevacizumab use, n (%)				
Yes	NR	NR	NR	NR
No	NR	NR	NR	NR
Response to 1L chemotherapy, n (%)				
Complete response	████████	████████	107 (73.3)	54 (74.0)
Partial response	████████	████████	39 (26.7)	19 (26.0)
No evidence of disease	██████	██████	0 (0.0)	0 (0.0)
CA-125 level, n (%)				
≤ULN	████████	████████	133 (91.1)	66 (90.4)
>ULN	██████	██████	13 (8.9)	7 (9.6)
Receipt of NACT, n (%)				
Yes	████████	████████	94 (64.4)*	43 (58.9)*
No	████████	████████	NR	NR
Timing of surgery, n (%)				
PCS/PDS or upfront	NR	NR	NR	NR

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

	PRIMA		SOLO-1	
	Niraparib [REDACTED]	Placebo [REDACTED]	Olaparib (n=146)	Placebo (n=73)
ICS/IDS	NR	NR	94 (64.4)	43 (58.9)

*Reported as “NACT/Interval surgery”, with consistent patient counts as interval cytoreductive surgery (ICS).

Abbreviations: 1L = first-line; ECOG-PS = Eastern Cooperative Oncology Group-performance status; FIGO = International Federation of Gynecology and Obstetrics; ICS = interval cytoreductive surgery; IDS = interval debulking surgery; PCS = primary cytoreductive surgery; PDS = primary debulking surgery; NR = not reported; ULN = upper limit of normal

Outcome Definitions

Outcome definitions for overall survival (OS) were consistently defined and comparable across all studies. However, noteworthy differences in PFS definition and assessment schedules were identified across trials. In particular, PFS (investigator-assessed and IRC-assessed) SOLO-1 consider progression an event, regardless of whether a patient received another anti-cancer therapy prior to progression; in contrast, PRIMA, PRIME, and ATHENA-MONO censored PFS at the last evaluable assessment prior to initiation of subsequent anti-cancer therapy. In PRIMA, only 15 out of 733 patients (2%) were censored at their last assessment before follow-up therapy. Therefore, this difference in censoring rules across studies is expected to have a minimal impact on ITC results. PFS definitions in PRIME and ATHENA-MONO are aligned, making Bucher ITCs of PFS from these studies possible.

Table 94. PFS Definitions Across Studies

Trial	PFS Definition	PFS Censoring Rules
PRIMA	Time from the date of randomization to the date of first documentation of progression or death, whichever occurs first	1. No baseline OR no post-baseline radiographic assessments = censor at randomization date 2. No progressive disease or death = censor at last evaluable assessment 3. Progressive disease or death occurred after two or more missed assessments = censor at last evaluable assessment prior to missed interval 4. Received subsequent anti-cancer therapy before progressive disease or death = censor at last evaluable assessment prior to initiation of subsequent anti-cancer therapy
PRIME	✓	✓
ATHENA-MONO	✓	✓

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Trial	PFS Definition	PFS Censoring Rules
SOLO-1	✓	1-3. ✓ 4. Progression is considered an event, regardless of if a patient receives another anti-cancer therapy prior to progression.

Abbreviations: PFS = progression-free survival
A green tick sign indicates alignment with PRIMA

Assessment Schedule for Tumour Response

Progression is evaluated at tumour assessment visits scheduled over the course of follow-up in each study, compared in the table below; differences in assessment schedules may introduce bias in ITCs -- known as assessment time bias. Consistent with the tumour assessment schedule in PRIMA, tumour response was assessed every 12 weeks in PRIME, ATHENA-MONO (up to 3 years), and SOLO-1 (up to 3 years). After the first 3 years, the assessment schedules in ATHENA-MONO and SOLO-1 changed from every 12 weeks to every 24 weeks.

Table 95. Comparison of Assessment Schedules Across Trials

Trial	Intervention	Comparator	Assessment Schedule for Tumor Response
PRIMA	Niraparib	Placebo	Assessed at screening, then every 12 weeks (+/- 1 week) until progression confirmed by BICR
PRIME	Niraparib	Placebo	Assessed at screening, then every 12 weeks (+/- 1 week) until progression confirmed by BICR
ATHENA-MONO	Rucaparib	Placebo	Assessed at screening, then every 12 weeks (+/- 1 week) for the first 3 years , and every 24 weeks thereafter until objective radiologic progressive disease
SOLO-1	Olaparib	Placebo	Assessed at baseline, then every 12 weeks (+/- 1 week) up to 3 years , and then every 24 weeks until objective radiological disease progression

Methods of analysis of studies included in indirect or mixed treatment comparisons

Due to a lack of head-to-head studies, ITC methods were required to estimate the relative efficacy and safety of niraparib vs relevant comparators of interest. Bucher's method for ITCs was applied where suitable, specifically in cases where trials were Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

linked through a common anchor arm, and it was clinically reasonable to assume that the distributions of treatment effect modifiers were balanced across trials. Simulated treatment comparisons (STCs) were considered within the BRCam population but were deemed inappropriate and unreliable due to counter-intuitive associations between PFS and both ECOG and age.

STC

An STC was explored by fitting parametric survival regression models using patient-level data from PRIMA (i.e., the index trial) to indirectly compare PFS across studies.

In the anchored setting, let us consider an index trial, AB, which investigates the relative efficacy of treatment B versus treatment A. We wish to make a comparison versus trial AC, which investigates the relative efficacy of treatment C versus treatment A. In this context, the common treatment, A, serves as an **anchor**, linking the studies and forming a network. In its general form, the STC regression model is given as:

$$g(\theta_i) = \beta_0 + \beta_T T_i + \beta_X X_i + \beta_Z Z_i + \beta_{TZ}(T_i Z_i)$$

where $g(\cdot)$ is a suitable link function, θ_i is the expected outcome for the i -th patient with treatment T_i in trial AB, β_0 is the intercept, β_T is the coefficient for active treatment, β_X is the vector of coefficients for prognostic variables denoted by X , β_Z denotes the vector of coefficients for EMs Z , and β_{TZ} is the vector of coefficients for interactions between treatment and EMs.

STC can be used to estimate either marginal or conditional treatment effects. The conventional implementation of STC (i.e., by centering the covariates to mean values in the comparator population as described in the previous section) targets a conditional estimand. In the case of non-collapsible measures of effect (e.g., hazard ratios), marginal and conditional estimands do not coincide due to nonlinearity. This can cause systematic bias in STC if we were to compare an adjusted conditional HR $d_{BA(AC)}$ with the marginal HRs $d_{CA(AC)}$ reported for the comparators.

$$\hat{d}_{BC(AC)} = d_{BA(AC)} - d_{CA(AC)}$$

Therefore, we used an extension of conventional STC all analyses, which enables the estimation of marginal effects. The specific steps followed in the STC analyses to estimate marginal HRs are summarized in the following table.

Table 96. Steps for Implementation of Anchored STC for TTE Outcomes

Step	Description
1. (Best parametric distribution)	Fit parametric survival distributions (exponential, Weibull, Gompertz, log-normal, log-logistic, gamma, and generalized gamma) to the observed outcomes using IPD from PRIMA study and including only treatment as the covariate. The best fitting distribution was identified using goodness of fit statistics (e.g., Akaike's information criteria [AIC] and Bayesian information criteria [BIC]) and observed vs predicted plots.
2. (STC regression model)	Using the best fitting distribution identified in step 1, a predictive equation was generated adjusting for treatment, all identified effect modifiers in imbalance, and their interactions with treatment without centering.
3. (Uncertainty of regression parameters)	For the regression coefficients in the predictive equation of step 2, 100* sets of coefficient vectors were simulated assuming a multi-variate normal distribution with mean and variance-covariance matrix as computed from the regression equation. We can denote this dataset as dat_{beta} . Each row $j = 1$ to 100^* , denotes a new set of parameter estimates.
4. (Patient profiles)	Using the reported baseline characteristics information for the comparator study, patient profiles were simulated separately for each comparator treatment arm. For the active comparator treatment arm and control, the mean target values for simulation are provided in Baseline Characteristics. The simulation assumed that the correlation structure of these baseline characteristics is the same as in PRIMA. For each arm, this step was repeated a large number of times. 50* datasets were be simulated, each with k (i.e., expected sample size of arms in PRIMA) patients. We can denote these datasets as $dat_{Tx1,i}$ and $dat_{Tx0,i}$, where i ranges from 1 to 50 and each i-th dataset has k rows. For $i = 1$ to 50, assign treatment = Niraparib to each $dat_{Tx1,i}$ and treatment = placebo to each $dat_{Tx0,i}$.
5. (Simulate outcomes)	For each value of i (step 4) and j (step 3, dat_{beta}), simulate survival times for patients in $dat_{Tx1,i}$ and $dat_{Tx0,i}$. Pool these two dataset to generate dat_{ij} . This results in $50 \times 100 = 5000$ simulated datasets
6. (Marginal index treatment effect in comparator population)	For each dat_{ij} , fit a Cox PH model using treatment as the only predictor giving marginal hazard for niraparib vs placebo in the comparator study $HR_{(NIRA)(Comp),ij}$.
7. (PAIC)	For each value of i and j, the relative effect of interest (i.e., niraparib the active comparator in the comparator population) can be estimated on the log scale as $d_{NIRA \text{ vs } Comp (Comp),ij} = d_{(NIRA)(Comp),ij} - d_{(Comp)(Comp)}$ With standard error $SE(\hat{d}_{(NIRA \text{ vs } Comp)(Comp),ij}) = \sqrt{SE(d_{(NIRA)(Comp),ij})^2 + SE(d_{(Comp)(Comp)})^2}$

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Step	Description
	Where $d = \log(\text{HR})$. Both $d_{(NIRA)(Comp),ij}$ and its standard error will be available from the step 6, while $d_{(Comp)(Comp)}$ (i.e., relative effect of the active comparator vs placebo in the comparator population) and associated standard error was derived from the comparator publication.
8. (Average results)	All the $i \times j$ log-HRs and corresponding variances were pooled using Rubin's rule. The final result represents the effect of Niraparib vs comparator (in the log-scale) expected in the comparator-like population: $d_{(NIRA \text{ vs } Comp)(Comp)}$
9. (Reporting)	Construct confidence intervals and p-values, then summarize results in a table or a forest plot. Convert the final results on the natural scale, $HR_{(NIRA \text{ vs } Comp)(Comp)}$.
10. (Bucher ITC)	Calculate unadjusted relative effects using Bucher's ITC approach, to assess the impact of population adjustment.

Abbreviations: AIC = Akaike's information criteria; BIC = Bayesian information criteria; niraparib = niraparib; HR = hazard ratio; IPD = individual participant data; ITC = indirect treatment comparison; PAIC = population-adjusted indirect comparison; PH = proportional hazard; STC = simulated treatment comparison; TTE = time-to-event

Covariates for Adjustment and Comparator Population

Table 97 provides information on the EMs and PFs that were included in STCs of niraparib (PRIMA) vs each olaparib (SOLO-1). Variables with green tick marks were included as covariates in the outcome regression models for STCs (as both a main effect and interaction term with treatment). Variables with red x marks were omitted from the STC analyses due to insufficient data, and in these cases, it is unknown whether there exist residual imbalances in EMs and/or PFs across studies. Lastly, variables with an asterisk were implicitly matched (at least partially) by aligning subgroup definitions across studies.

Table 97. Summary of Covariates Included in STCs

Population	Availability	Age (median)	FIGO Stage	Prior beva	ECOG PS	Response to 1L Chemo	Histology	BRCAm	CA-125 level	Tumor location	NACT	Residual disease status	History of surgery	Timing of surgery
BRCAm and high-risk	Include in STC?	✓	✓	✗	✓	✓	✗	*	✓	✗	✓	*	*	✗
	niraparib / Placebo	██████	IV: ██████	NR	0: ██████	PR: ██████	NR	*	≤ULN: ██████	Ovary: ██████	██████	*(partially)	*(partially)	✗
	olaparib / Placebo	54 / 54	IV: 27.4% / 35.6%	✗	0: 73.3% / 74.0%	PR: 26.7% / 26.0%	✗	*	≤ULN: 91.1% / 90.4%	✗	64.4% / 58.9%	*	*	ICS: 64.4% / 58.9%

✓: To be adjusted by including as a covariate (main effect and interaction term with treatment) in the STC regression model.

✗: Data not available to include in STC.

*: Implicitly matched based on subgroup definition.

§Reported as NACT/ICS.

^aMean age.

ECOG PS = Eastern Cooperative Oncology Group performance status; FIGO = International Federation of Gynaecology and Obstetrics; HRd = homologous recombination deficiency; HRp = homologous recombination proficiency; ICS = interval cytoreductive surgery; PR = partial response; STC = simulated treatment comparison; ULN = upper limit of normal

Bucher ITC

A Bucher ITC involves a similar anchored comparison of d_{BA} and d_{CA} as STC, but instead of comparing the adjusted marginal effect of B versus A (i.e., $d_{BA(AC)}$) versus the unadjusted relative effect of C versus A (i.e., d_{CA}), as in anchored STC, the unadjusted marginal effect of B versus A (i.e., d_{BA}) is contrasted with the unadjusted marginal effect of C versus A (i.e., d_{CA}). As PFS is the only outcome to be compared using Bucher ITC, d generally represents log HRs on PFS.

That is, a Bucher ITC between B and C is estimated using the published marginal effect for B versus A and the published marginal effect for C versus A:

$$\hat{d}_{BC} = d_{BA} - d_{CA}$$

with standard error:

$$SE(\hat{d}_{BC}) = \sqrt{SE(d_{BA})^2 + SE(d_{CA})^2},$$

Where $SE(d_{BA})$ and $SE(d_{CA})$ were derived from 95% confidence intervals reported in each trial publication.

Programming language for indirect or mixed treatment comparisons

All indirect treatment comparisons and associated statistical analyses were conducted in R (version 4.5.0).

Risk of bias of studies included in indirect or mixed treatment comparisons

The key areas of concern that may lead to biased ITCs are summarized in the following table.

Table 98. Summary of Areas of Concern

Area of Concern	Issue	Conclusion from ITC FA
Study design heterogeneity	Maximum treatment durations	The maximum treatment duration differed across studies (up to 36 months in PRIMA/PRIME vs 24 months for comparators). Note, the maximum treatment durations generally align with current treatment guidelines.
	Determination of HRD status	Differences were identified in the timing and type of HRD test administered. This is a limitation and cannot be addressed in any ITC.

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Area of Concern	Issue	Conclusion from ITC FA
	Subsequent treatment use	Across studies, there was heterogeneity in the subsequent use of PARPi treatments (and potentially other subsequent treatments), which may distort ITCs of OS and PFS2. Due to a lack of data, it would not be possible to adjust PARPi's by intended use (treatment vs maintenance), line of therapy, or specific treatment, all of which are expected to confound OS and PFS2.
	Country representation	The PRIME trial was conducted exclusively in sites in China. If region is an effect modifier, then comparisons vs ATHENA-MONO may be methodologically flawed.
Population heterogeneity	Visible residual disease (VRD) status (clinical risk)	PRIMA required patients with stage III disease to have VRD following primary debulking surgery (i.e., high-risk), whereas all comparator studies included patients regardless of residual disease. This is a key limitation for ITCs. It is possible to more closely align inclusion criteria by comparing PRIMA against higher-risk subgroup data published for SOLO-1 (but not ATHENA-MONO).
	Biomarker status (BRCAm)	SOLO-1 only enrolled BRCAm patients, where all other studies enrolled patients regardless of BRCAm status. Inclusion criteria would need to be aligned by conducting ITC vs SOLO-1 in the high-risk, BRCAm subgroup.
Outcome heterogeneity	PFS assessors	PFS assessment (BICR vs INV) in PRIMA (primary endpoint: BICR PFS) differed vs comparator trials, where the primary endpoint was PFS by INV. PFS was assessed both by INV and BICR in PRIMA. To reduce potential bias, outcome definitions in PRIMA should be aligned with those in comparator studies.
	Immature OS	OS data was relatively immature for comparator studies. ATHENA-MONO and PRIME have less mature OS data compared with PRIMA and SOLO-1, which may limit ITCs.
	PFS Definitions	Censoring rules for PFS differed in SOLO-1 compared with the other RCTs.

Abbreviations: 1L = first-line; BICR = blinded independent central review; EAG = evidence assessment group; FA = feasibility assessment; INV = investigator-assessed; ITC = indirect treatment comparison; NICE TA = National Institute for Health and Care Excellence technical appraisal; OS = overall survival; PARPi = poly(adenosine diphosphate-ribose) polymerase inhibitor; PFS = progression-free survival

B1.2 Participant flow in the relevant randomised controlled trials

Participant flow in the PRIMA and PRIME trials is provided below.

B.1.2.1 PRIMA

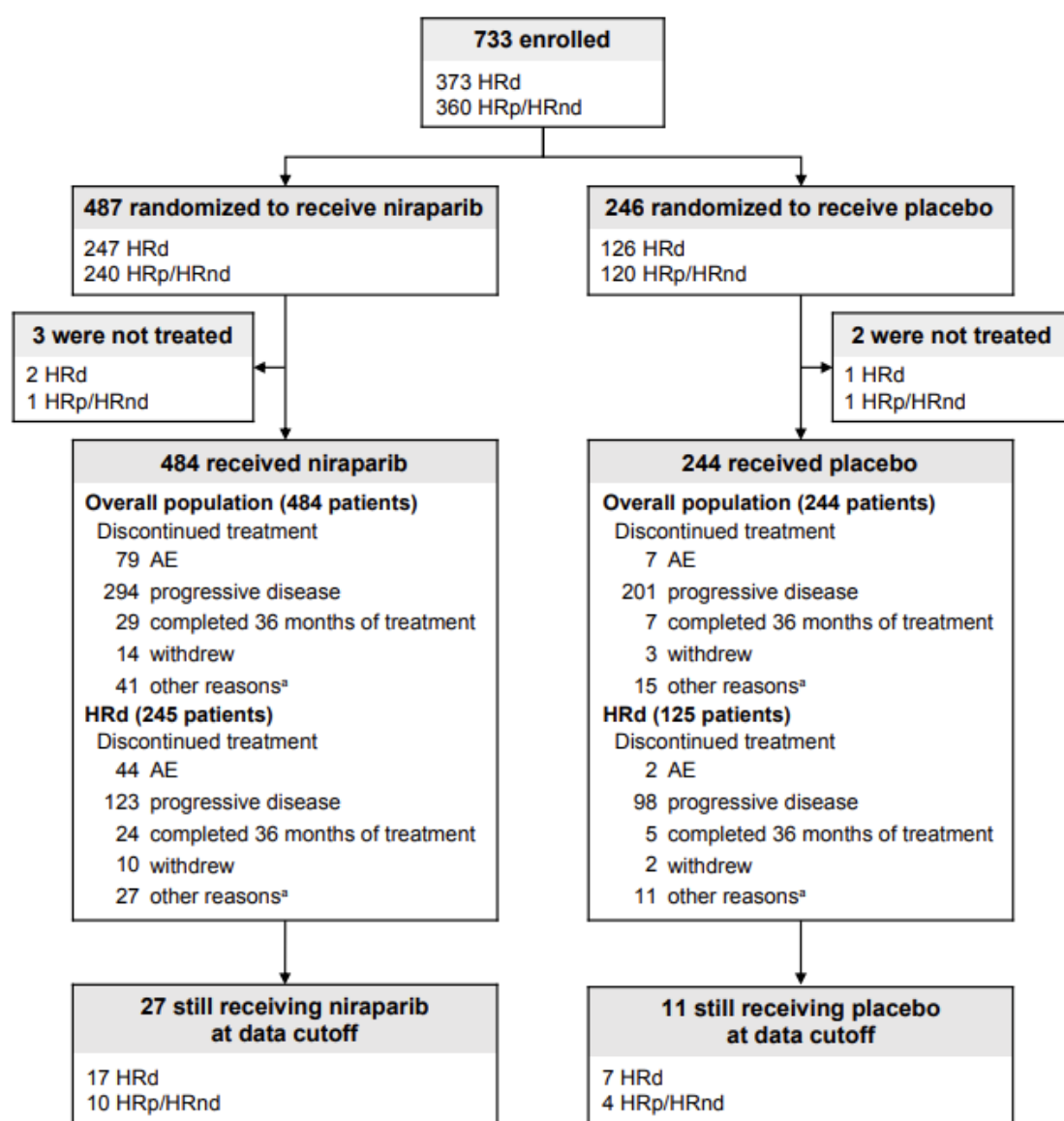
Nine hundred eighty nine patients were screened¹² and 733 patients were enrolled in the PRIMA trial, with 487 randomised to the niraparib group and 246 to the placebo

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

group (ITT population).¹⁶ Three patients in the niraparib group and two in the placebo group did not receive the assigned treatment.¹⁶

As of the data cutoff on April 8, 2024, 27 patients were still receiving niraparib and 11 were still on placebo, while 457 and 233 patients, respectively, had discontinued treatment.¹⁶ Twenty-nine patients in the niraparib group and 7 in the placebo group completed 36 months of treatment.¹⁶ Consent withdrawal occurred in 14 patients in the niraparib group and 3 patients in the placebo group.¹⁶ Details on participant flow in the ITT population and the HRd subgroup are shown in Figure 31.

Figure 31. Participant flow in the PRIMA trial¹⁶



Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Abbreviations: AE = adverse event; HRd = homologous recombination deficient/proficient; HRd = homologous recombination proficient; HRnd = homologous recombination no data

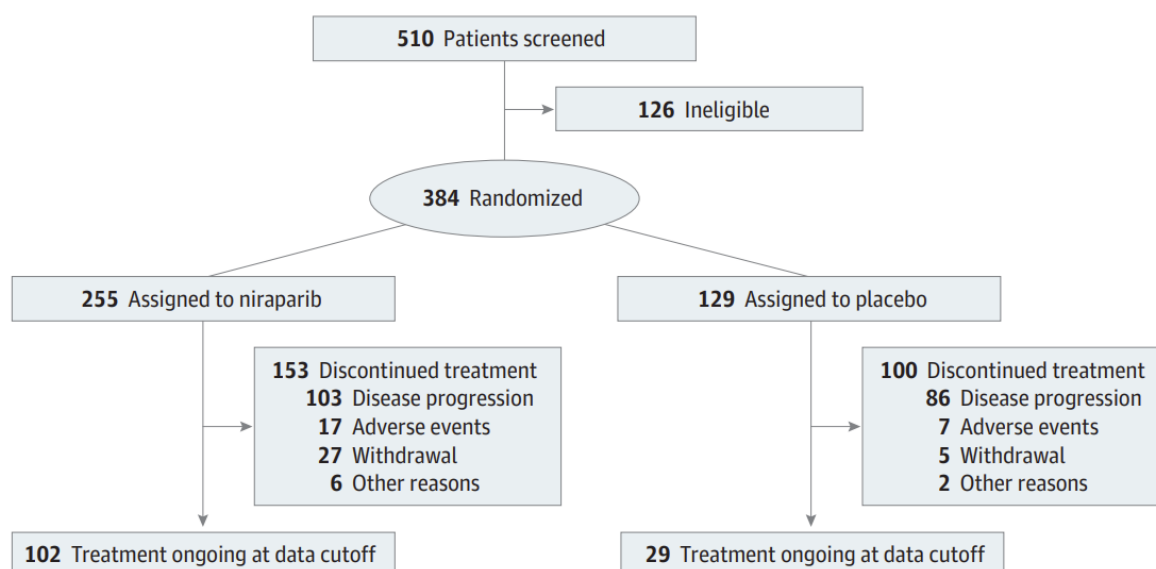
Data cut-off: April 8, 2024.

^a Includes patients who discontinued because of the investigator's decision or nonadherence.

B.1.2.2 PRIME

Of 510 screened patients, 384 were randomised in the PRIME trial, with 255 assigned to niraparib and 129 to the placebo group.¹³ At the data cut-off (September 30, 2021), 102 niraparib patients and 29 placebo patients were still undergoing treatment.¹³ Consent withdrawal occurred in 27 patients treated with niraparib and 5 patients from the placebo group (Figure 32).¹³ Details on participant flow in the ITT population are shown in Figure 32.

Figure 32. Participant flow in the PRIME trial¹³



Data cut-off: September 30, 2021.

B1.3 Critical appraisal for each study

Risk of bias was assessed in six RCTs.²⁰ All six RCTs were assessed as being at low risk of bias overall; all were double-blind, provided details of the randomisation process, and had baseline characteristics that were evenly balanced between treatment arms (Table 99).²⁰

The single-arm trial, OVARIO,¹³⁷ was found to be at moderate risk of bias due to concerns around the awareness of the investigators of the intervention received by Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

study participants and concerns with handling of missing data.²⁰ The single-arm trial by Oda 2024¹³⁸ was not assessed, since there was no full-text publication available (and insufficient information in the congress abstract).²⁰

Twenty-one RWE studies were assessed for risk of bias.²⁰ Across the RWE studies, the overall risk of bias was deemed moderate (Table 100).²⁰ This was due to the potential for confounding, which is greater in observational studies.²⁰ The only study deemed at low risk of bias was PRED1CT.^{20,92}

Table 99. Quality Assessment for the identified RCTs using the Cochrane Risk of Bias Assessment Tool 2.0

Question	ATHENA-MONO ¹⁴	PAOLA-1 ⁶⁴	PRIMA ¹²	PRIME ¹³	SOLO-1 ¹⁵	FLAMES ¹³⁹
1.1 Was the allocation sequence random?	Yes	Yes	Yes	Yes	Yes	Yes
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Yes	Yes	Yes	Yes	Yes	PY
Note for 1.1&1.2	Random assignment was computer-generated (block size of 10).	Randomization was performed centrally with the use of a block design	None	Random assignment, double-blinded	Randomisation was performed centrally with a block design, with stratification according to clinical response after platinum-based chemotherapy (complete or partial)	Randomisation was achieved via an interactive web response system using block randomization methods with a block size of six

Question	ATHENA-MONO ¹⁴	PAOLA-1 ⁶⁴	PRIMA ¹²	PRIME ¹³	SOLO-1 ¹⁵	FLAMES ¹³⁹
1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	No	No	No	No	No	PN
Note for 1.3	None	The baseline characteristics were well balanced between the trial groups	None	None	None	The patient demographic and baseline clinical characteristics were well balanced between the senaparib and placebo arms
1.0 Assessor's Judgement	Low	Low	Low	Low	Low	Low
1.0 General note	None	None	None	None	None	None
2.1 Were participants aware of their assigned intervention during the trial?	No	No	No	No	No	No

Question	ATHENA-MONO ¹⁴	PAOLA-1 ⁶⁴	PRIMA ¹²	PRIME ¹³	SOLO-1 ¹⁵	FLAMES ¹³⁹
2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	No	No	No	No	No	No
Note for 2.1&2.2	Double -blind study	Double -blind study	Double -blind study	Double -blind study	Quadruple-blind study	Double -blind study
2.3 If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NA	NA	NA	NA	NA	NA
Note for 2.3	NA	NA	NA	NA	NA	NA
2.4 If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?	NA	NA	NA	NA	NA	NA
Note for 2.4	NA	NA	NA	NA	NA	NA

Question	ATHENA-MONO¹⁴	PAOLA-1⁶⁴	PRIMA¹²	PRIME¹³	SOLO-1¹⁵	FLAMES¹³⁹
2.5 If N/PN/Ni to 2.4: Were these deviations likely to have affected the outcome?	NA	NA	NA	NA	NA	NA
Note for 2.5	NA	NA	NA	NA	NA	NA
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Yes	Yes	Yes	Yes	Yes	Yes
Note for 2.6	ITT population	ITT population	ITT population	ITT population	ITT population	ITT population
2.7 If N/PN/Ni to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyze participants in the group to which they were randomised?	NA	NA	NA	NA	NA	NA
Note for 2.7	NA	NA	NA	NA	NA	NA
2.0 Assessor's Judgement	Low	Low	Low	Low	Low	Low
2.0 General Notes	None	None	None	None	None	None

Question	ATHENA-MONO ¹⁴	PAOLA-1 ⁶⁴	PRIMA ¹²	PRIME ¹³	SOLO-1 ¹⁵	FLAMES ¹³⁹
3.1 Were data for this outcome available for all, or nearly all, participants randomised?	PY	Yes	Yes	PY	Yes	Yes
Note for 3.1	All efficacy data was available for ITT population, safety, response, and HRQoL data was only available for a portion of the ITT population	A total of 535 of the 537 patients assigned to olaparib plus bevacizumab (olaparib group) and 267 of the 269 patients assigned to placebo plus bevacizumab (placebo group) received the trial intervention; 2 patients in each group withdrew before receiving the trial intervention	Five patients who did not receive either niraparib or placebo after randomisation were excluded from the safety analysis.	27 patients in the treatment arm and 5 in the placebo arm withdrew from treatment, it was not described how missing data was handled in the analysis	None	None
3.2 If N/PN/Ni to 3.1: Is there evidence that the result was not biased by missing outcome data?	NA	NA	NA	NA	NA	NA
Note for 3.2	NA	NA	NA	NA	NA	NA

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Question	ATHENA-MONO¹⁴	PAOLA-1⁶⁴	PRIMA¹²	PRIME¹³	SOLO-1¹⁵	FLAMES¹³⁹
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	NA	NA	NA	NA	NA
Note for 3.2&3.3	NA	NA	NA	NA	NA	NA
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	NA	NA	NA	NA	NA
Note for 3.4	NA	NA	NA	NA	NA	NA
3.0 Assessor's judgement	Low	Low	Low	Low	Low	Low
3.0 General notes	The limited populations in safety and HRQoL are not uncommon due to compliance and analysis schedule	None	None	None	None	None
4.1 Was the method of measuring the outcome inappropriate?	No	No	No	No	No	No

Question	ATHENA-MONO ¹⁴	PAOLA-1 ⁶⁴	PRIMA ¹²	PRIME ¹³	SOLO-1 ¹⁵	FLAMES ¹³⁹
Note for 4.1	Both investigator and independent review measured outcomes	Both investigator and independent review measured outcomes	Both investigator and independent review measured outcomes	Standard outcome assessment measures were used	Pre-specified outcomes	Standard outcome assessment measures were used
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	No	No	No	No	No	No
Note for 4.2	Double-blind	Blinded review	Blinded review	Blinded review	Blinded review	Double-blind
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants ?	No	No	No	No	No	No
Note for 4.3	Double-blind	Double-blind	Double-blind	Double-blind	Quadruple-blind	Double-blind
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	NA	NA	No	NA	NA

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Question	ATHENA-MONO¹⁴	PAOLA-1⁶⁴	PRIMA¹²	PRIME¹³	SOLO-1¹⁵	FLAMES¹³⁹
Note for 4.4&4.5	NA	NA	NA	NA	NA	NA
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	NA	NA	NA	NA	NA
Note for 4.5	NA	NA	NA	NA	NA	NA
4.0 Assessor's judgement	Low	Low	Low	Low	Low	Low
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalised before unblinded outcome data were available for analysis?	Yes	Yes	Yes	Yes	NI	Yes
Note for 5.1	None	None	None	The statistical analysis plan and clinical trial protocol are included as supplements	None	The statistical analysis plan is provided

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Question	ATHENA-MONO ¹⁴	PAOLA-1 ⁶⁴	PRIMA ¹²	PRIME ¹³	SOLO-1 ¹⁵	FLAMES ¹³⁹
5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple outcome measurements (e.g., scales, definitions, time points) within the outcome domain?	No	No	No	No	No	No
Note for 5.2	All timepoints and subsets of data were reported	All timepoints for data collection across different treatment arms comparable	All timepoints for data collection across different treatment arms comparable	Only one timepoint is available, all pre-specified subgroups are reported on	All timepoints and subsets of data were reported	None
5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple analyses of the data?	PN	No	No	PN	PN	No

Question	ATHENA-MONO ¹⁴	PAOLA-1 ⁶⁴	PRIMA ¹²	PRIME ¹³	SOLO-1 ¹⁵	FLAMES ¹³⁹
Note for 5.3	None	None	None	It is not clear whether adjusted values were analyzed	None	None
5.0 Assessor's judgement	Low	Low	Low	Low	Low	Low
5.0 General note	None	None	None	None	None	None
Assessor's overall judgement	Low	Low	Low	Low	Low	Low

HRQoL = health-related quality of life; ITT = intention to treat; NA = not applicable; NI = no information; PN = probably no; PY = probably yes; RCT = randomised controlled trial

Table 100. Quality Assessment for the identified RWE studies using the ROBINS-I tool

Question	OVARIO Hardesty 2022 ¹³⁷	Hashimoto 2023 ¹⁴⁰	NCT05734911 Zhao 2023 ¹⁴¹	Shin 2021 ¹⁴²	Bellier 2023 ¹²¹	Kim 2024 ⁹⁶	Zheng 2021 ¹⁴³	Chen 2024 ¹⁴³	CHARIZMA Salani 2025 ⁹¹	Bruno 2024 ⁹⁷	Nakamura 2024 ¹⁴⁴	NCT05153603 Li 2024 ¹⁴⁵	COMB1NE Thaker 2024 ¹⁴⁶	AR1ZE Chase 2025 ⁹³	Ha 2024 ¹⁴⁷	SW1TCH Rimel 2024 ¹⁴⁸	Lee 2024 ¹⁴⁹	Jeong 2024 ¹⁵⁰	Graves 2025 ¹⁵⁰	Adjei 2024 ¹⁵¹	Han 2024 ¹⁵²	PRED1CT Chase 2024 ⁹²
1.1 Is there potential for confounding of the effect of intervention in this study?	PN	PY	PY	PY	PY	PY	PY	PY	PN	PY	PY	PY	PN	PN	PY	PN	PN	PN	No	PY	No	No

Question	OVARIO Hardesty 2022 ¹³⁷	Hashimoto 2023 ¹⁴⁰	NCT05734911 Zhao 2023 ¹⁴¹	Shin 2021 ¹⁴²	Bellier 2023 ¹²¹	Kim 2024 ⁹⁶	Zheng 2021 ¹⁴³	Chen 2024 ¹⁴³	CHAR1ZMA Salani 2025 ⁹¹	Bruno 2024 ⁹⁷	Nakamura 2024 ¹⁴⁴	NCT05153603 Li 2024 ¹⁴⁵	COMB1NE Thaker 2024 ¹⁴⁶	AR1ZE Chase 2025 ⁹³	Ha 2024 ¹⁴⁷	SW1TCH Rimel 2024 ¹⁴⁸	Lee 2024 ¹⁴⁹	Jeong 2024 ¹⁵⁰	Graves 2025 ¹⁵⁰	Adjei 2024 ¹⁵¹	Han 2024 ¹⁵²	PRED1CT Chase 2024 ⁹²
If N/PN to 1.1: the study can be considered to be at low-risk of bias due to confounding and no further signaling questions need be considered	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
If Y/PY to 1.1: determine whether there is a need to assess time-varying confounding:	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	NA	No	No	No	No	No	No	No	No	No	Y	No	NA	NA	No	NA	NA	NA	NA	No	NA	NA

Question	OVARIO Hardesty 2022 ¹³⁷	Hashimoto 2023 ¹⁴⁰	NCT05734911 Zhao 2023 ¹⁴¹	Shin 2021 ¹⁴²	Bellier 2023 ¹²¹	Kim 2024 ⁹⁶	Zheng 2021 ¹⁴³	Chen 2024 ¹⁴³	CHAR1ZMA Salani 2025 ⁹¹	Bruno 2024 ⁹⁷	Nakamura 2024 ¹⁴⁴	NCT05153603 Li 2024 ¹⁴⁵	COMB1NE Thaker 2024 ¹⁴⁶	AR1ZE Chase 2025 ⁹³	Ha 2024 ¹⁴⁷	SW1TCH Rimel 2024 ¹⁴⁸	Lee 2024 ¹⁴⁹	Jeong 2024 ¹⁵⁰	Graves 2025 ¹⁵⁰	Adjei 2024 ¹⁵¹	Han 2024 ¹⁵²	PRED1CT Chase 2024 ⁹²
If N/PN, answer questions relating to baseline confounding (1.4 to 1.6) If Y/PY, go to question 1.3.	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	PN	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

Question	OVARIO Hardesty 2022 ¹³⁷	Hashimoto 2023 ¹⁴⁰	NCT05734911 Zhao 2023 ¹⁴¹	Shin 2021 ¹⁴²	Bellier 2023 ¹²¹	Kim 2024 ⁹⁶	Zheng 2021 ¹⁴³	Chen 2024 ¹⁴³	CHAR1ZMA Salani 2025 ⁹¹	Bruno 2024 ⁹⁷	Nakamura 2024 ¹⁴⁴	NCT05153603 Li 2024 ¹⁴⁵	COMB1NE Thaker 2024 ¹⁴⁶	AR1ZE Chase 2025 ⁹³	Ha 2024 ¹⁴⁷	SW1TCH Rimel 2024 ¹⁴⁸	Lee 2024 ¹⁴⁹	Jeong 2024 ¹⁵⁰	Graves 2025 ¹⁵⁰	Adjei 2024 ¹⁵¹	Han 2024 ¹⁵²	PRED1CT Chase 2024 ⁹²
If N/PN, answer questions relating to baseline confounding (1.4 to 1.6) If Y/PY, answer questions relating to both baseline and time-varying confounding (1.7 and 1.8)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	NA	NI	Yes	NI	PY	Yes	Yes	Yes	NI	PY	PY	Yes	NI	NI	PN	NI	NI	NI	PY	PY	PY	Yes

Question	OVARIO Hardesty 2022 ¹³⁷	Hashimoto 2023 ¹⁴⁰	NCT05734911 Zhao 2023 ¹⁴¹	Shin 2021 ¹⁴²	Bellier 2023 ¹²¹	Kim 2024 ⁹⁶	Zheng 2021 ¹⁴³	Chen 2024 ¹⁴³	CHAR1ZMA Salani 2025 ⁹¹	Bruno 2024 ⁹⁷	Nakamura 2024 ¹⁴⁴	NCT05153603 Li 2024 ¹⁴⁵	COMB1NE Thaker 2024 ¹⁴⁶	AR1ZE Chase 2025 ⁹³	Ha 2024 ¹⁴⁷	SW1TCH Rimel 2024 ¹⁴⁸	Lee 2024 ¹⁴⁹	Jeong 2024 ¹⁵⁰	Graves 2025 ¹⁵⁰	Adjei 2024 ¹⁵¹	Han 2024 ¹⁵²	PRED1CT Chase 2024 ⁹²
1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	NA	NI	Yes	NI	NI	Yes	Yes	Yes	NI	Yes	Yes	PY	NI	NI	NA	NI	NI	NI	PY	PY	PY	Yes
1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	NA	NI	No	NI	No	No	No	No	NI	No	No	NI	NI	NI	No	NI	NI	NI	PN	PN	PN	PN

Question	OVARIO Hardesty 2022 ¹³⁷	Hashimoto 2023 ¹⁴⁰	NCT05734911 Zhao 2023 ¹⁴¹	Shin 2021 ¹⁴²	Bellier 2023 ¹²¹	Kim 2024 ⁹⁶	Zheng 2021 ¹⁴³	Chen 2024 ¹⁴³	CHAR1ZMA Salani 2025 ⁹¹	Bruno 2024 ⁹⁷	Nakamura 2024 ¹⁴⁴	NCT05153603 Li 2024 ¹⁴⁵	COMB1NE Thaker 2024 ¹⁴⁶	AR1ZE Chase 2025 ⁹³	Ha 2024 ¹⁴⁷	SW1TCH Rimel 2024 ¹⁴⁸	Lee 2024 ¹⁴⁹	Jeong 2024 ¹⁵⁰	Graves 2025 ¹⁵⁰	Adjei 2024 ¹⁵¹	Han 2024 ¹⁵²	PRED1CT Chase 2024 ⁹²
1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	NA	NI	PY	NI	NI	NI	Yes	No	NI	Yes	Yes	No	NI	PY	NA	NI	NI	NI	NI	PY	NA	Yes
1.8. If <u>Y/PY</u> to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	NA	NA	Yes	NA	NA	NA	Yes	NA	NA	PY	PY	PY	NA	PY	NA	NA	NA	NA	NA	PY	NA	Yes
Risk of bias judgement	Low	Mod	Mod	Mod	Mod	Mod	Mod	Mod	Mod	Mod	Mod	Mod	Mod	Mod	Mod	Mod	Mod	Mod	Mod	Mod	Mod	Low

Question	OVARIO Hardesty 2022 ¹³⁷	Hashimoto 2023 ¹⁴⁰	NCT05734911 Zhao 2023 ¹⁴¹	Shin 2021 ¹⁴²	Bellier 2023 ¹²¹	Kim 2024 ⁹⁶	Zheng 2021 ¹⁴³	Chen 2024 ¹⁴³	CHAR1ZMA Salani 2025 ⁹¹	Bruno 2024 ⁹⁷	Nakamura 2024 ¹⁴⁴	NCT05153603 Li 2024 ¹⁴⁵	COMB1NE Thaker 2024 ¹⁴⁶	AR1ZE Chase 2025 ⁹³	Ha 2024 ¹⁴⁷	SW1TCH Rimel 2024 ¹⁴⁸	Lee 2024 ¹⁴⁹	Jeong 2024 ¹⁵⁰	Graves 2025 ¹⁵⁰	Adjei 2024 ¹⁵¹	Han 2024 ¹⁵²	PRED1CT Chase 2024 ⁹²
Optional: What is the predicted direction of bias due to confounding?	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?	No	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	PN	No
If N/PN to 2.1: go to 2.4	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Question	OVARIO Hardesty 2022 ¹³⁷	Hashimoto 2023 ¹⁴⁰	NCT05734911 Zhao 2023 ¹⁴¹	Shin 2021 ¹⁴²	Bellier 2023 ¹²¹	Kim 2024 ⁹⁶	Zheng 2021 ¹⁴³	Chen 2024 ¹⁴³	CHAR1ZMA Salani 2025 ⁹¹	Bruno 2024 ⁹⁷	Nakamura 2024 ¹⁴⁴	NCT05153603 Li 2024 ¹⁴⁵	COMB1NE Thaker 2024 ¹⁴⁶	AR1ZE Chase 2025 ⁹³	Ha 2024 ¹⁴⁷	SW1TCH Rimel 2024 ¹⁴⁸	Lee 2024 ¹⁴⁹	Jeong 2024 ¹⁵⁰	Graves 2025 ¹⁵⁰	Adjei 2024 ¹⁵¹	Han 2024 ¹⁵²	PRED1CT Chase 2024 ⁹²
2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	NA	PY	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	
2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	NA	No	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	

Question	OVARIO Hardesty 2022 ¹³⁷	Hashimoto 2023 ¹⁴⁰	NCT05734911 Zhao 2023 ¹⁴¹	Shin 2021 ¹⁴²	Bellier 2023 ¹²¹	Kim 2024 ⁹⁶	Zheng 2021 ¹⁴³	Chen 2024 ¹⁴³	CHAR1ZMA Salani 2025 ⁹¹	Bruno 2024 ⁹⁷	Nakamura 2024 ¹⁴⁴	NCT05153603 Li 2024 ¹⁴⁵	COMB1NE Thaker 2024 ¹⁴⁶	AR1ZE Chase 2025 ⁹³	Ha 2024 ¹⁴⁷	SW1TCH Rimel 2024 ¹⁴⁸	Lee 2024 ¹⁴⁹	Jeong 2024 ¹⁵⁰	Graves 2025 ¹⁵⁰	Adjei 2024 ¹⁵¹	Han 2024 ¹⁵²	PRED1CT Chase 2024 ⁹²
2.4. Do start of follow-up and start of intervention coincide for most participants?	Yes	PY	PY	PY	PY	PY	PY	PY	Yes	PY	PY	PY	PY	Yes	PY	PY	PY	PY	Yes	Yes	Yes	Yes
2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	NA	NI	NA	NI	NA	Yes	NI	NI	NA	NA	NA	No	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Risk of bias judgement	Low	Mod	Mod	Mod	Low	Mod	Mod	Mod	Low	Low	Low	Mod	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low

Question	OVARIO Hardesty 2022 ¹³⁷	Hashimoto 2023 ¹⁴⁰	NCT05734911 Zhao 2023 ¹⁴¹	Shin 2021 ¹⁴²	Bellier 2023 ¹²¹	Kim 2024 ⁹⁶	Zheng 2021 ¹⁴³	Chen 2024 ¹⁴³	CHAR1ZMA Salani 2025 ⁹¹	Bruno 2024 ⁹⁷	Nakamura 2024 ¹⁴⁴	NCT05153603 Li 2024 ¹⁴⁵	COMB1NE Thaker 2024 ¹⁴⁶	AR1ZE Chase 2025 ⁹³	Ha 2024 ¹⁴⁷	SW1TCH Rimel 2024 ¹⁴⁸	Lee 2024 ¹⁴⁹	Jeong 2024 ¹⁵⁰	Graves 2025 ¹⁵⁰	Adjei 2024 ¹⁵¹	Han 2024 ¹⁵²	PRED1CT Chase 2024 ⁹²
Optional: What is the predicted direction of bias due to selection of participants into the study?	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3.1 Were intervention groups clearly defined?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	PY	Yes	PY	PY	PY	PY	PY	Yes	Yes
3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Yes	No	No	No	Yes	NI	NI	NI	Yes	Yes	Yes	Yes	Yes	PY	Yes	PN	PN	PN	PY	PY	Yes	Yes

Question	OVARIO Hardesty 2022 ¹³⁷	Hashimoto 2023 ¹⁴⁰	NCT05734911 Zhao 2023 ¹⁴¹	Shin 2021 ¹⁴²	Bellier 2023 ¹²¹	Kim 2024 ⁹⁶	Zheng 2021 ¹⁴³	Chen 2024 ¹⁴³	CHAR1ZMA Salani 2025 ⁹¹	Bruno 2024 ⁹⁷	Nakamura 2024 ¹⁴⁴	NCT05153603 Li 2024 ¹⁴⁵	COMB1NE Thaker 2024 ¹⁴⁶	AR1ZE Chase 2025 ⁹³	Ha 2024 ¹⁴⁷	SW1TCH Rimel 2024 ¹⁴⁸	Lee 2024 ¹⁴⁹	Jeong 2024 ¹⁵⁰	Graves 2025 ¹⁵⁰	Adjei 2024 ¹⁵¹	Han 2024 ¹⁵²	PRED1CT Chase 2024 ⁹²
3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	No	No	No	No	No	No	No	No	No	No	No	No	No	PN	No	PN	PN	PN	PN	PN	No	PN
Risk of bias judgement	Low	Mod	Mod	Mod	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Mod	Mod	Mod	Low	Low	Low	Low
Optional: What is the predicted direction of bias due to classification of interventions?	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Question	OVARIO Hardesty 2022 ¹³⁷	Hashimoto 2023 ¹⁴⁰	NCT05734911 Zhao 2023 ¹⁴¹	Shin 2021 ¹⁴²	Bellier 2023 ¹²¹	Kim 2024 ⁹⁶	Zheng 2021 ¹⁴³	Chen 2024 ¹⁴³	CHAR1ZMA Salani 2025 ⁹¹	Bruno 2024 ⁹⁷	Nakamura 2024 ¹⁴⁴	NCT05153603 Li 2024 ¹⁴⁵	COMB1NE Thaker 2024 ¹⁴⁶	AR1ZE Chase 2025 ⁹³	Ha 2024 ¹⁴⁷	SW1TCH Rimel 2024 ¹⁴⁸	Lee 2024 ¹⁴⁹	Jeong 2024 ¹⁵⁰	Graves 2025 ¹⁵⁰	Adjei 2024 ¹⁵¹	Han 2024 ¹⁵²	PRED1CT Chase 2024 ⁹²
4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	No	No	No	No	No	No	No	No	N	N	N	N	N	PN	N	PN	PN	PN	N	N	PN	PN
4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups <i>and</i> likely to have affected the outcome?	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	

Question	OVARIO Hardesty 2022 ¹³⁷	Hashimoto 2023 ¹⁴⁰	NCT05734911 Zhao 2023 ¹⁴¹	Shin 2021 ¹⁴²	Bellier 2023 ¹²¹	Kim 2024 ⁹⁶	Zheng 2021 ¹⁴³	Chen 2024 ¹⁴³	CHAR1ZMA Salani 2025 ⁹¹	Bruno 2024 ⁹⁷	Nakamura 2024 ¹⁴⁴	NCT05153603 Li 2024 ¹⁴⁵	COMB1NE Thaker 2024 ¹⁴⁶	AR1ZE Chase 2025 ⁹³	Ha 2024 ¹⁴⁷	SW1TCH Rimel 2024 ¹⁴⁸	Lee 2024 ¹⁴⁹	Jeong 2024 ¹⁵⁰	Graves 2025 ¹⁵⁰	Adjei 2024 ¹⁵¹	Han 2024 ¹⁵²	PRED1CT Chase 2024 ⁹²
4.3. Were important co-interventions balanced across intervention groups?	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4.4. Was the intervention implemented successfully for most participants?	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4.5. Did study participants adhere to the assigned intervention regimen?	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Question	OVARIO Hardesty 2022 ¹³⁷	Hashimoto 2023 ¹⁴⁰	NCT05734911 Zhao 2023 ¹⁴¹	Shin 2021 ¹⁴²	Bellier 2023 ¹²¹	Kim 2024 ⁹⁶	Zheng 2021 ¹⁴³	Chen 2024 ¹⁴³	CHAR1ZMA Salani 2025 ⁹¹	Bruno 2024 ⁹⁷	Nakamura 2024 ¹⁴⁴	NCT05153603 Li 2024 ¹⁴⁵	COMB1NE Thaker 2024 ¹⁴⁶	AR1ZE Chase 2025 ⁹³	Ha 2024 ¹⁴⁷	SW1TCH Rimel 2024 ¹⁴⁸	Lee 2024 ¹⁴⁹	Jeong 2024 ¹⁵⁰	Graves 2025 ¹⁵⁰	Adjei 2024 ¹⁵¹	Han 2024 ¹⁵²	PRED1CT Chase 2024 ⁹²
4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Risk of bias judgement	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Optional: What is the predicted direction of bias due to deviations from the intended interventions?	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
5.1 Were outcome data available for all, or nearly all, participants?	NI	PY	Yes	NI	Yes	Yes	Yes	NI	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	PY	Yes	Yes

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Question	OVARIO Hardesty 2022 ¹³⁷	Hashimoto 2023 ¹⁴⁰	NCT05734911 Zhao 2023 ¹⁴¹	Shin 2021 ¹⁴²	Bellier 2023 ¹²¹	Kim 2024 ⁹⁶	Zheng 2021 ¹⁴³	Chen 2024 ¹⁴³	CHAR1ZMA Salani 2025 ⁹¹	Bruno 2024 ⁹⁷	Nakamura 2024 ¹⁴⁴	NCT05153603 Li 2024 ¹⁴⁵	COMB1NE Thaker 2024 ¹⁴⁶	AR1ZE Chase 2025 ⁹³	Ha 2024 ¹⁴⁷	SW1TCH Rimel 2024 ¹⁴⁸	Lee 2024 ¹⁴⁹	Jeong 2024 ¹⁵⁰	Graves 2025 ¹⁵⁰	Adjei 2024 ¹⁵¹	Han 2024 ¹⁵²	PRED1CT Chase 2024 ⁹²
5.2 Were participants excluded due to missing data on intervention status?	No	Yes	No	NI	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
5.3 Were participants excluded due to missing data on other variables needed for the analysis?	No	Yes	Yes	NI	Yes	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	Yes
5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	NA	NA	NA	NA	NA	NA	NA	NI	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	PY	

Question	OVARIO Hardesty 2022 ¹³⁷	Hashimoto 2023 ¹⁴⁰	NCT05734911 Zhao 2023 ¹⁴¹	Shin 2021 ¹⁴²	Bellier 2023 ¹²¹	Kim 2024 ⁹⁶	Zheng 2021 ¹⁴³	Chen 2024 ¹⁴³	CHAR1ZMA Salani 2025 ⁹¹	Bruno 2024 ⁹⁷	Nakamura 2024 ¹⁴⁴	NCT05153603 Li 2024 ¹⁴⁵	COMB1NE Thaker 2024 ¹⁴⁶	AR1ZE Chase 2025 ⁹³	Ha 2024 ¹⁴⁷	SW1TCH Rimel 2024 ¹⁴⁸	Lee 2024 ¹⁴⁹	Jeong 2024 ¹⁵⁰	Graves 2025 ¹⁵⁰	Adjei 2024 ¹⁵¹	Han 2024 ¹⁵²	PRED1CT Chase 2024 ⁹²
5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	NA	NI	PY	NA	PY	NI	NA	NI	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Risk of bias judgement	Mod	Mod	Mod	NI	Mod	Mod	Low	Mod	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Optional: What is the predicted direction of bias due to missing data?	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	PY	No	PY	No	No	PY	PY	PY	PN	PN	PN	PY	No	PN	PN	No	No	No	No	No	No	PN

Question	OVARIO Hardesty 2022 ¹³⁷	Hashimoto 2023 ¹⁴⁰	NCT05734911 Zhao 2023 ¹⁴¹	Shin 2021 ¹⁴²	Bellier 2023 ¹²¹	Kim 2024 ⁹⁶	Zheng 2021 ¹⁴³	Chen 2024 ¹⁴³	CHAR1ZMA Salani 2025 ⁹¹	Bruno 2024 ⁹⁷	Nakamura 2024 ¹⁴⁴	NCT05153603 Li 2024 ¹⁴⁵	COMB1NE Thaker 2024 ¹⁴⁶	AR1ZE Chase 2025 ⁹³	Ha 2024 ¹⁴⁷	SW1TCH Rimel 2024 ¹⁴⁸	Lee 2024 ¹⁴⁹	Jeong 2024 ¹⁵⁰	Graves 2025 ¹⁵⁰	Adjei 2024 ¹⁵¹	Han 2024 ¹⁵²	PRED1CT Chase 2024 ⁹²
6.2 Were outcome assessors aware of the intervention received by study participants?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6.3 Were the methods of outcome assessment comparable across intervention groups?	Yes	NA	NA	Yes	NA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6.4 Were any systematic errors in measurement of the outcome related to intervention received?	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No

Question	OVARIO Hardesty 2022¹³⁷	Hashimoto 2023¹⁴⁰	NCT05734911 Zhao 2023¹⁴¹	Shin 2021¹⁴²	Bellier 2023¹²¹	Kim 2024⁹⁶	Zheng 2021¹⁴³	Chen 2024¹⁴³	CHAR1ZMA Salani 2025⁹¹	Bruno 2024⁹⁷	Nakamura 2024¹⁴⁴	NCT05153603 Li 2024¹⁴⁵	COMB1NE Thaker 2024¹⁴⁶	AR1ZE Chase 2025⁹³	Ha 2024¹⁴⁷	SW1TCH Rimel 2024¹⁴⁸	Lee 2024¹⁴⁹	Jeong 2024¹⁵⁰	Graves 2025¹⁵⁰	Adjei 2024¹⁵¹	Han 2024¹⁵²	PRED1CT Chase 2024⁹²
Risk of bias judgement	Mod	Mod	Mod	Mod	Mod	Mod	Mod	Mod	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Optional: What is the predicted direction of bias due to measurement of outcomes?	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
7.1. ... multiple outcome measurements within the outcome domain?	No	No	No	No	No	No	No	No	No	No	No	No	PN	PN	No	No	PN	No	No	No	No	No
7.2 ... multiple <i>analyses</i> of the intervention-outcome relationship?	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No
7.3 ... different <i>subgroups</i> ?	No	No	No	No	No	No	No	No	No	No	No	No	PY	PY	No	No	No	No	No	No	No	No
Risk of bias judgement	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Mod	Mod	Low	Low	Low	Low	Low	Low	Low	Low

Question	OVARIO Hardesty 2022 ¹³⁷	Hashimoto 2023 ¹⁴⁰	NCT05734911 Zhao 2023 ¹⁴¹	Shin 2021 ¹⁴²	Bellier 2023 ¹²¹	Kim 2024 ⁹⁶	Zheng 2021 ¹⁴³	Chen 2024 ¹⁴³	CHAR1ZMA Salani 2025 ⁹¹	Bruno 2024 ⁹⁷	Nakamura 2024 ¹⁴⁴	NCT05153603 Li 2024 ¹⁴⁵	COMB1NE Thaker 2024 ¹⁴⁶	AR1ZE Chase 2025 ⁹³	Ha 2024 ¹⁴⁷	SW1TCH Rimel 2024 ¹⁴⁸	Lee 2024 ¹⁴⁹	Jeong 2024 ¹⁵⁰	Graves 2025 ¹⁵⁰	Adjei 2024 ¹⁵¹	Han 2024 ¹⁵²	PRED1CT Chase 2024 ⁹²
Optional: What is the predicted direction of bias due to selection of the reported result?	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Overall bias																						
Risk of bias judgement	Mod	Mod	Mod	Mod	Mod	Mod	Mod	Mod	Mod	Mod	Mod	Mod	Mod	Mod	Mod	Mod	Mod	Mod	Mod	Mod	Mod	Low
Optional: What is the overall predicted direction of bias for this outcome?	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

mod = moderate; NA = not applicable; NI = no information; PN = probably no; PY = probably yes; ROBINS-I = Risk of Bias in Non-Randomised Studies – of Interventions; RWE = real-world evidence

B1.4 RWE studies identified in the SLR

Table 101. Summary of study and patient characteristics in the identified RWEs for niraparib

Study, author, year	Study design and location	Therapy	Population/Su bgroup	Dose	Baseline characteristics, n (%)						
					N	Median age (range), years	FIGO stage (III-IV)	ECOG PS	BRCAm	BRCAwt	HRd
Apostol 2023	Retrospective, Italy	Niraparib	Overall population	Starting dose: 200 mg or 300 mg (for those weighing ≥77 kg and platelet count ≥150,000 µL)	124	NR	NR	NR	NR	NR	NR
Salani 2025 Backes 2023 Coleman 2023 Salani 2024 Backes 2025 (CHAR1Z MA)	Retrospective Flatiron Health database, US	Niraparib	Overall population	Starting dose: 100 mg, 200 mg, or 300 mg ISD: 200 mg for body weight <77 kg or platelet count <150,000/µL; 300 mg for body weight ≥77 kg and platelet count ≥150,000/µL	560	67.0 (61–75)	III: NR IV: NR	0–1: 450 (80.4) 2–4: 57 (10.2) Missing: 53 (9.5)	66 ^a (45.8)	78 ^a (54.2) 389 ^b (69.5)	144 (25.7)
			HRd		144	64 (57–73)	III: 76 (52.8) IV: 43 (29.9)	0–1: 122 (84.7) 2–4: 10 (6.9)	66 (45.8)	78 (54.2)	144 (100)
			BRCAm/HRd		66	63 (54–73)	III–IV: 55 (83.3)	0–1: 60 (90.9) 2–4: 3 (4.5)	66 (100)	0 (0)	66 (100)
			BRCAwt/HRd		78	65 (60–72)	III–IV: 64 (82.1)	0–1: 62 (79.5) 2–4: 7 (9)	0 (0)	78 (100)	78 (100)
Bruno 2024	Retrospective, Italy	Niraparib	Overall population	200 mg/300 mg	124	61 (35–84)	124 (100)	0: 101 (81.5)	1 (0.8)	123 (99.2)	NR

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Study, author, year	Study design and location	Therapy	Population/Su bgroup	Dose	Baseline characteristics, n (%)						
					N	Median age (range), years	FIGO stage (III-IV)	ECOG PS	BRCAm	BRCAwT	HRd
								1: 23 (18.5)			
Chase 2025 Chase 2024 (AR1ZE)	Retrospective Flatiron Health database, US	Niraparib	Overall population (PRIMA-like cohort)	100 mg/200 mg/300 mg	390	68.0 (NR)	III: 202 (49.0) IV: 188 (48.2)	0–1: 306 (78.5) 2: 49 ⁱ (12.6)	99 ^j (25.4)	NR	NR
		Niraparib	Overall population (Stage III NVRD cohort)	100 mg/200 mg/300 mg	63	64.0 (NR)	III: 63 (100) IV: 0	0–1: 52 (82.5) 2: 3 ⁱ (4.8)	21 ^j (33.3)	NR	NR
Chen 2024	Retrospective, China	Niraparib	Overall population	NR	60	55.42 ^c (NR)	III: 44 (73.3) IV: 10 (16.7)	NR	8 (13.3)	52 (86.7)	NR
		Olaparib	Overall population	NR	104	52.71 ^c (NR)	III: 79 (76) IV: 14 (13.5)	NR	92 (88.5)	9 (8.7)	NR
Chase 2024 (PRED1CT)	Retrospective Flatiron Health database, US	Niraparib	Overall population	NR	526	NR	NR	0–1: 422 (80.2) 2–4: 55 (10.5)	58 (11)	367 ^d (69.8)	76 ^e (14.4)
Ha 2024	Retrospective, South Korea	Niraparib	Overall population	100mg/200 mg/300 mg	64	52 (32–76)	NR	NR	11 (15.9)	58 (84.1)	NR
		Olaparib	Overall population	300 mg (tablet) or 400 mg (capsule)	27	57 (45–82)	NR	NR	27 (100) ^f p<0.001 vs. niraparib	0 (0)	NR
Han 2024	Retrospective Korean National Health Insurance	Niraparib	Overall population (full analysis set – before matching)	Maximum 200 mg	118	55 (49–63)	NR	NR	NR	NR	NR

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Study, author, year	Study design and location	Therapy	Population/Su bgroup	Dose	Baseline characteristics, n (%)						
					N	Median age (range), years	FIGO stage (III-IV)	ECOG PS	BRCAm	BRCAwT	HRd
	Service, South Korea	Olaparib	Overall population (full analysis set – before matching)	Maximum daily dose 600 mg (tablet)	104	56 (50–66)	NR	NR	NR	NR	NR
Hannaway 2023	Retrospective, Canada	Niraparib	Overall population (all BRCAwt/HRD unknown)	NR	83	NR	III: NR IV: 21 (25.0)	NR	0 (0)	83 (100)	NR
Hashimoto 2023	Retrospective, Japan	Niraparib	Overall population	300 mg: if the patient weighed ≥77 kg and had a platelet count of ≥150,000/μL 200 mg: if the patient weighed ≤77 kg or had a platelet count of ≤150,000/μL	45	60.0 (38.0–86.0)	III: 27 (60.0) IV: 17 (37.8)	0: 38 (84.4) 1: 7 (15.6) 2: 0	2 (4.5)	20 (44.4)	5 (11.1)
Khaja 2024	Retrospective, UK	Niraparib	Overall population	NR	19	74.0 (NR)	III: 12 (63.1) IV: 7 (36.8)	0: 1 (5.3) 1: 16 (84.3) 2: 2 (10.5)	NR	NR	3 (15.8)
Kim 2024	Retrospective, South Korea	Niraparib	Matched cohort (all BRCAm)	200mg: Patients with a body weight of <77 kg or a platelet count of ≤150,000/μL at baseline 300mg: other patients	31	60 (52–64)	III: 17 (54.8) IV: 14 (45.2)	NR	31 (100)	0 (0)	NR

Study, author, year	Study design and location	Therapy	Population/Su bgroup	Dose	Baseline characteristics, n (%)						
					N	Median age (range), years	FIGO stage (III-IV)	ECOG PS	BRCAm	BRCAw t	HRd
		Olaparib	Overall cohort (all BRCAm)	300 mg	80	56 (49.5–63)	III: 41 (51.3) IV: 39 (48.7)	NR	80 (100)	0 (0)	NR
Li 2022	Retrospective, China	Niraparib	Overall population	NR	93	NR	NR	NR	NR	NR	NR
Nakamura 2024	Retrospective, Japan	Niraparib	Overall population	300 mg	60	NR	III: 29 (48.3) IV: 31 (51.7)	NR	1 (1.7)	24 (40)	2 (3.3)
		Olaparib	Overall population	300 mg	30	NR	III: 18 (60) IV: 12 (40)	NR	30 (100)	0 (0)	4 (100) ^g
		Olaparib + bevacizumab	Overall population	Olaparib: 300 mg Bevacizumab: 15 mg per kg body weight	27	NR	III: 19 (70.4) IV: 8 (29.6)	NR	7 (25.9)	8 (29.6)	27 (100)
Piedimonte 2024	Retrospective, Canada	Niraparib	Overall population (all BRCAw t/HRD unknown)	NR	52	64.1 ^c (NR)	III: 42 (80.7) IV: 5 (9.6)	NR	NR	52 (100)	NR
Shin 2021	Retrospective, South Korea	Niraparib (200 mg)	Overall population	Starting dose: 200 mg	16	NR	III: 9 (56.2) IV: 7 (43.8)	NR	4 (25.0)	12 (75.0)	NR
		Niraparib (100 mg or discontinuation)	Overall population	Lowered dose: 100 mg	16	NR	III: 8 (50.0) IV: 8 (50.0)	NR	2 (12.5)	14 (87.5)	NR
Rimel 2024 (SW1TCH)	Retrospective Flatiron Health database, US	Niraparib	Overall population	100 mg (4.3%) 200 mg (patients <77 kg or with a platelet count of	93	67 (37-83)	III: 50 (53.8) IV: 33 (35.5)	0–1: 70 (75.3) 2–4: 11 (11.8)	8 (8.6)	10 (10.8)	18 (19.4)

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Study, author, year	Study design and location	Therapy	Population/Su bgroup	Dose	Baseline characteristics, n (%)						
					N	Median age (range), years	FIGO stage (III-IV)	ECOG PS	BRCAm	BRCAw t	HRd
				< 150,000 µ/L; 53.8%) 300 mg (patients ≥77 kg or with a platelet count of ≥150,000 µ/L; 34.4%) Unknown (7.5%)				Missing: 12 (12.9)			
Wenxin 2023	Retrospective, China	Niraparib	Overall population	NR	102	58.0 (NR)	III–IV: 86 (94.3)	NR	19 (18.6)	60 (58.8)	37 (36.6)
Zhao 2023 (NCT0573 4911)	Retrospective, China	Niraparib	Overall population	NR	199	57.0 (NR)	III: NR IV: 40 (20.1)	0: 165 (82.9) 1: 30 (15.1) 2: 4 (2.0)	40 (20.1)	131 (65.8)	66 (33.2)
de la Motte Rouge 2022	Prospective, France	Niraparib	Overall population	200 mg/300 mg	67	70.7° (NR)	III: 49 (73.1) IV: 18 (26.9)	0: 32 (48.0) 1: 31 (46.0) 2: 4 (6.0)	NR	NR	2 (33.0) ^h
Jeong 2024	Prospective, South Korea	Niraparib	Overall population	200 mg: Patients with a body weight of <77 kg or platelet count of < 150,000 µ/L at baseline 300 mg: The remaining patients	53	54 (34–70)	III: 22 (41.5) IV: 31 (58.5)	NR	23 (43.4)	30 (56.6)	32 (60.4)

Study, author, year	Study design and location	Therapy	Population/Su bgroup	Dose	Baseline characteristics, n (%)						
					N	Median age (range), years	FIGO stage (III-IV)	ECOG PS	BRCAm	BRCAwT	HRd
Zuo 2024 Zheng 2024 (RENI-1)	Prospective, China	Niraparib	Overall population	<u>Starting dose:</u> 100 mg (3.5%) 200 mg (95.6%) 100 mg/200 mg alternating (0.9%) <u>Stable dose:</u> 100 mg (11.5%) 200 mg (84.1%) 100 mg/200 mg alternating (4.4%)	227	57.0 (32.0–78.0)	III: 144 (63.4) IV: 66 (29.1)	0: 134 (59.0) 1: 90 (39.7) 2: 3 (1.3)	47 (20.7)	163 (71.8)	116 (51.1)
Hasson 2024 (MONITOR-UK)	Ambispective, UK	Niraparib	Overall population	<u>Starting dose:</u> 100 mg: 8 (5%) 200 mg: 130 (79%) 300 mg: 27 (16%) <u>Highest dose:</u> 100 mg: 5 (3%) 200 mg: 128 (78%) 300 mg: 32 (19%)	164	70 (62–75)	IIIA: 22 (13) IIIB: 16 (10) IIIC: 74 (45) IVA: 27 (16) IVB: 26 (16)	NR	Germline BRCA1m: 2 (1) Germline BRCA2m: 1 (1) Somatic BRCA1m: 5 (3) Somatic BRCA2m: 1 (1)	154 (93)	NR
		Niraparib	Germline BRCAm	NR	3	62 (57–65)	IIIA: 1 (33) IIIB: 0 (0) IIIC: 0 (0) IVA: 2 (67) IVB: 0 (0)	NR	Germline BRCA1m: 2 (67) Germline BRCA2m: 1 (33)	0 (0)	NR

Abbreviations: BRCAm = BRCA mutation; BRCAwT = BRCA wild type; ECOG = Eastern Cooperative Oncology Group; FIGO = International Federation of Gynaecology and Obstetrics; HRd = homologous recombination deficient; HRp = homologous recombination proficient; NR = not reported; NVRD = no visible residual disease; PARPi = poly(adenosine diphosphate-ribose) polymerase inhibitor; PS = performance score

^a HRd and/or BRCAm

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

^b HRD-positive negative or BRCAwt/HRd

^c Mean

^d BRCAwt/HRp or BRCA/HRD unknown

^e BRCAwt/HRd

^f Patients are not all BRCAm by study design. This is coincidental.

^g Out of n=4 analysed; n=26 were not analysed

^h Of those assessed

ⁱ ECOG 2–4

^j HRd and/or BRCAm

Table 102. Summary of effectiveness results of niraparib in RWEs

Study, author, year	Population	Treatment arm (n)	Median follow-up, months	Median PFS, months (95% CI)	Median OS, months (95% CI)	Median TFST / TTNT*, months (95% CI)
Apostol 2023	Overall population	Niraparib 200 mg (NR)	NR	Mean: 28.0 (NR)	NR	NR
	Overall population	Niraparib 100 mg (NR)		Mean: not reached	NR	NR
Salani 2025	Overall population	Niraparib (560)	14.2	11.4 (10.1, 12.2)	NR	12.4 (11.5, 13.8)*
Backes 2023	BRCAm/HRd	Niraparib (66)	17.0	25.4 (15.9, not reached)	NR	24.9 (16, not reached)*
Coleman 2023	BRCAw/HRd	Niraparib (78)	17.0	14.2 (8.6, 18.6)	NR	15.1 (10.3, 19.8)*
Salani 2024	HRd	Niraparib (144)	17.0	18.2 (13.9, 24.2)	NR	19.6 (14.9, 23.9)*
Backes 2025 (CHARIZMA)	HRp	Niraparib (71)	13.8	NR	NR	11.7 (9.4, 17.3)*
	BRCAw	Niraparib (346)	13.8	NR	NR	12.4 (11.7, 14.6)*
Bruno 2024	Overall population	Niraparib 100 mg (9)	38	Mean: 27 (NR)	NR	NR
	Overall population	Niraparib 200 mg (188)		Mean: 27 (NR)	NR	NR
Chase 2025 (ARIZE)	Overall population (PRIMA-like cohort)	Niraparib (390)	16.2	10.1 (9.1, 11.9)	NR	11.7 (10.8, 12.9)*
	Overall population (stage III NVRD cohort)	Niraparib (63)	19.7	25.2 (12.6, not reached)	NR	17.3 (17.3, not reached)*
Chen 2024	Overall population	Niraparib (60)	17	Mean: 22.1 (not evaluable)	NR	NR
	Overall population	Olaparib (104)	17	Mean: 27 (not evaluable)	NR	NR
Chase 2024 (PREDICT)	Overall population	Niraparib (526)	14.1	NR	NR	11.2 (9.9, 12.4)*
Ha 2024	Overall population	Niraparib (69)	NR	NR	NR	NR
	Overall population	Olaparib (27)	NR	NR	NR	NR
Han 2024	Overall population	Niraparib (118)	NR	NR	NR	NR
	Overall population	Olaparib (104)	NR	NR	NR	NR

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Study, author, year	Population	Treatment arm (n)	Median follow-up, months	Median PFS, months (95% CI)	Median OS, months (95% CI)	Median TFST / TTNT*, months (95% CI)
Hannaway 2023	Overall population (all BRCAwt/HRD unknown)	Niraparib (83)	15.3	Median (range) 12.7 (1.1 to -29.2)	NR	NR
Hashimoto 2023	Overall population	Niraparib (45)	NR	NR	NR	NR
Khaja 2024	Overall population	Niraparib (19)	14	13.0 (11.7, 14.4)	NR	NR
Kim 2024	Matched cohort (all BRCAm)	Niraparib (31)	NR	Median (range) 31.463 (6.115–31.463)	Not reached	Not reached
	Matched cohort (all BRCAm)	Olaparib (80)	NR	Not reached	Not reached	31.8 (6.4, 31.8) [minimum, maximum]
Li 2022	Overall population	Niraparib (93)	8.7	Mean: not reached	NR	NR
Nakamura 2024	Overall population	Niraparib (60)	NR	10.3 (7, 13.5)	NR	NR
Piedimonte 2024	Overall population (all BRCAwt/HRD unknown)	Niraparib (52)	NR	13.0 (5.21, 20.8)	NR	NR
		Control (38)	NR	18.6 (15.9, 21.3)	NR	NR
Shin 2021	Overall population	Niraparib 200 mg (16)	NR	NR	NR	NR
		Niraparib 100 mg (16)	NR	NR	NR	NR
Rimel 2024 (SW1TCH)	Overall population	Niraparib (93)	16.3	NR	NR	12.9 (11.5, 19)
Wenxin 2023	Overall population	Niraparib (102)	10.5	Not reached	NR	NR
	BRCAm	Niraparib (19)	10.5	Not reached	NR	NR
	BRCAwt	Niraparib (60)	10.5	14.4 (NR)	NR	NR
	BRCA unknown	Niraparib (23)	10.5	14.6 (NR)	NR	NR
	HRd	Niraparib (37)	10.5	Not reached	NR	NR
	HRp	Niraparib (13)	10.5	Not reached	NR	NR
Zhao 2023 (NCT05734911)	Overall population	Niraparib (199)	17.8	Not reached	NR	NR
	BRCAm	Niraparib (40)	17.8	NE	NR	NR
	BRCAwt	Niraparib (131)	17.8	22.8 (15.4, NE)	NR	NR

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Study, author, year	Population	Treatment arm (n)	Median follow-up, months	Median PFS, months (95% CI)	Median OS, months (95% CI)	Median TFST / TTNT*, months (95% CI)
	HRd	Niraparib (66)	17.8	NE	NR	NR
	HRp	Niraparib (52)	17.8	15.3 (12.5, NE)	NR	NR
de la Motte Rouge 2022	Overall population	Niraparib (67)	NR	NR	NR	NR
Jeong 2024	Overall population	Niraparib (53)	NR	NR	NR	NR
Zuo 2024 Zheng 2024 (RENI-1)	Overall population	Niraparib (227)	23.9	24.2 (15.5, 33.0)	NR	NR
	BRCAm	Niraparib (47)	23.9	Not reached	NR	NR
	BRCAwt	Niraparib (163)	23.9	Not reached	NR	NR
	BRCA unknown	Niraparib (17)	23.9	11.5 (NR)	NR	NR
	HRd	Niraparib (118)	23.9	Not reached	NR	NR
	BRCAwt/HRd	Niraparib (71)	23.9	Not reached	NR	NR
	HRp	Niraparib (65)	23.9	17.5 (NR)	NR	NR
Hasson 2024 (MONITOR-UK)	Overall population	Niraparib (165)	17.3	12.0 (9.4, 15.6)	NR	NR
	Germline BRCAm	NR	NR	NR	NR	NR

Abbreviations: BRCAm = BRCA mutation; BRCAwt = BRCA wild type; CI = confidence interval; HRd = homologous recombination deficient; HRp = homologous recombination proficient; NA = not applicable; NE = not evaluable; NR = not reported; NVRD = no visible residual disease; OS = overall survival; PFS = progression-free survival; TTST = time to first subsequent treatment; TTNT = time to next treatment

Table 103. Summary of safety results of niraparib in RWEs

Study, author, year	Population	Treatment arm (n) ^a	SAE, n (%)	Deaths, n (%)	Grade ≥3 AE (%)	Discontinuation due to AE, N (%)	Dose interruption due to AE, N (%)	Dose reduction/modification due to AE, N (%)
Apostol 2023	Overall population	Niraparib 200 mg (NR)	NR	NR	NR	NR	NR	NR
	Overall population	Niraparib 100 mg (NR)	NR	NR	NR	NR	NR	NR
Salani 2025 Backes 2023 Coleman 2023 Salani 2024 Backes 2025 (CHARIZMA)	Overall population	Niraparib (560)	NR	NR	NR	147 (39.6)	NR	181 (69.1)
	BRCAm/HRd	Niraparib (66)	NR	NR	NR	NR	NR	NR
	BRCAwt/HRd	Niraparib (78)	NR	NR	NR	NR	NR	NR
	HRd/early discontinuers	Niraparib (30)	NR	NR	NR	NR (73.3)	NR	NR
	HRd/non-early discontinuers	Niraparib (114)	NR	NR	NR	NR (17.2)	NR	NR
Bruno 2024	Overall population	Niraparib (124)	NR	NR	NR	8 (6.5)	NR	88 (71)
Chase 2025 (ARIZE)	Overall population (PRIMA-like cohort)	Niraparib (390)	NR	NR	NR	NR	NR	NR
	Overall population (stage III NVRD cohort)	Niraparib (63)	NR	NR	NR	NR	NR	NR
Chen 2024	Overall population	Niraparib (60)	NR	NR	NR	1 (1.7) ^b	28 (46.7)	31 (51.7)
	Overall population	Olaparib (104)	NR	NR	NR	7 (6.7)	26 (25)	33 (31.7)

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Study, author, year	Population	Treatment arm (n) ^a	SAE, n (%)	Deaths, n (%)	Grade ≥3 AE (%)	Discontinuation due to AE, N (%)	Dose interruption due to AE, N (%)	Dose reduction/modification due to AE, N (%)
Chase 2024 (PRED1CT)	Overall population	Niraparib (526)	NR	NR	NR	NR	NR	NR
Ha 2024	Overall population	Niraparib (64)	NR	NR	12 (17.4) ^e	2 (2.9)	NR	NR
	Overall population	Olaparib (27)	NR	NR	4 (14.8) ^e	1 (3.7)	NR	NR
Han 2024	Overall population	Niraparib (118)	NR	NR	NR	24 (20.34)	NR	NR
	Overall population	Olaparib (104)	NR	NR	NR	0 (0)	NR	NR
Hannaway 2023	Overall population	Niraparib (83)	NR	NR	15 (18) ^e	NR	NR	NR
Hashimoto 2023	Overall population	Niraparib (45)	NR	NR	NR	4 (8.9)	28 (62.2)	18 (40)
Khaja 2024	Overall population	Niraparib	NR	NR	NR	NR	NR	NR
Kim 2024	Matched cohort (all BRCAm)	Niraparib (31)	NR	NR	NR	1 (3.2)	18 (58.1)	21 (67.7)
	Matched cohort (all BRCAm)	Olaparib (80)	NR	NR	NR	4 (5)	15 (18.8)	28 (35)
Li 2022	Overall population	Niraparib (93)	NR	NR	NR	NR	NR	NR
Nakamura 2024	Overall population	Niraparib (60)	NR	NR	NR	NR	NR	NR
Piedimonte 2024	Overall population (all BRCAwt/HRD unknown)	Niraparib (52)	NR	NR	NR	NR	NR	NR
		Control (38)	NR	NR	NR	NR	NR	NR

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Study, author, year	Population	Treatment arm (n) ^a	SAE, n (%)	Deaths, n (%)	Grade ≥3 AE (%)	Discontinuation due to AE, N (%)	Dose interruption due to AE, N (%)	Dose reduction/modification due to AE, N (%)
Shin 2021	Overall population	Niraparib (32)	NR	NR	NR	NR	NR	16 (50)
Rimel 2024 (SW1TCH)	Overall population	Niraparib (93)	NR	NR	NR	27 (44.3)	NR	NR
Wenxin 2023	Overall population	Niraparib (102)	NR	NR	18 (17.6) ^d	1 (0.98)	37 (36.3)	30 (29.4)
Zhao 2023 (NCT05734911)	Overall population	Niraparib (199)	NR ^d	0 (0) ^d	113 (56.8) ^d	11 (5.5)	79 (39.7)	47 (23.6)
de la Motte Rouge 2022	Overall population	Niraparib (67)	NR	NR	NR	4 (5.9)	NR	NR
Jeong 2024	Overall population	Niraparib	NR	NR	NR	NR	NR	NR
Zuo 2024 Zheng 2024 (RENI-1)	Overall population	Niraparib (227)	10 (4.4) ^c	NR ^c	Any: 37 (16.3) TR: 35 (15.4)	12 (5.3)	56 (24.7)	46 (20.3)
Hasson 2024 (MONITOR-UK)	Overall population	Niraparib (165)	NR	NR	NR	10 (6)	NR ^f	NR
	Germline BRCAm	NR	NR	NR	NR	NR	NR	NR

Abbreviations: AE = adverse event; BRCAm = BRCA mutation; BRCAwt = BRCA wild type; CI = confidence interval; HRd = homologous recombination deficient; HRp = homologous recombination proficient; NR = not reported

^a Safety analysis set

^b Grade ≥3 tachycardia

^c Treatment-related

^d Treatment-emergent

^e Outcome type not reported

^f Reported for >4 weeks due to TEAE in DET

Appendix C: Subgroup analysis

C1.1 Primary efficacy outcomes (PFS)

C.1.1.1 PRIMA



Abbreviations: BRCAm = BRCA mutation; CI = confidence interval; HRd = homologous recombination deficient;
PFS = progression-free survival
Source: Monk 2024¹⁶

[REDACTED]

[REDACTED]

[REDACTED]

Abbreviations: BRCAwt = BRCA wild type; CI = confidence interval; PFS = progression-free survival
Source: Monk 2024¹⁶

[REDACTED]

[REDACTED]

[REDACTED]

Abbreviations: CI = confidence interval; HRp = homologous recombination proficient; PFS = progression-free survival

Source: Monk 2024¹⁶

C.1.1.2 PRIME

[REDACTED]

[REDACTED]

Abbreviations: BICR = blinded independent central review; CI = confidence interval; HR = homologous recombination deficient; NE = not estimable; NR = not reached; PFS = progression-free survival

Source: Li 2023

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

[REDACTED]

[REDACTED]

Abbreviations: BICR = blinded independent central review; BRCAm = BRCA mutated; BRCAwt = BRCA wild type; CI = confidence interval; NE = not estimable; NR = not reached; PFS = progression-free survival
Source: Li 2023

[REDACTED]

[REDACTED]

[REDACTED]

Abbreviations: BICR = blinded independent central review; CI = confidence interval; HRD = homologous recombination deficiency; HRp = homologous recombination proficient; NE = not estimable; PFS = progression-free survival
Source: Li 2023

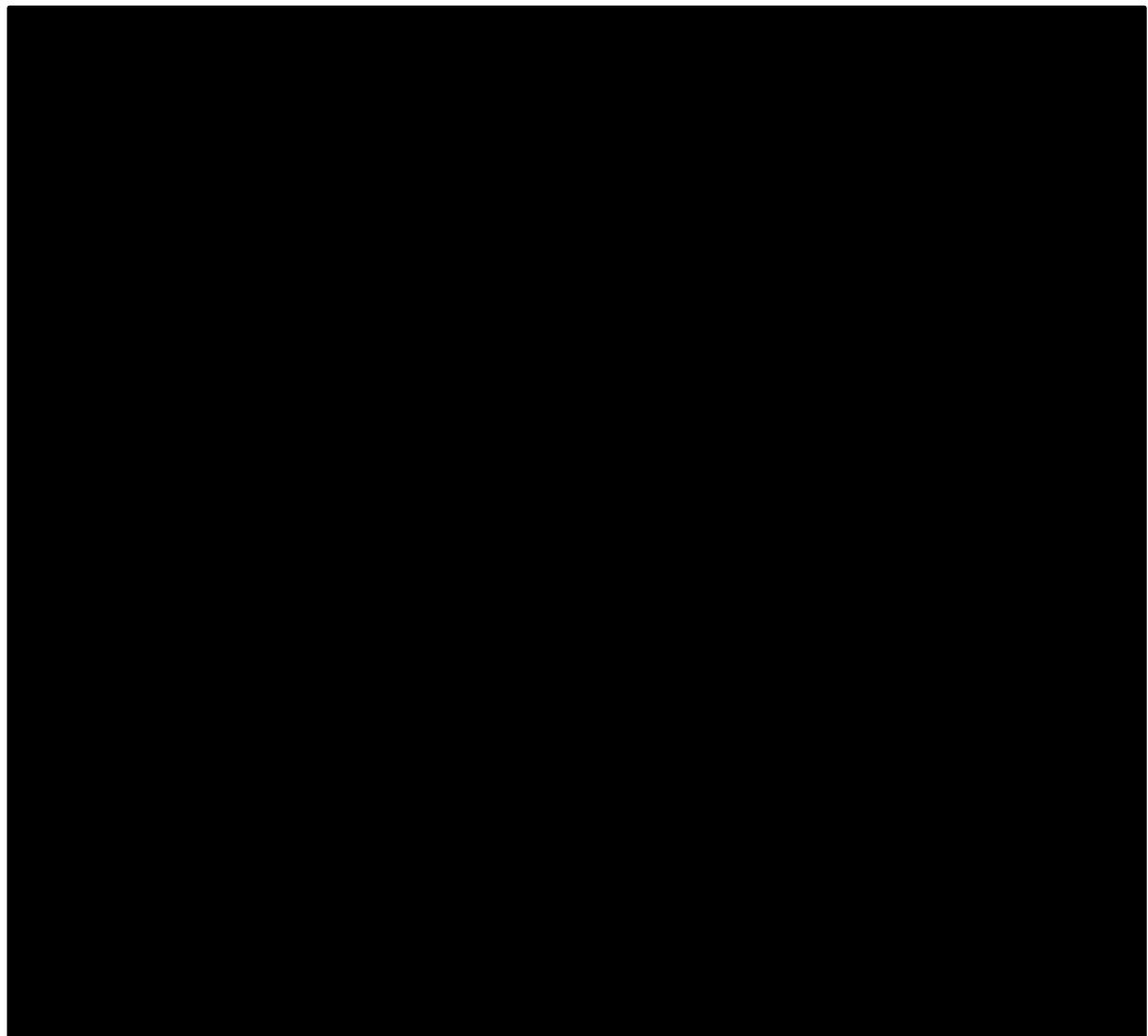
Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

C1.2 Secondary efficacy outcomes (OS)

C.1.2.1 PRIMA

The forest plot for OS by subgroups from the final analysis is presented in [REDACTED].

[REDACTED]



Abbreviations: BRCAm = breast cancer gene mutation; BRCAwt = breast cancer gene wild type; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; FIGO = International Federation of Gynaecology and Obstetrics; FSD = fixed starting dose; HRD = homologous recombination deficiency; HRd = homologous recombination deficient; HRnd = homologous recombination no data; HRp = homologous recombination proficient; ISD = individual starting dose; NACT = neoadjuvant chemotherapy; OS = overall survival; PBCT = platinum-based chemotherapy; PFS = progression-free survival; PS = performance status
Source: Monk 2024¹⁶

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

At the final analysis data cut (8 April 2024), OS in the overall population was not statistically significant (Section 2.4.4), therefore, statistical testing did not proceed to the HRd population.¹⁶ OS results by HRD and BRCA status (HRd, HRd/BRCAm, HRd/BRCAwT and HRp) are presented in Table 104.

In the HRd population, median OS was 71.9 months in the niraparib arm and 69.8 months in the placebo arm (HR: 0.95; 95% CI: 0.70, 1.29).¹⁶ In the niraparib arm there were ■■■ (■■■%) deaths and in the placebo arm there were ■■ (■■%) deaths.⁸⁴In the HRp population, median OS was 36.6 months in the niraparib arm and 32.2 months in the placebo arm (HR: 0.93; 95% CI: 0.69, 1.26).¹⁶ OS results by HRD and BRCA status were consistent with the overall population.¹⁶

Table 104. OS by HRD and BRCA status (final analysis, cut-off 8 April 2024)

	Niraparib (n=487)	Placebo (n=246)
HRd		
N	247	126
OS median (95% CI), months	71.9 ██████████	69.8 ██████████
HR (95% CI)	0.95 (0.705, 1.290)	
HRd/BRCAm		
N	152	71
OS median (95% CI), months	79.5 ██████████	NE ██████████
HR (95% CI)	0.94 (0.627, 1.412)	
HRd/BRCAwt		
N	94	55
OS median (95% CI), months	58.4 ██████████	68.9 ██████████
HR (95% CI)	0.97 (0.616, 1.530)	
HRp		
N	169	80
OS median (95% CI), months	36.6 ██████████	32.2 ██████████
HR (95% CI)	0.93 (0.687,1.263)	

Abbreviations: BRCAm = breast cancer susceptibility gene mutated; BRCAwT = breast cancer susceptibility gene wild type; CI = confidence interval; HR = hazard ratio; HRD = homologous recombinant deficiency; HRd = homologous recombinant deficient; HRp = homologous recombinant proficiency; OS = overall survival

^a HRD test not determined

Source: OS CSR 2024⁸⁴ and Monk 2024¹⁶

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

The OS Kaplan-Meier curve for niraparib versus placebo in the HRd population is presented in xxxxxx 40.

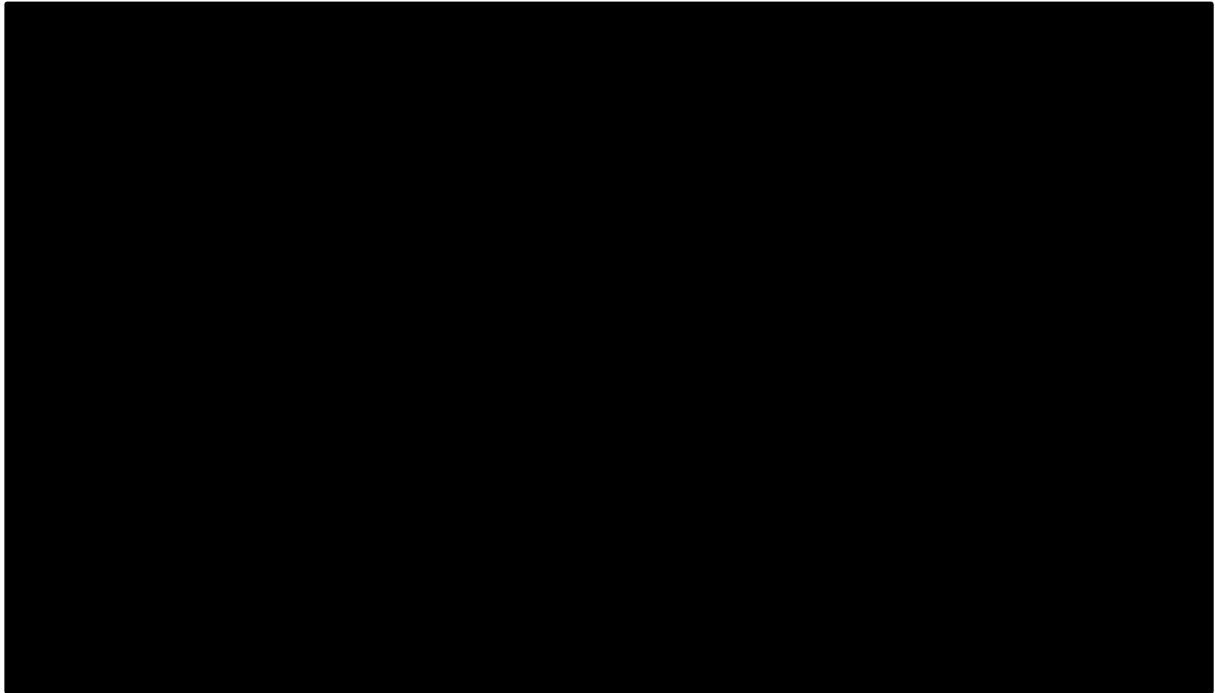
[REDACTED]

[REDACTED]



Abbreviation: CI = confidence interval; HRd = homologous recombination deficient; OS = overall survival
Source: Monk 2024¹⁶

The OS Kaplan-Meier curve for niraparib versus placebo in the HRp population is presented in xxxxxx 41.



Abbreviation: CI = confidence interval; HRp = homologous recombination proficient; OS = overall survival
Source: Monk 2024¹⁶

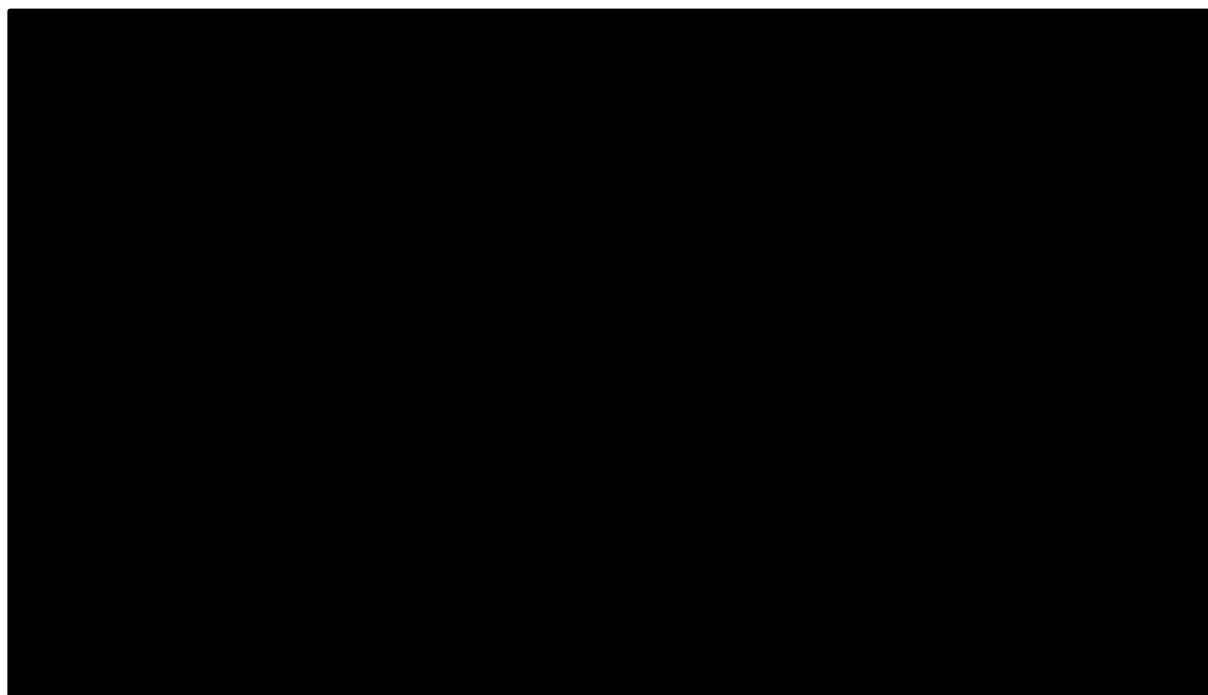
The OS Kaplan-Meier curves for the HRd/BRCAm population and HRd/BRCAw populations are presented in xxxxxx 42 and xxxxxx 43.

[REDACTED]

[REDACTED]

[REDACTED]

Abbreviation: BRCAm = breast cancer mutation; CI = confidence interval; HRd = homologous recombination deficient; OS = overall survival
Source: Monk 2024¹⁶



Abbreviation: BRCAwt = breast cancer wild type; CI = confidence interval; HRd = homologous recombination deficient; OS = overall survival
Source: Monk 2024¹⁶

C.1.2.2 PRIME

OS results for the HRd subgroup are presented in Table 105. Data for OS are immature but show a numerical benefit for niraparib over placebo (HR: 0.88; 95% CI: 0.43, 1.78).¹³

Table 105. Overall survival in the HRd population

Outcome	Niraparib (N=170)	Placebo (N=87)
Events, n (%)	21 (12.4)	12 (13.8)
Median OS	NR	NR
24-month survival, %	89.3	89.6
Hazard ratio (95% CI)	0.88 (0.43, 1.78)	

Abbreviations: CI = confidence interval; HR = hazard ratio; HRD = homologous recombination deficiency; NR = not reached; OS = overall survival
Source: Li 2023¹³

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

C1.3 Subsequent treatments

C.1.3.1 PRIMA

Table 106. Subsequent treatments in the PRIMA study in the BRCAm population⁸⁷

Subsequent treatment		Niraparib, n (%) (N = 152)	Placebo, n (%) (N = 71)
Any second-line therapy			
Carboplatin			
Cisplatin			
Taxane			
Doxorubicin			
Gemcitabine			
Bevacizumab			
Cyclophosphamide			
PARPi	Any		
	Niraparib		
	Olaparib		
	Rucaparib		
	Talazoparib		
Checkpoint inhibitor			
Antibody drug conjugate			
Hormonal Therapy			
Other			
Any third-line therapy			
Carboplatin			
Cisplatin			
Taxane			
Doxorubicin			
Gemcitabine			
Bevacizumab			
Cyclophosphamide			
PARPi	Any		
	Niraparib		
	Olaparib		
	Rucaparib		
	Talazoparib		
Checkpoint inhibitor			

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

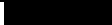
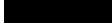
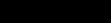
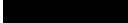
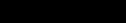
Subsequent treatment	Niraparib, n (%) (N = 152)	Placebo, n (%) (N = 71)
Antibody drug conjugate	██████	█
Hormonal Therapy	██████	██████
Other	██████	██████

Abbreviations: PARPi = poly (ADP-ribose) polymerase

Table 107. Subsequent treatments in the PRIMA study in the HRD/BRCAwt population⁸⁷

Subsequent treatment		Niraparib, n (%) (N = 310)	Placebo, n (%) (N = 163)
Any second-line therapy			
Carboplatin		██████	██████
Cisplatin		██████	██████
Taxane		██████	██████
Doxorubicin		██████	██████
Gemcitabine		██████	██████
Bevacizumab		██████	██████
Cyclophosphamide		██████	██████
PARPi	Any	██████	██████
	Niraparib	██████	██████
	Olaparib	██████	██████
	Rucaparib	██████	██████
	Talazoparib	█	█
Checkpoint inhibitor		██████	██████
Antibody drug conjugate		██████	██████
Hormonal Therapy		██████	██████
Other		██████	██████
Any third-line therapy			
Carboplatin		██████	██████
Cisplatin		██████	██████
Taxane		██████	██████
Doxorubicin		██████	██████
Gemcitabine		██████	██████
Bevacizumab		██████	██████
Cyclophosphamide		██████	██████
PARPi	Any	██████	██████
	Niraparib	██████	██████
	Olaparib	██████	██████
	Rucaparib	██████	█

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Subsequent treatment		Niraparib, n (%) (N = 310)	Placebo, n (%) (N = 163)
	Talazoparib		
Checkpoint inhibitor			
Antibody drug conjugate			
Hormonal Therapy			
Other			

Abbreviations: PARPi = poly (ADP-ribose) polymerase

C1.4 Impact of niraparib dosing on efficacy

C.1.4.1 PRIMA

xxxxxx 44 shows the changes in niraparib dosing during the PRIMA trial. Between 13% to 55% of patients who initially received 300 mg (individual or fixed dosing) were on a 100 mg dose after 12 months, and 33% to 81% were on a 200 mg dose. For patients who started treatment at 200 mg, the dose was reduced to 100 mg in 58% of cases.

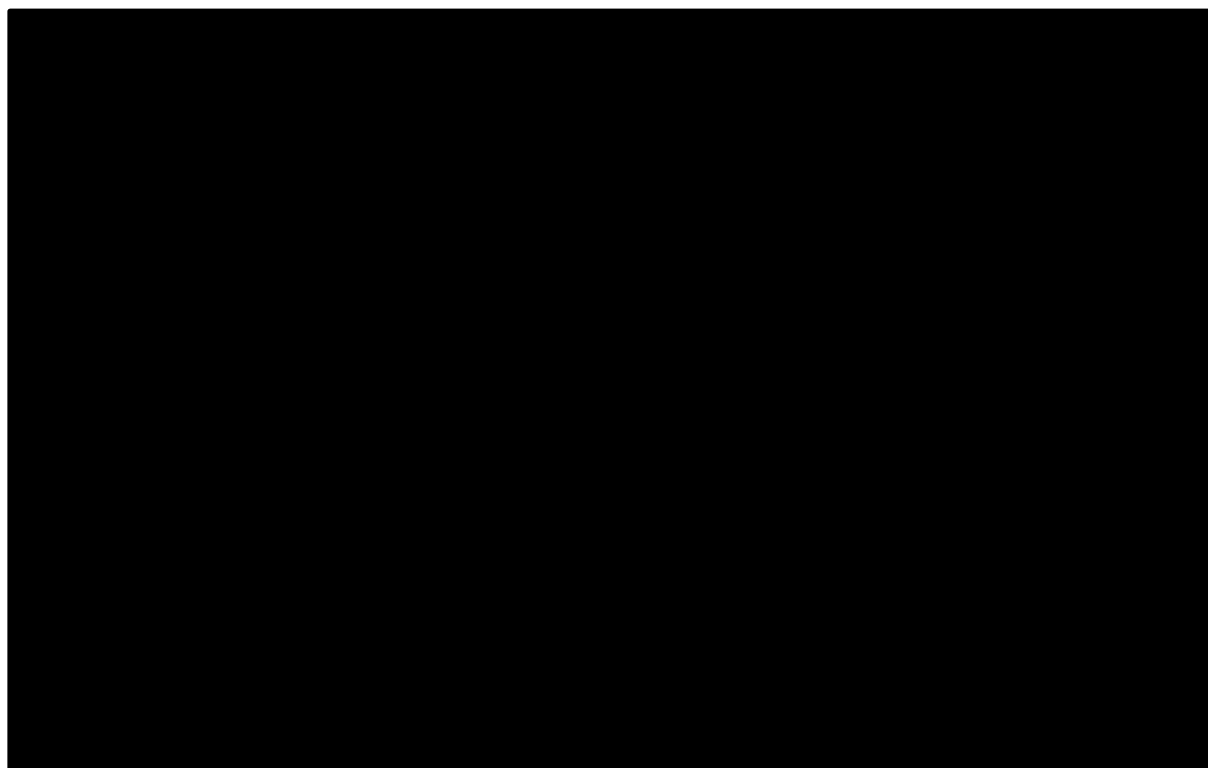
[REDACTED]

[REDACTED]

Abbreviations: BW = body weight; FSD = fixed starting dose; ISD = individualised starting dose; PC = platelet count
Percentage of patients at niraparib dose level by month. Percentages may not total 100 because of rounding.
(A) Subgroup A: 300-mg FSD, baseline BW ≥ 77 kg and PC $\geq 150,000/\mu\text{L}$ (n = 72). (B) Subgroup B: 300-mg ISD, baseline BW ≥ 77 kg and PC $\geq 150,000/\mu\text{L}$ (n = 34). (C) Subgroup C: 300-mg FSD, baseline BW < 77 kg or PC $< 150,000/\mu\text{L}$ (n = 243). (D) Subgroup D: 200-mg ISD (n = 122). Data cutoff date: May 17, 2019.
Source: Mirza 2023⁷⁴

Niraparib's efficacy in prolonging PFS, compared to placebo, was similar for patients who received individualised dosing versus fixed dosing across both the overall population and the HRd/HRp populations (xxxxxx 45).⁷⁴

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer



Abbreviations: CI = confidence interval; FSD = fixed starting dose; ISD = individualised starting dose; HRD = homologous recombination deficient; HRp = homologous recombination proficient; PFS = progression free survival
The original data cutoff date was 17 May 2019. The updated data cutoff date was 17 November 2019
Source: Mirza 2023⁷⁴

Appendix D: Adverse reactions

A summary of TEAEs leading to dose reductions in the PRIME trial is presented in Table 108.

Table 108. TEAEs leading to dose reductions in the ITT population^a

TEAE, n (%)	Niraparib (N=255)	Placebo (N=129)
Platelet count decreased^b	62 (24.3)	4 (3.1)
Anaemia	26 (10.2)	2 (1.6)
Neutrophil count decreased^c	25 (9.8)	1 (0.8)
White blood cell count decreased^d	8 (3.1)	0
Vomiting	4 (1.6)	0
Nausea	4 (1.6)	0
Palpitation	2 (0.8)	0
Hypertension	2 (0.8)	0
γ-Glutamyl transferase increased	1 (0.4)	0
Alanine transaminase increased	1 (0.4)	1 (0.8)
Fatigue	1 (0.4)	0
Febrile neutropenia	1 (0.4)	0
Mucositis oral	1 (0.4)	0
Dizziness	1 (0.4)	0
Hypoesthesia	1 (0.4)	0
Vertigo	1 (0.4)	0
Abdominal distention	1 (0.4)	0
Alkaline phosphatase increased	1 (0.4)	0
Aspartate transaminase increased	0	1 (0.8)
Gastrointestinal pain	0	1 (0.8)
Hyperglycaemia	0	1 (0.80)

Abbreviations: TEAE = treatment-emergent adverse event

^a Dose reduction includes both direct dose reduction and dose reduction following treatment interruption

^b Included reports of platelet count decreased and thrombocytopenia

^c Included reports of neutrophil count decreased and neutropenia

^d Included reports of white blood cell count decreased and leukopenia

Source: Li 2023¹³

Appendix E: Published cost-effectiveness studies

E1.1 Identification and selection of relevant studies

A non-clinical SLR was undertaken to identify published economic evaluations and cost-effectiveness studies of treatments for people with advanced epithelial (FIGO stage III to IV) high-grade ovarian, fallopian tube, or primary peritoneal cancer in the 1L maintenance setting.¹⁵³ Studies were identified using a search strategy across relevant platforms (via the Ovid platform, as well as conference proceedings and HTA websites).¹⁵³ Inclusion and exclusion criteria were applied to studies to determine those most relevant for this submission.¹⁵³ This appendix details the objectives, methodology and findings of the SLR.

The SLR was originally conducted in February 2019 and was subsequently updated in February 2020, March 2023 and February 2025.¹⁵³

E.1.1.1 Search strategy

The 2019 SLR and subsequent updates were conducted based on the reporting standards of the PRISMA, general methodological requirements outlined in the Cochrane Handbook for Systematic Reviews of Interventions¹⁰³ and key HTA bodies, such as NICE.¹⁵³

The literature database searches included a combination of free-text and controlled vocabulary terms specific to each database.¹⁵³ Systematic literature searches were conducted via the Ovid platform to identify peer-reviewed studies of interest in the following electronic literature databases:¹⁵³

- MEDLINE and MEDLINE In-process
- Embase
- Evidence-Based Medicine Reviews: CENTRAL
- NHS EED (via CRD)
- National Health Service HTA (via INAHTA for 2025 update)

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

- INAHTA
- Sheffield Centre for Health and Related Research Health Utilities Database
- EuroQol
- EconLit (added for 2025 update and not restricted by time to ensure records are identified for the timeframe of the original SLR and previous updates)

Grey literature searches were also conducted to identify relevant research that may not have been published in peer-reviewed journals.¹⁵³ Conferences not indexed in Embase from the previous three years (2023 through February 2025) were hand-searched from the respective conference websites.¹⁵³ Conference proceedings from the following key conferences were searched:¹⁵³

- ESGO
- ASCO
- ESMO: annual meeting, Asia congress, gynaecological cancers congress and Anticancer Therapies
- ASGO
- SGO
- NCRI (up to July 2023 when it ceased to operate)
- EACR
- ISPOR: annual meeting; Europe annual; Asia Pacific
- IGCS (added for 2025 SLR update)
- BGCS (added for 2025 SLR update)

In addition, a search of prior HTA submissions was undertaken for the following HTA bodies to identify any relevant data not otherwise available in peer-reviewed journals or conference abstracts:¹⁵³

- NICE
- SMC

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

- NCPE
- Canada: Canada's Drug Agency (CDA))/pCODR
- PBAC

The literature search was validated via manual review of the bibliographies of relevant systematic reviews (i.e., published in the past three years) identified from the database searches.¹⁵³

Search strategies for electronic databases are provided in Table 109 to Table 113. The database searches were run on 10 February 2025.¹⁵³ Hand-search strategies for conference and HTA websites are provided in Table 114 to Table 118, and Table 119 to Table 122, respectively.¹⁵³

Table 109. Search strategies for Embase and MEDLINE (original & previous SLR updates)

Index	Description	Search terms	Hits
1	Population	'ovarian cancer'/exp OR 'ovar* cancer*:ti,ab OR 'fallopian tube cancer*:ti,ab OR 'peritoneal cancer'/exp OR 'periton* cancer*:ti,ab OR ((ovar* OR fallopian OR 'fallopian tube*' OR periton* OR granulosa OR krukenberg* OR oviduct* OR 'uterine tube*') NEXT/3 (neoplas* OR cancer* OR tumour* OR tumor* OR carcino* OR malignan* OR adenocarcino* OR metast* OR mesothelioma*)) OR dysgerminoma* OR gynandroblastoma*	Original SLR: 179,027
			Update: 192,065
2	Drug (maintenance)	'PARP inhibitor'/exp OR 'PARP inhibitor*:ti,ab OR 'poly (ADP-ribose) polymerase inhibitor':ti,ab OR niraparib/exp OR niraparib:ti,ab OR zejula:ti,ab OR MK4827:ti,ab OR 'MK 4827':ti,ab OR olaparib/exp OR olaparib:ti,ab OR lynparza:ti,ab OR 'AZD 2281':ti,ab OR AZD2281:ti,ab OR rucaparib/exp OR rucaparib:ti,ab OR veliparib/exp OR veliparib:ti,ab OR talazoparib/exp OR talazoparib:ti,ab OR pazopanib/exp OR pazopanib:ti,ab OR votrient:ti,ab OR bevacuzimab/exp OR bevacuzimab:ti,ab OR avastin:ti,ab OR altuzan:ti,ab	Original SLR: 19,930
			Update: 23,183

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Index	Description	Search terms	Hits
3	Study types: RCT Filter (https://www.sign.ac.uk/search-filters.html)	('clinical trial'/de OR 'randomized controlled trial'/de OR 'controlled clinical trial'/de OR 'multicenter study'/de OR 'Phase 3 clinical trial'/de OR 'Phase 4 clinical trial'/de OR 'randomization'/de OR 'single blind procedure'/de OR 'double blind procedure'/de OR 'crossover procedure'/de OR 'placebo'/de OR 'randomi*ed controlled trial':ti,ab OR rct:ti,ab OR 'random allocation':ti,ab OR 'randomly allocated':ti,ab OR 'allocated randomly':ti,ab OR (allocated NEXT/2 random):ti,ab OR 'single blind*':ti,ab OR 'double blind*':ti,ab OR ((treble OR triple) NEXT/1 blind*):ti,ab OR placebo*:ti,ab OR 'prospective study'/de) NOT ('case study'/de OR 'case report':ti,ab OR 'abstract report'/de OR 'letter'/de OR 'editorial'/de OR 'note'/de)	Original SLR: 1,979,541
			Update: 2,156,154
4	Observation study filter (https://www.sign.ac.uk/search-filters.html)	'clinical trial'/de OR 'case control study' OR 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR ('prospective study'/de NOT 'randomized controlled trial'/de) OR 'cohort analysis'/de OR (cohort NEXT/1 (study OR studies)) OR (('case control' NEXT/1 (study OR studies)):ti,ab) OR (('follow up' NEXT/1 (study OR studies)):ti,ab) OR ((observational NEXT/1 (study OR studies)):ti,ab) OR ((epidemiologic* NEXT/1 (study OR studies)):ti,ab) OR (('cross sectional' NEXT/1 (study OR studies)):ti,ab)	Original SLR: 2,956,349
			Update: 3,284,461
5	Combine filters and restrict date	#1 AND #2 AND (#3 OR #4)	Original SLR: 1,025
		#1 AND #2 AND (#3 OR #4) AND [13-2-2019]/sd NOT [27-2-2020]/sd AND [humans]/lim	Update: 296

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Table 110. Embase (via Ovid) search strategy (last search date: 10 February 2025)

#	Search Terms	Hits 21 Mar 2023	Hits 10 Feb 2025	Source
1	exp ovarian cancer/ or (ovar* cancer* or fallopian tube cancer*).ti,ab. or exp peritoneal cancer/ or (periton* cancer* or ((ovar* or fallopian or fallopian tube* or periton* or granulosa or krukensberg* or oviduct* or uterine tube*) adj3 (neoplas* or cancer* or tumour* or tumor* or carcino* or malignan* or adenocarcino* or metast* or mesothelioma*)) or dysgerminoma* or gynandroblastoma*).ti,ab.	218625	243574	1
2	socioeconomics/ or cost benefit analysis/ or cost effectiveness analysis/ or cost of illness/ or economic evaluation/ or cost utility analysis/ or cost control/ or economic aspect/ or financial management/ or health care cost/ or health care financing/ or health economics/ or hospital cost/ or (fiscal or financial or finance or funding).ti,ab. or cost minimization analysis/ or ((cost adj estimate*) or (cost adj variable*) or (unit adj cost*)).ti,ab.	1108225	1238937	4
3	quality adjusted life year/ or socioeconomics/	192975	209986	5
4	("value of life" or qaly* or qald* or qale* or qtime* or quality adjusted or adjusted life year* or "disability adjusted life" or daly* or (index adj3 wellbeing) or (quality adj3 wellbeing) or qwb or multiattribute* or multi attribute*).ti,ab.	44397	51191	5
5	(utility adj3 (score* or scoring or valu* or measur* or evaluat* or scale* or instrument* or weight or weights or weighting or information or data or unit or units or health* or life or estimate* or elicit* or disease* or mean or cost* or expenditure* or gain or gains or loss or losses or lost or analysis or index* or indices or overall or reported or calculate* or range* or increment* or state or states or status)).ti,ab.	65778	73982	5
6	(utility or utilities or disutili* or hsu or hsuvs or "health* year* equivalent*" or hye or hyes or hui or hui1 or hui2 or hui3 or "illness state*" or "health state*" or "euro qual" or "euro qual5d" or "euro qol5d" or eq 5d or eq5 d or eq5d or euroqual or euroqol or euroqual5d or euroqol5d or eq sdq or eqsdq or short form* or shortform* or sf36* or "sf 36*" or "sf thirtysix" or "sf thirty six" or sf6 or "sf 6" or sf6d or "sf 6d" or "sf six" or sfsix or sf8 or "sf 8" or "sf eight" or sfeight or sf12 or "sf 12" or "sf twelve" or sftwelve or sf16 or "sf 16" or "sf sixteen" or sfsixteen or sf20 or "sf 20" or "sf twenty" or sftwenty or 15d or	514857	578279	5

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

#	Search Terms	Hits 21 Mar 2023	Hits 10 Feb 2025	Source
	15 d or "15 dimension" or "standard gamble*" or sg or "time trade off*" or "time tradeoff*" or tto or timetradeoff*).ab,ti.			
7	or/2-6	1594219	1784938	NA
8	1 and 7	8402	10263	NA
9	exp PARP inhibitor/ or (PARP inhibitor* or "poly (ADP-ribose) polymerase inhibitor").ti,ab. or exp niraparib/ or exp olaparib/ or exp rucaparib/ or exp veliparib/ or exp talazoparib/ or exp pazopanib/ or exp bevacizumab/ or (niraparib or zejula or MK4827 or MK 4827 or olaparib or lynparza or AZD 2281 or AZD2281 or rucaparib or veliparib or talazoparib or pazopanib or vortient or bevacizumab or avastin or altuzan).ti,ab.	101729	116878	1
10	clinical trial/ or randomized controlled trial/ or controlled clinical trial/ or multicenter study/ or phase 3 clinical trial/ or phase 4 clinical trial/ or randomization/ or single blind procedure/ or double blind procedure/ or crossover procedure/ or placebo/ or prospective study/	2694075	2908213	2
11	(randomi*ed controlled trial* or rct or random allocation or randomly allocated or allocated randomly or placebo or (allocated adj2 random) or (single blind* or double blind*) or ((treble or triple) adj blind*)).ti,ab.	787265	862993	2
12	10 and 11	2910580	627075	2
13	case study/ or case report.ti,ab. or abstract report/ or letter/ or editorial/ or note/	3517616	3772204	2
14	12 not 13	2772407	617468	2
15	clinical trial/ or case control study/ or family study/ or longitudinal study/ or retrospective study/ or (prospective study/ not randomized controlled trial/) or cohort analysis/ or ((cohort or case control or follow up or observational or epidemiologic* or cross sectional) adj (study or studies)).ti,ab.	4556045	5184009	3
16	14 or 15	5481397	5549753	NA
17	1 and 9 and 16	5010	5028	NA
18	8 or 17	12872	14650	NA
19	(animal* not human*).sh,hw.	4816856	5004753	6
20	18 not 19	12699	14477	NA
21	limit 20 to yr="2020 -Current"	4151	-	7
22	limit 20 to yr="2023 -Current"	-	2852	7

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Table 111. Cochrane Central Register of Controlled Trials (via Ovid; last search date: 10 February 2025)

#	Search terms	Hits Mar 23 2023	Hits 10 Feb 2025
1	exp Ovarian Neoplasms/ or (ovar* cancer* or fallopian tube cancer*).ti,ab. or exp peritoneal neoplasms/ or (periton* cancer* or ((ovar* or fallopian or fallopian tube* or periton* or granulosa or krukenberg* or oviduct* or uterine tube*) adj3 (neoplas* or cancer* or tumour* or tumor* or carcino* or malignan* or adenocarcino* or metast* or mesothelioma*)) or dysgerminoma* or gynandroblastoma*).ti,ab.	8871	9916
2	socioeconomic factors/ or cost benefit analysis/ or cost-effectiveness analysis/ or "cost of illness"/ or cost control/ or financial management/ or health care costs/ or "health care economics and organizations"/ or hospital costs/ or (fiscal or financial or finance or funding).ti,ab. or "costs and cost analysis"/ or ((cost adj estimate*) or (cost adj variable*) or (unit adj cost*)).ti,ab.	37019	46928
3	Quality-Adjusted Life Years/ or Socioeconomic Factors/	6041	7062
4	("value of life" or qaly* or qald* or qale* or qtime* or quality adjusted or adjusted life year* or "disability adjusted life" or daly* or (index adj3 wellbeing) or (quality adj3 wellbeing) or qwb or multiattribute* or multi attribute*).ti,ab.	7163	8715
5	(utility adj3 (score* or scoring or valu* or measur* or evaluat* or scale* or instrument* or weight or weights or weighting or information or data or unit or units or health* or life or estimate* or elicit* or disease* or mean or cost* or expenditure* or gain or gains or loss or losses or lost or analysis or index* or indices or overall or reported or calculate* or range* or increment* or state or states or status)).ti,ab.	6172	7394
6	(utility or utilities or disutili* or hsuv or hsuvs or "health* year* equivalent*" or hye or hyes or hui or hui1 or hui2 or hui3 or "illness state*" or "health state*" or "euro qual" or "euro qual5d" or "euro qol5d" or eq 5d or eq5 d or eq5d or euroqual or euroqol or euroqual5d or euroqol5d or eq sdq or eqsdq or short form* or shortform* or sf36* or "sf 36*" or "sf thirtysix" or "sf thirty six" or sf6 or "sf 6" or sf6d or "sf 6d" or "sf six" or sfsix or sf8 or "sf 8" or "sf eight" or sfeight or sf12 or "sf 12" or "sf twelve" or sftwelve or sf16 or "sf 16" or "sf sixteen" or sfsixteen or sf20 or "sf 20" or "sf twenty" or sftwenty or 15d or 15 d or "15 dimension" or "standard gamble*" or sg or "time trade off*" or "time tradeoff*" or tto or timetradeoff*).ab,ti.	53749	65273
7	or/2-6	89024	109662
8	1 and 7	518	675

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

9	exp "Poly(ADP-ribose) Polymerase Inhibitors"/ or (PARP inhibitor* or "poly (ADP-ribose) polymerase inhibitor").ti,ab. or exp bevacizumab/ or (niraparib or zejula or MK4827 or MK 4827 or olaparib or lynparza or AZD 2281 or AZD2281 or rucaparib or veliparib or talazoparib or pazopanib or vortient or bevacizumab or avastin or altuzan).ti,ab.	9119	10554
10	clinical trial/ or randomized controlled trial/ or controlled clinical trial/ or multicenter study/ or random allocation/ or single-blind method/ or double-blind method/ or cross-over studies/ or placebos/ or prospective studies/	305328	352507
11	(randomi*ed controlled trial* or rct or random allocation or randomly allocated or allocated randomly or placebo or (allocated adj2 random) or (single blind* or double blind*) or ((treble or triple) adj blind*)).ti,ab.	672521	784216
12	10 or 11	800476	931826
13	case reports/ or case report.ti,ab. or letter/ or editorial/	2419	2814
14	12 not 13	799325	930486
15	clinical trial/ or case-control studies/ or longitudinal studies/ or retrospective studies/ or (prospective studies/ not randomized controlled trial/) or cohort studies/ or ((cohort or case control or follow up or observational or epidemiologic* or cross sectional) adj (study or studies)).ti,ab.	174636	205051
16	14 or 15	842443	980008
17	1 and 9 and 16	589	732
18	8 or 17	995	1256
19	(animal* not human*).sh,hw.	2684	3379
20	18 not 19	995	1256
21	limit 20 to yr="2020 -Current"	407	-
22	limit 20 to yr="2023 -Current"	-	218

Table 112. INAHTA search strategy (last search date: 10 February 2025)

#	Search terms	Hits 10 Feb 2025
1	exp Ovarian Neoplasms/ or (ovar* cancer* or fallopian tube cancer*).ti,ab. or exp peritoneal neoplasms/ or (periton* cancer* or ((ovar* or fallopian or fallopian tube* or periton* or granulosa or krukensberg* or oviduct* or uterine tube*) adj3 (neoplas* or cancer* or tumour* or tumor* or carcino* or malignan* or adenocarcino* or metast* or mesothelioma*)) or dysgerminoma* or gynandroblastoma*).ti,ab.	-
2	2023- current	286

Table 113. EconLit (last search date: 10 February 2025)

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

#	Search terms	Hits 10 Feb 2025
1	Ovarian cancer.mp. [mp=heading words, abstract, title, country as subject]	29
2	fallopian tube cancer.mp. [mp=heading words, abstract, title, country as subject]	0
3	peritoneal cancer.mp. [mp=heading words, abstract, title, country as subject]	0
4	1 or 2 or 3	29

Table 114. EACR Congress

Conference	Search terms	Hits 21 Mar 2023	Hits 06 Feb 2025
EACR 2024	Ovarian cancer	-	214
	Fallopian tube cancer	-	2
	Peritoneal cancer	-	34
EACR 2023	Ovarian cancer	-	157
	Fallopian tube cancer	-	0
	Peritoneal cancer	-	1
EACR 2022	Ovarian cancer	55	-
	Fallopian tube cancer	0	-
	Peritoneal cancer	1	-
EACR 2021	Ovarian cancer	76	-
	Fallopian tube cancer	0	-
	Peritoneal cancer	0	-

EACR = European Association for Cancer Research

Table 115. ISPOR Asia congress (indexed in Embase from 2023)

Conference	Search terms	Hits 21 Mar 2023
ISPOR Asia 2022	Ovarian cancer	0
	Fallopian tube cancer	0
	Peritoneal cancer	0

ISPOR = International Society of Pharmacoeconomics and Outcomes Research

Table 116. ESMO Gynaecological Cancer Congress (abstracts only)

Conference	Search terms	Hits 21 Mar 2023	Hits 06 Feb 2025
ESMO Gynaecological Cancer 2024	Ovarian cancer	-	340
	Fallopian tube cancer	-	6
	Peritoneal cancer	-	78
	Ovarian cancer	50	-
	Fallopian tube cancer	2	-

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Conference	Search terms	Hits 21 Mar 2023	Hits 06 Feb 2025
ESMO Gynaecological Cancer 2023	Peritoneal cancer	2	-
ESMO Gynaecological Cancer 2022	Ovarian cancer	27	-
	Fallopian tube cancer	2	-
	Peritoneal cancer	3	-

ESMO = European Society for Medical Oncology

Table 117. NCRI congress (up to 2023 as it ceased to operate in July 2023)

Conference	Search terms	Hits 21 March 2023
NCRI 2021	Ovarian cancer	9
	Fallopian tube cancer	0
	Peritoneal cancer	1
NCRI 2020	Ovarian cancer	9
	Fallopian tube cancer	0
	Peritoneal cancer	4

NCRI = National Cancer Research Institute

Table 118. BGSC congress

Conference	Search terms	Hits 21 March 2023
BGCS 2024	Ovarian cancer	156
	Fallopian tube cancer	0
	Peritoneal cancer	2
BGCS 2023	Ovarian cancer	184
	Fallopian tube cancer	0
	Peritoneal cancer	5
BGCS 2022	Ovarian cancer	45
	Fallopian tube cancer	1
	Peritoneal cancer	6
BGCS 2021	Ovarian cancer	40
	Fallopian tube cancer	0
	Peritoneal cancer	7

BGCS = British Gynaecological Cancer Society

Table 119. NICE searches (technology appraisal guidance only)

HTA body	Search terms	Hits 21 Mar 2023	Hits 05 Feb 2025
NICE	Ovarian cancer	12	4
	Fallopian tube cancer	7	4

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

HTA body	Search terms	Hits 21 Mar 2023	Hits 05 Feb 2025
	Peritoneal cancer	7	4
	Olaparib	6	6
	Rucaparib	1	1
	Bevacizumab	14	4

HTA = health technology assessment; NICE = National Institute for Health and Care Excellence

Table 120. CDA-AMC searches (reimbursement review reports only)

HTA body	Search terms	Hits 21 Mar 2023	Hits 05 Feb 2025
CDA-AMC	Ovarian cancer	5	8
	Fallopian tube cancer	0	1
	Peritoneal cancer	0	1

CDA-AMC = Canada's Drug Agency – Agence des Medicaments du Canada; HTA = health technology assessment

Table 121. SMC searches (medicine advices only)

HTA body	Search terms	Hits 21 Mar 2023	Hits 05 Feb 2025
SMC	Ovarian cancer	14	0
	Fallopian tube cancer	12	0
	Peritoneal cancer	12	0

HTA = health technology assessment; SMC = Scottish Medicines Consortium

Table 122. NCPE searches

HTA body	Search terms	Hits 21 Mar 2023	Hits 05 Feb 2025
NCPE	Ovarian cancer	5	2
	Fallopian tube cancer	5	2
	Peritoneal cancer	5	2

HTA = health technology assessment; NCPE = National Centre for Pharmacoeconomics

E.1.1.2 Study selection

Once the searches were conducted, the resulting titles and abstracts were uploaded to Distiller Systematic Review software.¹⁵³ The study selection process involved evaluating publications retrieved by the searches against predetermined PICOS criteria to establish the studies that were eligible for inclusion in the SLR.¹⁵³ The PICOS criteria used for economic evaluations in the 2025 SLR update are presented in Table 123.¹⁵³

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Table 123. PICOS selection criteria for economic evaluations

Inclusion	Exclusion
Population^a	
• Adult women with advanced (stage III) or metastatic (stage IV) OC receiving 1L maintenance therapy^b • Subgroups of interest: ○ Bevacizumab use in 1L setting ○ High risk^c ○ <i>BRCAM</i> or <i>BRCAWt</i> ○ HRD-positive ○ Homologous recombination proficient (HRD-negative) ○ Homologous recombination unknown (HRun) ○ <u>High-risk subgroups</u>: high risk + <i>BRCAM</i>, high risk + HRD-positive, high risk + HRD-positive + <i>BRCAWt</i>, high risk + HRD-negative ○ <u>HRD-positive subgroups</u>: HRD-positive + <i>BRCAWt</i> ○ Receipt of neoadjuvant chemotherapy (NACT) ○ Depth of response to 1L therapy (e.g., CR subgroup or PR subgroup)	• Patients with early disease stages (stage I or II) • Any other indication • Patients who progressed during or following 1L treatment (i.e., second- or later-line settings)
Interventions	
Systemic pharmacological treatment managing the disease, including, but not limited to:^d • Bevacizumab • Single PARPi (e.g., niraparib alone) • Single PARPi + bevacizumab • Single PARPi + immunotherapy	• Radiotherapy • Surgery
Comparators	
No restriction	N/A

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Inclusion	Exclusion
Outcomes	
Economic evaluation outcomes, including, but not limited to: • Total QALYs • Total LYG • Total costs • Incremental costs • Incremental QALYs • ICER/ICUR	Any other outcome (data relevant to the other SLRs will be flagged to ensure all relevant information is identified). Studies with no outcomes specific for the maintenance phase will be excluded.
Study design	
• Cost-effectiveness analyses • Cost-utility analyses • Economic evaluations conducted alongside clinical trials • SLRs/NMAs (to be hand-searched for relevant studies)^e	• Cost-benefit study • Cost-minimisation study • Cost-consequence analyses • Budget impact models • Burden of disease study • Resource use study • Reviews • Non-SLRs (i.e., targeted reviews) • Case reports • Case studies • Commentaries, editorials, and letters • Consensus reports
Additional limits	
Timeframe	
• Full texts: since 2023 • Conference proceedings: since 2023	• Full-text references published prior to 2023 • Conference proceedings published prior to 2023
Language	
English	Non-English language studies will be flagged for consideration in local market submissions.

1L = first-line; HRD = homologous recombination deficiency; HRR = homologous recombination repair; ICER = incremental cost-effectiveness ratio; ICUR = incremental cost-utility ratio; LYG = life-years gained; N/A = not applicable; NMA = network meta-analysis; OC = ovarian cancer; QALY = quality-adjusted life years; RWE = real-world evidence; SLR = systematic literature review

^a Studies will be considered eligible if at least 80% of the study population meets the inclusion criteria or if relevant subgroup data are available. The 80% threshold is based on recommendations by IQWiG26 and is frequently applied in SLRs for HTA submission.

^b Studies in the full 1L and 1L induction settings will be flagged but not included.

^c The definition of high-risk will be recorded in the data extraction file.

^d These treatments can be administered as monotherapy or as part of a combination therapy.

^e Not included in full-text screening.

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

In the first phase of screening, the title and abstract of all records were examined by two independent reviewers to determine their eligibility for inclusion in the SLR.¹⁵³ Disagreements between the reviewers were resolved by a third independent reviewer, as necessary.¹⁵³ Studies were designated as excluded or included for full-text review based on the inclusion and exclusion criteria described above (Table 123).¹⁵³ For abstracts that were deemed relevant during title and abstract screening, the corresponding full-text articles were retrieved for further screening.¹⁵³

In the second phase of screening, each full-text paper was assessed by two independent reviewers.¹⁵³ Disagreements between the reviewers were resolved by a third independent reviewer, as necessary.¹⁵³ Studies were designated as excluded or included for full-text review based on the inclusion and exclusion criteria above (Table 123).¹⁵³ For each excluded study, a reason for exclusion was specified.¹⁵³

E.1.1.3 Data extraction and quality assessment

From the final list of included studies, data were extracted into individual data extraction tables (DET) designed in Microsoft Excel®.¹⁵³ Data were extracted into the DET by one reviewer, and a second reviewer assessed the entries to ensure consistency and accuracy against the source article as a validation step.¹⁵³

Quality assessment of the included economic evaluations was conducted using the Drummond checklist.¹⁵⁴ Evidence from conference abstracts was not quality assessed, given the limited information provided.¹⁵³

E.1.1.4 Results

Overview of search results

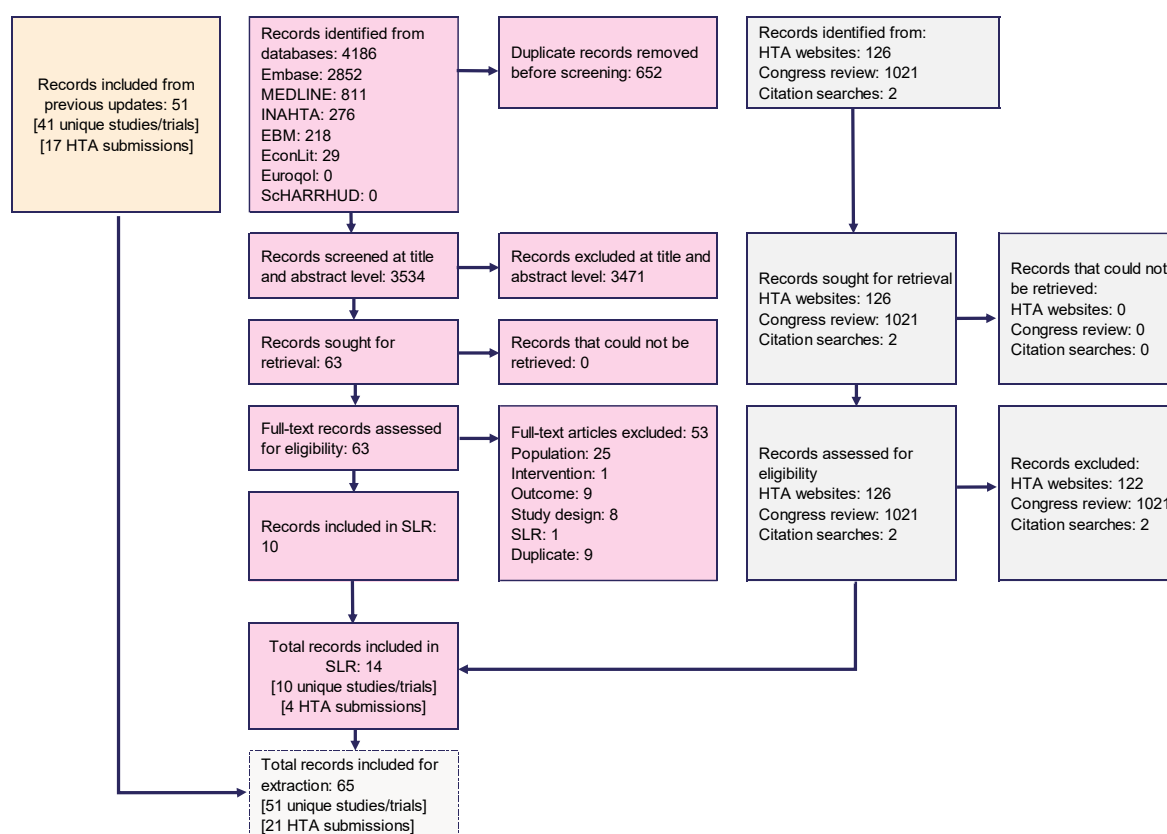
The original SLR was conducted in February 2019, and an initial update was performed in February 2020, which resulted in the inclusion of 10 publications representing nine unique studies and 2 HTA submissions.¹⁵³ A second update was conducted in March 2023, resulting in the inclusion of 42 new publications covering 33 unique studies.¹⁵³ In combination with the prior reviews, this resulted in a total of 52 publications, which included 42 unique studies and 17 HTA submissions.¹⁵³

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

The database searches for the current update were performed on 07 February 2025 and yielded 4,186 records.¹⁵³ Of 3,534 unique records screened at the title and abstract level that remained after removing 652 duplicates, 63 were deemed eligible for full-text screening, while the others were excluded.¹⁵³ After the full-text review, a total of 10 records were included for synthesis from the database searches, and 5 records were added from grey literature searches (HTA websites).¹⁵³ Therefore, a total of 15 records were included in the 2025 SLR update.¹⁵³

Accounting for the original SLR and subsequent updates, a total of 65 records were included, representing 51 unique studies and included 21 HTA submissions.¹⁵³ The PRISMA flow diagram is shown in Figure 46.¹⁵³

Figure 46. PRISMA flow diagram



CENTRAL = Cochrane Central Register of Controlled Trials; EACR = European Association for Cancer Research; ESGO = European Society of Gynaecological Oncology; ESMO = European Society for Medical Oncology; HTA = health technology assessment; INAHTA = International Network of Agencies for Health Technology Assessment; NHS EED = National Health Service Economic Evaluations Database; PRISMA = Preferred Reporting Items for Systematic reviews and Meta-Analyses; SGO = Society of Gynaecologic Oncology; SLR = systematic literature review

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Overview of included studies

From the original SLR and subsequent updates, a total of 65 records were included following full-text screening, including 49 economic evaluations or cost-effectiveness studies of treatment strategies (Table 124).¹⁵³ These included 21 HTA submissions. Characteristics of these 49 studies are presented in Table 125.¹⁵³

Table 124. List of included economic evaluations and cost-effectiveness studies

SLR search	Study ID	Primary/secondary publication	Citation
Original SLR (2020)	1	Primary	Cohn, D. E., Barnett, J. C., Wenzel, L., Monk, B. J., Burger, R. A., Myers, E., & Havrilesky, L. J. (2014). A cost-utility analysis of Gynecologic Oncology Group protocol 218: The importance of incorporating prospectively collected quality-of-life scores in health outcomes research. <i>Gynecologic Oncology</i> , 133, 4.
SLR update (2023)	9	Primary	Tan, D. S., Chan, J. J., Hettle, R., Ghosh, W., Viswambaram, A., & Yu, C. C. (2021). Cost-effectiveness of olaparib versus routine surveillance in the maintenance setting for patients with BRCA-mutated advanced ovarian cancer after response to first-line platinum-based chemotherapy in Singapore. <i>Journal of Gynecologic Oncology</i> , 32(2), e27.
Original SLR (2020)	9	Secondary	Tan, D. S., Chan, J. J., Loke, J. K., Hettle, R., Ghosh, W., Viswambaram, A., & Yu, C. C. (2019). Cost-effectiveness of olaparib vs routine surveillance in the maintenance setting for patients with BRCA-mutated advanced ovarian cancer after response to first-line platinum-based chemotherapy in Singapore. <i>Annals of Oncology</i> , 30, ix79-ix80.
Original SLR (2020)	10	Primary	Wolford, J. E., Bai, J., Minion, L. E., Keller, R., Eskander, R. N., Chan, J. K., ... & Tewari, K. S. (2018). Cost-effectiveness of maintenance therapy in advanced ovarian cancer: Paclitaxel, bevacizumab, niraparib, rucaparib, olaparib, and pembrolizumab.
Original SLR (2020)	11	Primary	Wolford, J. E., Liang, S. Y., Tewari, K. S., Eskander, R. N., Kapp, D. S., Mann, A. K., & Chan, J. K. (2019). An economic analysis: examining the cost-effectiveness of bevacizumab and olaparib as upfront maintenance treatment of advanced ovarian cancer. <i>Gynecologic Oncology</i> , 154, 25.

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

SLR search	Study ID	Primary/secondary publication	Citation
SLR update (2023)	13	Primary	Penn, C. A., Wong, M. S., & Walsh, C. S. (2020). Cost-effectiveness of maintenance therapy based on molecular classification following treatment of primary epithelial ovarian cancer in the United States. <i>JAMA Network Open</i> , 3(12), e2028620-e2028620.
SLR update (2023)	13	Secondary	Penn, C., Wong, M., & Walsh, C. S. (2020). Cost-effectiveness of various maintenance therapies based on mutation status following first-line treatment of primary epithelial ovarian cancer in the United States.
SLR update (2023)	14	Primary	Moya-Alarcón, C., González-Domínguez, A., Ivanova-Markova, Y., Gimeno-Ballester, V., Barretina-Ginesta, M. P., Pérez-Fidalgo, J. A., & Redondo, A. (2022). Olaparib as first line in BRCA-mutated advanced ovarian carcinoma: Is it cost-effective in Spain?. <i>Gynecologic Oncology</i> , 164(2), 406-414.
SLR update (2023)	15	Primary	Elsea, D., Fan, L., Mihai, A., Moustaid, F. E., Simmons, D., Monberg, M., & Muston, D. (2022). Cost-effectiveness analysis of olaparib in combination with bevacizumab compared with bevacizumab monotherapy for the first-line maintenance treatment of homologous recombination deficiency-positive advanced ovarian cancer. <i>PharmacoEconomics-open</i> , 6(6), 811-822.
SLR update (2023)	16	Primary	Huepenbecker, S., Deshmukh, A., Sun, C., Rajan, S., Harrison, R., Giordano, S., & Meyer, L. (2022). Cost-utility analysis of management strategies after frontline treatment of women with epithelial ovarian cancer (339). <i>Gynecologic Oncology</i> , 166, S174-S175.
SLR update (2025)	17	Primary	Cedillo, S., Gari, C., Aceituno, S., Manso, L., Lleti, A. C. C., Bosch, P. V., Casado, A., Fidalgo, A. P. (2024). Cost-effectiveness of olaparib plus bevacizumab versus bevacizumab monotherapy in the maintenance of patients with homologous recombination deficiency-positive advanced ovarian cancer after response to first-line platinum-based chemotherapy <i>International Journal of Gynecological Cancer</i> , 34(2), 277 EP - 284
SLR update (2023)	17	Secondary	Perez-Fidalgo, J. A., Cercos Lleti, A. C., Manso, L., Casado Herraiez, A., Ventayol Bosch, P., Garí, C., ... & Cedillo Gomez, S. (2022). Cost-effectiveness of Olaparib plus Bevacizumab versus Bevacizumab in the maintenance of patients with HRD+ advanced ovarian cancer after response to first-line platinum-based chemotherapy in Spain.

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

SLR search	Study ID	Primary/secondary publication	Citation
SLR update (2023)	18	Primary	Okumura, L., Massaoka, M. H., Licursi, C., Mihai, A., & Ryan, J. (2022). EE50 Olaparib As Maintenance Therapy for Women with Ovarian Cancer and Homologous Recombination Deficiency in Brazil: What Clinical and Cost Data Have Highest Impact on Cost-Effectiveness Analysis?. <i>Value in Health</i> , 25(7), S345.
SLR update (2023)	19	Primary	Lim, S., Moss, H., Havrilesky, L., O'Cearbhaill, R., Abu-Rustum, N., Liang, M., ... & Aviki, E. (2021). A novel, out-of-pocket, cost-effectiveness analysis comparing a frontline niraparib-for-all to a biomarker-based strategy in patients with advanced ovarian cancer. <i>Gynecologic Oncology</i> , 162, S77.
SLR update (2023)	20	Primary	Fan, L., Muston, D., Elsea, D., El Moustaid, F., Mihai, A., Simmons, D., ... & Monberg, M. (2021). Olaparib in combination with bevacizumab compared to bevacizumab monotherapy for the first-line maintenance treatment of advanced ovarian cancer: a cost-effectiveness analysis. <i>Gynecologic Oncology</i> , 162, S216-S217.
SLR update (2023)	24	Primary	Hernández, J. M., Solorzano, J., Murtiera, S., Perichon, S., Cerccone, J., & Leon, A. (2020). PCN96 OLAPARIB COST-EFFECTIVENESS AS A MAINTENANCE TREATMENT OPTION FOR NEWLY DIAGNOSED BRCA-MUTATED OVARIAN CANCER WHO ARE IN RESPONSE AFTER FIRST-LINE PLATINUM-BASED CHEMOTHERAPY IN COSTA RICA. <i>Value in Health</i> , 23, S40.
SLR update (2023)	25	Primary	Castillo-Fernandez, O., Murtiera, S., Solorzano, J., Martin, C., Sosa, J. A., Law, M. L., ... & Leon, A. (2020). PCN85 COST-EFFECTIVENESS OF OLAPARIB AS A MAINTENANCE TREATMENT OPTION FOR NEWLY DIAGNOSED BRCA-MUTATED OVARIAN CANCER WHO ARE IN RESPONSE AFTER FIRST-LINE PLATINUM-BASED CHEMOTHERAPY IN PANAMA. <i>Value in Health</i> , 23, S38.
SLR update (2023)	26	Primary	Muston, D., Hettle, R., Monberg, M., McLaurin, K. K., Gao, W., Swallow, E., ... & Moore, K. (2020). Cost-effectiveness of olaparib as a maintenance treatment for women with newly diagnosed advanced ovarian cancer and BRCA1/2 mutations in the United States. <i>Gynecologic Oncology</i> , 159(2), 491-497.

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

SLR search	Study ID	Primary/secondary publication	Citation
SLR update (2023)	26	Secondary	Muston, D. R., Monberg, M. J., McLaurin, K., Sackeyfio, A., Hettle, R., Signorovitch, J., ... & Moore, K. N. (2020). Cost-effectiveness analysis of olaparib as a maintenance monotherapy for patients with newly diagnosed advanced ovarian cancer and a BRCA1/2 mutation: A United States payer perspective. <i>Gynecologic Oncology</i> , 159, 140-141.
SLR update (2023)	27	Primary	Barrington, D. A., Tubbs, C., Smith, H. J., Straughn Jr, J. M., Senter, L., & Cohn, D. E. (2020). Niraparib maintenance in frontline management of ovarian cancer: a cost effectiveness analysis. <i>International Journal of Gynecological Cancer</i> , 30(10), 1569-1575.
SLR update (2023)	28	Primary	Gonzalez, R., Havrilesky, L. J., Myers, E. R., Secord, A. A., Dottino, J. A., Berchuck, A., & Moss, H. A. (2020). Cost-effectiveness analysis comparing "PARP inhibitors-for-all" to the biomarker-directed use of PARP inhibitor maintenance therapy for newly diagnosed advanced stage ovarian cancer. <i>Gynecologic oncology</i> , 159(2), 483-490.
SLR update (2023)	28	Secondary	Gonzalez, R., Havrilesky, L. J., Secord, A. A., Myers, E. R., Dottino, J. A., & Moss, H. A. (2020). Just OK is not OK: How well does PARP inhibitor frontline maintenance therapy need to work in biomarker negative ovarian cancer for universal treatment to represent a value-based therapeutic option?. <i>Gynecologic Oncology</i> , 159, 21-22.
SLR update (2023)	29	Primary	Armeni, P., Borsoi, L., Fornaro, G., Jommi, C., Colombo, N., & Costa, F. (2020). Cost-effectiveness and net monetary benefit of olaparib maintenance therapy versus No maintenance therapy after first-line platinum-based chemotherapy in newly diagnosed advanced BRCA1/2-mutated ovarian cancer in the Italian national health service. <i>Clinical therapeutics</i> , 42(7), 1192-1209.
SLR update (2023)	30	Primary	Muston, D., Hettle, R., McLaurin, K., Fan, L., & Monberg, M. J. (2020). PCN72 Biomarker Testing to Guide Cost Effective Use of PARPi in Patients with Newly Diagnosed Ovarian Cancer. <i>Value in Health</i> , 23, S434.
SLR update (2023)	31	Primary	Richardson, M. T., Kapp, D. S., Chan, J. E., Liang, S. Y., Mann, A. K., Monk, B. J., ... & Chan, J. K. (2020). Upfront maintenance with anti-vascular versus PARP inhibitors in advanced ovarian cancer: A cost-effective analysis. <i>Gynecologic Oncology</i> , 159, 21.

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

SLR search	Study ID	Primary/secondary publication	Citation
SLR update (2025)	34	Primary	Yong, C. M.,Yehgambaram, P. A. P.,Lee, S. W. H. (2024). Cost-effectiveness analysis of olaparib maintenance therapy for BRCA mutation ovarian cancer in the public sector in Malaysia PLoS ONE, 19(2 February), e0298130
SLR update (2025)	35	Primary	Zhu, Y.,Liu, K.,Cao, H.,Zhu, H. (2023). The cost-effectiveness analysis of maintenance olaparib plus Bevacizumab in patients with advanced ovarian cancer: based on the final survival results from PAOLA-1 trial Journal of Ovarian Research, 16(1), 168
SLR update (2025)	35	Secondary	Zhu, Y.,Yang, Q.,Liu, K.,Cao, H.,Zhu, H. (2024). Olaparib plus bevacizumab as a first-line maintenance treatment for patients with advanced ovarian cancer by molecular status: an updated PAOLA-1 based cost-effectiveness analysis Journal of Gynecologic Oncology, 35(1), e2
SLR update (2025)	36	Primary	Giuliani, J.,Mantoan, B.,Ferrario, L.,Candela, M. V.,Aprile, G. (2023). Cost-effectiveness of poly-(ADP-ribose) polymerase (PARP)-inhibitors for the maintenance treatment after responding to first- and second-line chemotherapy in advanced ovarian cancer Journal of Oncology Pharmacy Practice, 29(2), 457 EP - 464
SLR update (2025)	37	Primary	Perrier, L.,Zarca, K.,Cadet, T.,Morelle, M.,Cropet, C.,Borges, A.,Cecere, S. C.,Palacio, I.,Polterauer, S.,Yoshida, H.,Vuytsteke, P.,Colombo, N.,Nottrup, T. J.,Abdeddaim, C.,El-Balat, A.,Cinieri, S.,Herrero, A.,Kaminski, M. C.,Pujade-Lauraine, E.,Durand-Zaleski, I.,Ray-Coquard, I. (2023). Cost-Effectiveness of Olaparib Plus Bevacizumab First-Line Maintenance in Ovarian Cancer Alongside the PAOLA-1 Trial Value in Health, 26(12 Supplement), S61 EP - S62
Original SLR (2020)	HS-1	Primary	NICE 2019 (TA598). Olaparib for maintenance treatment of BRCA mutation-positive advanced ovarian, fallopian tube or peritoneal cancer after response to first-line platinum-based chemotherapy
SLR update (2025)	HS-1	Secondary	NICE. 2024 (TA962). Olaparib for maintenance treatment of BRCA mutation-positive advanced ovarian, fallopian tube or peritoneal cancer after response to first-line platinum-based chemotherapy
Original SLR (2020)	HS-2	Primary	CADTH 2019. Lynparza for Newly Diagnosed Ovarian Cancer – Details

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

SLR search	Study ID	Primary/secondary publication	Citation
SLR update (2023)	HS-3	Primary	NICE 2021 (TA693). Olaparib plus bevacizumab for maintenance treatment of advanced ovarian, fallopian tube or primary peritoneal cancer
SLR update (2025)	HS-3	Secondary	NICE. 2024 (TA946). Olaparib with bevacizumab for maintenance treatment of advanced high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer
SLR update (2023)	HS-4	Primary	NICE 2021 (TA673). Niraparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy.
SLR update (2023)	HS-5	Primary	SMC 2021. Olaparib (Lynparza)
SLR update (2023)	HS-6	Primary	SMC 2021. Nirapaib (Zejula)
SLR update (2023)	HS-7	Primary	SMC 2019. Olaparib (Lynparza)
SLR update (2023)	HS-8	Primary	NCPE 2023. Olaparib (Lynparza®) in combination with bevacizumab (1L maintenance HRD positive ovarian cancer). HTA ID: 21011
SLR update (2023)	HS-9	Primary	NCPE 2022. Niraparib (Zejula®) for 1L maintenance OVCA. HTA ID: 21004
SLR update (2023)	HS-10	Primary	NCPE 2020. Olaparib (Lynparza®) (1L maintenance of BRCA-mutated advanced OVCA)
SLR update (2023)	HS-11	Primary	PBAC 2022. Olaparib: Tablet 100 mg, Tablet 150 mg; Lynparza®
SLR update (2023)	HS-11	Secondary	PBAC 2022. Olaparib: Tablet 100 mg, Tablet 150 mg; Lynparza®
SLR update (2023)	HS-12	Primary	PBAC 2019. Olaparib: Tablet 100 mg, Tablet 150 mg; Lynparza®. 2019
SLR update (2023)	HS-12	Secondary	PBAC 2020. Olaparib: Tablet 100 mg, Tablet 150 mg; Lynparza®. 2020
SLR update (2023)	HS-13	Primary	PBAC 2021. Niraparib: Capsule 100 mg; Zejula®. 2021

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

SLR search	Study ID	Primary/ secondary publication	Citation
SLR update (2023)	HS-13	Secondary	PBAC 2022. Niraparib: Capsule 100 mg; Zejula®
SLR update (2023)	HS-14	Primary	CADTH 2019. Lynparza for Newly Diagnosed Ovarian Cancer – Details
SLR update (2025)	HS-15	Primary	PBAC 2023. Niraparib: Capsule 100 mg; Zejula® - public summary document March 2023 PBAC meeting with July 2023 Addendum.
SLR update (2025)	HS-16	Primary	NICE. 2025 (TA1055). Rucaparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy

Table 125. Overview of included economic evaluations and cost-effectiveness studies (original SLR and subsequent updates)

Source	Region, currency (year), model perspective	Patient population	Interventions, comparators	Summary of model (structure and health states)	Time horizon	Source of clinical inputs
Cohn 2015 ¹⁵⁵	USA, USD (\$) 2013 Third-party payer	Patients with advanced epithelial ovarian cancer treated on GOG 218	Bevacizumab	Markov state transition structure ^a	Lifetime (60 years)	GOG-218
Tan 2021 ¹¹³	Singapore, SGD (\$) 2018 Healthcare payer	Newly diagnosed advanced ovarian cancer and a <i>BRCA1/2</i> mutation	Olaparib, routine surveillance	A four-state partitioned survival model: progression-free, progressed disease 1, progressed disease 2, death	Lifetime (50 years)	SOLO-1 and extrapolated beyond the period using parametric survival models.
Tan 2019 ¹⁵⁶ (Abstract only)	Singapore, SGD (\$) cost year NR Healthcare payer perspective	Patients with newly diagnosed advanced ovarian cancer and a <i>BRCA1/2</i> mutation	Olaparib, routine surveillance	Partitioned survival model including three health states	Lifetime (50 years)	SOLO-1

Source	Region, currency (year), model perspective	Patient population	Interventions, comparators	Summary of model (structure and health states)	Time horizon	Source of clinical inputs
Wolford 2018 ¹¹⁵ (Abstract only)	USA, USD (\$) cost year NR US Medicare	Patients with advanced ovarian cancer	Paclitaxel, bevacizumab, niraparib, olaparib, rucaparib, pembrolizumab	Markov model Health states included: response, haematological complications, non-haematological complications, progression, and death	NR	Clinical data for median PFS and toxicity: a) paclitaxel (GOG 212); b) bevacizumab (GOG 218, ICON 7, OCEANS, GOG 213); c) niraparib (NOVA), olaparib (SOLO-2), rucaparib (ARIEL-3); and d) pembrolizumab.
Wolford 2019 ¹⁵⁷ (Abstract only)	USA, USD (\$) cost year NR US Medicare	Patients with advanced ovarian cancer	Olaparib, bevacizumab	Markov model Health states included: response, complications, and progression	NR	GOG-218 and SOLO-1 and Norquist et al.

Source	Region, currency (year), model perspective	Patient population	Interventions, comparators	Summary of model (structure and health states)	Time horizon	Source of clinical inputs
Penn 2020 ¹⁵⁸	USA, USD (\$) 2020 US health system	Newly diagnosed, advanced (stage III or IV) epithelial ovarian cancer who had already undergone cytoreductive surgery and had a complete or partial response to platinum-based chemotherapy was eligible for entrance into 1 of 3 models: one for patients with a <i>BRCA</i> variant, one for patients who are homologous recombination deficient without a <i>BRCA</i> variant, or one for patients who are homologous recombination proficient	Olaparib, olaparib + bevacizumab, bevacizumab, niraparib, no maintenance	Decision model: Base case 1 - <i>BRCA</i> variant Base case 2 - Homologous recombination deficient, <i>BRCA</i> wild type Base case 3 - Homologous recombination proficient	24 months	SOLO-1, PRIMA, and PAOLA-1
Moya-Alarcon 2022 ¹¹¹	Spain, Euro (€) 2020 Spanish National Healthcare System	1L maintenance in advanced high-grade serous ovarian cancer and <i>BRCA</i> mutation	Olaparib, no maintenance	Semi-Markov partitioned survival model with four health states: progression-free state (PFSt), first-progression state (PS1), second-progression state (PS2), and death	Lifetime (50 years)	SOLO-1
Elsa 2022 ¹⁰⁹	USA, USD (\$) 2020 US health system	1L maintenance therapy after partial or complete response to platinum-based therapy in HRD-positive advanced ovarian cancer	Olaparib + bevacizumab, bevacizumab	Partitioned survival model with four states: progression-free, post-first progression, post-second progression, and death	Lifetime (50 years)	PAOLA-1

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Source	Region, currency (year), model perspective	Patient population	Interventions, comparators	Summary of model (structure and health states)	Time horizon	Source of clinical inputs
Huepenbecker 2022 ¹⁵⁹	USA, USD (\$) cost year NR US health system	Post-front-line treatment in stage III-IV epithelial ovarian cancer	Niraparib, olaparib, bevacizumab, and olaparib + bevacizumab, active surveillance ^b	Markov-based decision model	Lifetime	Published literature
Perez-Fidalgo 2022 ¹¹²	Spain, Euro (€) 2022 Spanish National Healthcare System	1L maintenance therapy after partial or complete response to platinum-based therapy in homologous recombination-positive advanced ovarian cancer	Olaparib + bevacizumab, bevacizumab	Partitioned survival model with four states: progression-free, post-first progression, post-second progression, and death	Lifetime	PAOLA-1
Okumura 2022 ¹⁶⁰	Brazil, Real (R\$) cost year NR Perspective NR	Patients with advanced HRD-positive ovarian cancer	Olaparib + bevacizumab, bevacizumab	Four-state partitioned survival decision analytic model	NR	PAOLA-1
Lim 2021 ¹⁶¹	USA, USD (\$) cost year NR Patient	Advanced ovarian cancer	Niraparib-for-all, biomarker-based strategy	Markov-based decision model	NR	PRIMA
Fan 2021 ¹¹⁰	USA, USD (\$) cost year NR US health system	Patients with advanced ovarian cancer	Olaparib + bevacizumab, bevacizumab	Cohort-level four-state partitioned survival model: progression-free, post-first progression, post-second progression, and death	Lifetime	PAOLA-1

Source	Region, currency (year), model perspective	Patient population	Interventions, comparators	Summary of model (structure and health states)	Time horizon	Source of clinical inputs
Hernandez 2020 ¹⁶²	Costa Rica, USD (\$) cost year NR Payer	Patients with advanced <i>BRC</i> Am ovarian cancer	Olaparib, routine surveillance	Three-state partitioned survival model	Lifetime (50 years)	SOLO-1
Castillo-Fernandez 2020 ¹⁶³	Panama, USD (\$) cost year NR Payer	Patients with advanced <i>BRC</i> Am ovarian cancer	Olaparib, routine surveillance	Three-state partitioned survival model	Lifetime (50 years)	SOLO-1
Muston 2020 ¹⁶⁴	USA, USD (\$) 2019 US third-party payer	Newly diagnosed advanced ovarian cancer and a <i>BRCA</i> 1/2 mutation	Olaparib, routine surveillance	Three-state partitioned survival model with a 1-month cycle Health states: progression-free state, radiologically confirmed progressive disease, and death from any cause	50 years	SOLO-1
Barrington 2020 ¹⁶⁵	USA, USD (\$) 2019 Third-party payer	Newly diagnosed advanced ovarian cancer	Niraparib, observation	Five decision analysis models to evaluate different patient populations	NR	PRIMA

Source	Region, currency (year), model perspective	Patient population	Interventions, comparators	Summary of model (structure and health states)	Time horizon	Source of clinical inputs
		Patient subgroups: overall group of unselected advanced ovarian cancer patients; the homologous recombination deficient group (includes <i>BRCA</i> mutation or tumour homologous recombination deficiency); the <i>BRCA</i> group harbouring germline or somatic <i>BRCA1/2</i> mutations; the homologous recombination deficient group without <i>BRCA1/2</i> mutations (homologous recombination deficiency non- <i>BRCA</i> group); and the non-homologous recombination deficient group				
Gonzalez 2020 ¹⁶⁶	USA, USD (\$) 2018 Third-party payer	Newly diagnosed advanced stage ovarian cancer who have completed primary treatment with surgery and chemotherapy	PARPi (PARPi-for-all), biomarker-directed use of PARPi	Modified Markov models with the following mutually exclusive Markov states were included: receiving primary chemotherapy treatment, completed chemotherapy, and on surveillance, and post-progression or dead	NR	VELIA, PRIMA, PAOLA-1 , the Cancer Genome Atlas

Source	Region, currency (year), model perspective	Patient population	Interventions, comparators	Summary of model (structure and health states)	Time horizon	Source of clinical inputs
Gonzalez 2020 ¹⁶⁷	USA, USD (\$) cost year NR Perspective NR	Patients with advanced ovarian cancer	PARPi (PARPi-for-all), biomarker-directed use of PARPi	A Markov-based decision model simulating the publicly available study designs of the PAOLA-1, VELIA, and PRIMA trials	NR	NR
Armeni 2020 ¹⁶⁸	Italy, Euro (€) 2019 Italian NHS	Patients with newly diagnosed, advanced, <i>BRCA</i> 1/2-mutated, high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are responding (completely or partially) to 1L PBC	Olaparib, routine surveillance	Cohort-based Markov model; three mutually exclusive states were considered, namely progression-free, progressed disease, and death	50 years	SOLO-1, NICE TA598, published literature (safety)
Muston 2020 ¹⁶⁹	USA, USD (\$) 2020 Third-party payer	Patients with advanced ovarian cancer at high risk for progression or death	Olaparib vs routine surveillance Niraparib vs routine surveillance Olaparib vs niraparib	Three-state partitioned survival model: progression-free, progressed disease, death	Lifetime	PRIMA and SOLO-1
Richardson 2020 ¹⁷⁰	USA, USD (\$) cost year NR Perspective NR	Advanced ovarian cancer	Bevacizumab, niraparib, olaparib	Markov model	NR	GOG 218, SOLO-1, PRIMA, and PAOLA-1 s

Source	Region, currency (year), model perspective	Patient population	Interventions, comparators	Summary of model (structure and health states)	Time horizon	Source of clinical inputs
Cedillo 2024 ¹⁰⁸	Spain, Euro (€) 2021 Spanish National Healthcare System	Patients with newly diagnosed HRD-positive advanced high-grade ovarian cancer (including patients with primary peritoneal and/or fallopian tube cancer) who responded after 1L platinum/taxane-based chemotherapy plus bevacizumab	Olaparib + bevacizumab, bevacizumab	Partitioned survival model with four health states (progression-free, post-progression 1, post-progression 2, and death) was developed based on independent curves of overall survival and progression-free survival for each comparator	Lifetime	PAOLA-1

Source	Region, currency (year), model perspective	Patient population	Interventions, comparators	Summary of model (structure and health states)	Time horizon	Source of clinical inputs
Yong 2024 ¹¹⁴	Malaysia, RM 2022 Malaysian health care	Patients in maintenance therapy following response to 1L platinum-based chemotherapy	Olaparib or routine surveillance	A hypothetical four-state partitioned survival with 1-month cycle, with a half-cycle correction, was developed to estimate the cost-effectiveness of two management strategies, treatment with olaparib or routine surveillance in women with ovarian cancer. The mutually exclusive health states included: progression-free state (PF), which can then transition to progressed disease 1 (PD1, post-first progression) state, progressed disease 2 (PD2, post-second progression) state, and death from any cause	28 years	SOLO-1
Zhu 2023 ¹⁷¹	USA, USD (\$) cost year NR USA health system	AOC patient population and HRD-positive patients, patients with <i>BRCA</i> mutations, homologous recombination proficient (HRD)-positive, or patients not harbouring <i>BRCA</i> mutations AOC	Olaparib + bevacizumab, bevacizumab	The developed state-transition model with progression-free survival, progressive disease, and death as mutually exclusive health states.	15 years	PAOLA-1

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Source	Region, currency (year), model perspective	Patient population	Interventions, comparators	Summary of model (structure and health states)	Time horizon	Source of clinical inputs
Zhu 2024 ¹⁷²	USA, USD (\$) 2022 USA societal	AOC patients, patients with a breast cancer susceptibility genes (<i>BRCA</i>) mutation, HRD-positive, or HRD-positive without <i>BRCA</i> mutations AOC	Olaparib + bevacizumab, bevacizumab	A comprehensive Markov model was used. This state-transition model combined effectiveness and total costs for hypothetical AOC patient groups, and it accounted for three mutually exclusive health states (PFS, PD, and death).	20 years	PAOLA-1
Giuliani 2023 ¹⁷³	Italy, Euro (€) 2020 Perspective NR	Patients in maintenance treatment after responding to 1L and 2L chemotherapy in EOC	PARP inhibitors (olaparib, niraparib, rucaparib and veliparib)	NR	NR	PRIMA/ENGOT-OV26; PAOLA-1/ENGOT-OV25; VELIA/GOG-3005; SOLO-1
Perrier 2023 ¹⁷⁴	France, Euro (€) 2022 French National Health	Newly diagnosed advanced ovarian cancer patients with a positive tumour HRD test	Olaparib + bevacizumab, bevacizumab	NR	60 months	PAOLA-1
HTA submissions						

Source	Region, currency (year), model perspective	Patient population	Interventions, comparators	Summary of model (structure and health states)	Time horizon	Source of clinical inputs
NICE 2019 (TA598) ¹⁰⁶	UK, GBP (£) 2018 UK NHS and PSS	Patients with newly diagnosed advanced BRCA1/2-mutated high grade epithelial ovarian, fallopian tube or primary peritoneal cancer that has responded (completely or partially) to first-line platinum-based chemotherapy.	Olaparib, routine surveillance	Partitioned survival model Health states included: progression-free disease, progressive disease, and death	Lifetime (50 years)	SOLO-1, UK population mortality
NICE 2024 (TA 962) ²⁷	England, GBP (£) cost year NR UK NHS and PSS	Patients with <i>BRCA</i> mutation-positive advanced ovarian, fallopian tube, or peritoneal cancer	Olaparib, routine surveillance	The model included 4 health states: progression-free, progressed disease 1, progressed disease 2, and death. Progression-free was assumed to be the entry health state. The model included half-cycle correction, assumed a 47-year time horizon, and applied the non-reference case discount (1.5%) for costs and quality-adjusted life years	Lifetime (47 years)	SOLO-1 as per original appraisal (TA598)

Source	Region, currency (year), model perspective	Patient population	Interventions, comparators	Summary of model (structure and health states)	Time horizon	Source of clinical inputs
CDA 2019 ¹⁷⁵	Canada, CAD (\$) 2018 Canadian Government	Patients with newly diagnosed, advanced, <i>BRCA</i> -mutated (germline or somatic), high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to 1L platinum-based chemotherapy	Olaparib, routine surveillance	A three-health-state partitioned-survival model was used, including: progression-free survival, post-progression, and death	30 years	SOLO-1 (Data cut-off: 17 May 2018) for PFS, PFS2, and OS data. SOLO-2 for treatment duration for subsequent PARP inhibitors
NICE 2021 (TA 693) ¹⁰⁷	England, GBP (£) cost year NR UK NHS and PSS	Women with newly diagnosed advanced ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial response) after completing 1L platinum-based chemotherapy with bevacizumab (15mg/kg) and whose tumours indicate deficiency in homologous recombination (HRD-positive)	Olaparib + bevacizumab, bevacizumab, routine surveillance	A four-state cohort-based partitioned survival model with states of progression-free, post progression 1, post progression 2, and death	Lifetime	PAOLA-1, UK population mortality

Source	Region, currency (year), model perspective	Patient population	Interventions, comparators	Summary of model (structure and health states)	Time horizon	Source of clinical inputs
NICE 2024 (TA 946) ⁷⁰	England, GBP (£) cost year NR UK NHS and PSS	Patients with advanced high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer and is HRD-positive (defined as having either a <i>BRCA1</i> or <i>BRCA2</i> mutation, or genomic instability)	Olaparib + bevacizumab, bevacizumab	The company presented a partitioned survival model with 4 health states to estimate the cost-effectiveness of olaparib with bevacizumab compared with bevacizumab monotherapy. The 4 health states were progression-free, first disease progression, second disease progression, and death.	42 years	PAOLA-1 as per the original appraisal (TA693)
NICE 2021 (TA 673) ²⁶	England, GBP (£) cost year NR UK NHS and PSS	Patients with advanced ovarian, fallopian tube, and peritoneal cancer after response to 1L platinum-based chemotherapy	Niraparib, routine surveillance	Partitioned survival model with three health states (progression-free disease, progressed disease, and death) Two 'sub-states' are included for progression-free disease; on-treatment and off-treatment	Lifetime (39 years)	PRIMA, published clinical evidence, UK population general mortality

Source	Region, currency (year), model perspective	Patient population	Interventions, comparators	Summary of model (structure and health states)	Time horizon	Source of clinical inputs
SMC (2368) 2021 ¹⁷⁶	Scotland, GBP (£) cost year NR NHS Scotland	Adult patients with advanced (FIGO stages III and IV) high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) following completion of 1L platinum-based chemotherapy in combination with bevacizumab and whose cancer is associated with homologous recombination deficiency (HRD) positive status defined by either a <i>BRCA1/2</i> mutation and/or genomic instability	Olaparib + bevacizumab, bevacizumab, routine surveillance	The partitioned survival model consisted of four mutually exclusive health states: a starting health state of progression-free disease, first radiologically confirmed progressed disease (PD-1), second progressed disease (PD-2), and death.	Lifetime (50 years)	PAOLA-1

Source	Region, currency (year), model perspective	Patient population	Interventions, comparators	Summary of model (structure and health states)	Time horizon	Source of clinical inputs
SMC (2338) 2021 ¹⁷⁷	Scotland, GBP (£) cost year NR NHS Scotland	Adult patients with advanced epithelial (FIGO Stages III or IV) high-grade ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) following completion of 1L platinum-based chemotherapy	Niraparib, routine surveillance; olaparib + bevacizumab (for market authorization population), olaparib (for BRCAm subgroup)	A partitioned survival cohort simulation model was used. The model consisted of three mutually exclusive health states: progression-free disease, progressed disease, and death	Lifetime (39 years)	PRIMA (ITT population), PAOLA-1 (market authorisation population), SOLO-1 (For the BRCA mutation subgroup, clinical equivalence between niraparib and olaparib)
SMC (2209) 2019 ¹⁷⁸	Scotland, GBP (£) cost year NR NHS Scotland	Adult patients with advanced (FIGO stages III and IV) <i>BRCA</i> 1/2-mutated (germline and/or somatic) high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) following completion of 1L platinum-based chemotherapy	Olaparib, routine surveillance	A three-state partitioned survival model was presented, consisting of three health states: progression-free (after response to 1L chemotherapy), progressed disease, and death.	Lifetime (50 years)	SOLO-1

Source	Region, currency (year), model perspective	Patient population	Interventions, comparators	Summary of model (structure and health states)	Time horizon	Source of clinical inputs
NCPE (21011) 2023 ¹⁷⁹	Ireland, Euro (€) cost year NR Perspective NR	Adults with advanced (FIGO stages III and IV) high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) following completion of 1L platinum-based chemotherapy in combination with bevacizumab, and whose cancer is associated with homologous recombination deficiency (HRD) positive status defined by either a <i>BRCA1/2</i> mutation and/or genomic stability	Olaparib + bevacizumab, bevacizumab	A four-state partitioned survival model with a progression-free state, progression, secondary progression, and death.	Lifetime (50 years)	PAOLA-1
NCPE (21004) 2022 ¹⁸⁰	Ireland, Euro (€) cost year NR Perspective NR	Adults with advanced epithelial (FIGO stages III and IV) high-grade ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) following completion of 1L platinum-based chemotherapy	Niraparib, routine surveillance	A three-state, partitioned survival, cost-effectiveness model. Health states: progression-free disease, progressed disease, and death without progression.	Lifetime (39 years)	PRIMA

Source	Region, currency (year), model perspective	Patient population	Interventions, comparators	Summary of model (structure and health states)	Time horizon	Source of clinical inputs
NCPE 2020 ¹⁸¹	Ireland, Euro (€) cost year NR Perspective NR	Adult patients with advanced (FIGO stages III and IV) <i>BRCA</i> 1/2-mutated (germline and/or somatic) high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) following completion of 1L platinum-based chemotherapy	Olaparib, routine surveillance	A four-state partitioned survival cost-utility model with progression-free state, first progression state, second progression state, and death	Lifetime (50 years)	SOLO-1
PBAC July 2022 ¹⁸²	Australia, AUD (\$) cost year NR Perspective NR	Patients with newly diagnosed, advanced (FIGO stage III-IV) high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to 1L platinum-based chemotherapy and found to have HRD-positive and <i>BRCA</i> pathogenic variant negative status.	Olaparib + bevacizumab, bevacizumab (HRD, <i>BRCA</i> testing)	Partitioned survival analysis with four health states: Cured, PFS for uncured patients, progressed disease, and death.	20 years	PAOLA-1

Source	Region, currency (year), model perspective	Patient population	Interventions, comparators	Summary of model (structure and health states)	Time horizon	Source of clinical inputs
PBAC November 2022 ¹⁸³	Australia, AUD (\$) cost year NR Perspective NR	Patient with newly diagnosed, advanced (FIGO stage III-IV) high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to 1L platinum-based chemotherapy and found to have HRD-positive and <i>BRCA</i> pathogenic variant negative status	Olaparib + bevacizumab, bevacizumab (HRD, <i>BRCA</i> testing)	Partitioned survival analysis with four health states: Cured, PFS for uncured patients, progressed disease, and death.	20 years	PAOLA-1
PBAC November 2019 ¹⁸⁴	Australia, AUD (\$) cost year NR Perspective NR	Patients with newly diagnosed, advanced (FIGO stage III-IV) high-grade epithelial ovarian cancer (including fallopian tube and primary peritoneal cancer) whose tumour tissue tests positive for a class 4 or 5 <i>BRCA</i> 1/2 mutation and who are in response (complete or partial) to platinum-based chemotherapy	Olaparib, routine surveillance	Health states: cured, progression-free following 1L platinum regimen for uncured, progression-free following 2L platinum regimen for uncured, progressive disease, and death	20 years	SOLO-1, Study 19

Source	Region, currency (year), model perspective	Patient population	Interventions, comparators	Summary of model (structure and health states)	Time horizon	Source of clinical inputs
PBAC July 2020 ¹⁸⁵	Australia, AUD (\$) cost year NR Perspective NR	Patients with newly diagnosed advanced (FIGO stage III-IV) high grade epithelial ovarian, fallopian tube and primary peritoneal cancer, with evidence of a BRCA1 or BRCA2 gene mutation (BRCAm), and who are in partial or complete response to platinum-based chemotherapy.	Olaparib, watch-and-wait	Modified Markov model: The resubmission used a partitioned survival model (i.e. area under the curve) to assign costs and QALYs over the time horizon of the model. However, in the extrapolated portion of the model, the PFS2 and OS curves were constructed using Markov-modelling techniques.	20 years	SOLO-1
PBAC July 2021 ¹⁸⁶	Australia, AUD (\$) cost year NR Perspective NR	Newly diagnosed advanced high-grade epithelial ovarian cancer who are in response to platinum-based therapy	Niraparib, standard medical management (SMM)	Partitioned survival model with three health states: progression-free, progressed, and death	20 years	PRIMA
PBAC March 2022 ¹⁸⁷	Australia, AUD (\$) cost year NR Perspective NR	Newly diagnosed advanced high-grade epithelial ovarian cancer who are in response to platinum-based therapy	Niraparib, standard medical management (SMM)	Partitioned survival model with three health states: progression-free, progressed, and death	20 years	PRIMA

Source	Region, currency (year), model perspective	Patient population	Interventions, comparators	Summary of model (structure and health states)	Time horizon	Source of clinical inputs
CDA 2021 ¹⁸⁸	Canada, CAD (\$) cost year NR Canadian publicly funded health care payer	Patients with newly diagnosed advanced epithelial ovarian, fallopian tube, and peritoneal cancer who are in a complete or partial response to 1L platinum-based chemotherapy	Niraparib, routine surveillance; active surveillance and olaparib (in the BRCAm population)	Partitioned survival model with health states: progressive disease, progression-free, and death	20 years	PRIMA, PAOLA-1 (data from the PAOLA-1 trial was included in the economic evaluation to represent the inclusion of stage III NVRD patients to align with the Health Canada indication).
PBAC March 2023 ¹⁸³	Australia, AUD (\$) cost year NR Perspective NR	Patients with newly diagnosed advanced epithelial ovarian, fallopian tube or primary peritoneal cancer that is both HRD-positive and <i>BRCA</i> wt	Niraparib, standard medical management (SMM)	Partitioned survival analysis with health states: Progression free (cured, not cured), progressed disease, death	20 years	PRIMA

Source	Region, currency (year), model perspective	Patient population	Interventions, comparators	Summary of model (structure and health states)	Time horizon	Source of clinical inputs
NICE (TA 1055) 2025 ²⁸	England, GBP (£) cost year NR UK NHS and PSS	Adult patients with advanced (FIGO Stages III and IV) high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) following completion of 1L platinum-based chemotherapy	Rucaparib, placebo; olaparib + bevacizumab, bevacizumab	A four-state partitioned de novo survival model was developed	Lifetime (40 years)	ATHENA-MONO, PAOLA-1

1L = first-line; AOC = advanced ovarian cancer; AUD = Australian dollar; CAD = Canadian dollar; EOC = epithelial ovarian cancer; FIGO = International Federation of Gynecology and Obstetrics; GBP = Great Britian pound; HRD = homologous recombination deficiency; ICER = Incremental cost-effectiveness ratio; ITT = intent to treat; NHS = National Health Service; NR = not reported; PARPi = poly(ADP-ribose) polymerase inhibitor; PBC = platinum-based chemotherapy; PD = progressed disease; PFD = progression-free disease; PFS = progression-free survival; PSS = Personal Social Services; RM = Malaysian Ringgit; RS = routine surveillance; SGD = Singapore dollar; SMM = standard medical management; USD = United States Dollar.

^a No ICER is reported, only model inputs.

^b The ICER was only reported for olaparib vs routine surveillance, despite inclusion of other PARPi.

E.1.1.5 Critical appraisal of the identified studies

Quality assessments of the included economic evaluations and cost-effectiveness studies with full-text publications, performed using the Drummond checklist,¹⁵⁴ are presented in Table 126.¹⁵³

Table 126. Quality assessment of economic evaluations and cost-effectiveness studies

Study question	CDA 2019 ¹⁷⁵	NICE 2019 (TA598) ¹⁰⁶	SMC 2019 ¹⁷⁸	Wolford 2019 ¹⁵⁷	Wolford 2019 ¹¹⁵	Tan 2021 ¹¹³	Penn 2020 ¹⁵⁸	Moya-Alarcón 2022 ¹¹¹	Eisea 2022 ¹⁰⁹	Muston 2020 ¹⁶⁴	Barrington 2020 ¹⁶⁵	Gonzalez 2020 ¹⁶⁶	Armeni 2020 ¹⁶⁸	NICE: 2021 (TA693) ¹⁰⁷	NICE: 2021 (TA673) ²⁶	SMC 2021 (2368) ¹⁷⁶	SMC 2021 (2338) ¹⁷⁷	SMC 2019 (2209) ¹⁷⁸	NCPE 2023 (21011) ¹⁷⁹	NCPE 2022 (21004) ¹⁸⁰	NCPE 2020 (olaparib) ¹⁸¹	PBAC Olaparib 2022 ¹⁸³	PABC Niraparib ¹⁸⁷	CDA Niraparib 2021 ¹⁸⁸	Cedillo 2024 ¹⁰⁸	Yong 2024 ¹¹⁴	Zhu 2023 ¹⁷¹	Zhu 2024 ¹⁷²	Giuliani 2023 ¹⁷³
Study design																													
1	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
2	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
3	Y	Y	N	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y	Y	Y	Y	N
4	N	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
5	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
6	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
7	N	Y	N	N	N	Y	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y	Y	N	N	N	Y	Y	N	N	Y	N	N	N
Data collection																													
8	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
9	N	Y	Y	N	N	Y	N	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y
10	N A	N A ^a	N	N	N	N A	N A	N A	N A	Y	N A	Y	Y	Y	Y	N A	N A	N A	Y	Y	N A	N A	N A	N A	N A	N A	N A	N A	N A
11	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
12	N	Y	Y	N	N	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	Y	Y	Y	N
13	N	Y ^b	N	N	N	N	Y	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	N	N	N

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Study question	CDA 2019 ¹⁷⁵	NICE 2019 (TA598) ¹⁰⁶	SMC 2019 ¹⁷⁸	Wolford 2019 ¹⁵⁷	Wolford 2019 ¹¹⁵	Tan 2021 ¹¹³	Penn 2020 ¹⁵⁸	Moya-Alarcón 2022 ¹¹¹	Elsa 2022 ¹⁰⁹	Muston 2020 ¹⁶⁴	Barrington 2020 ¹⁶⁵	Gonzalez 2020 ¹⁶⁶	Armeni 2020 ¹⁶⁸	NICE. 2021 (TA693) ¹⁰⁷	NICE. 2021 (TA673) ²⁶	SMC 2021 (2368) ¹⁷⁶	SMC 2021 (2338) ¹⁷⁷	SMC 2019 (2209) ¹⁷⁸	NCPE 2023 (21011) ¹⁷⁹	NCPE 2022 (21004) ¹⁸⁰	NCPE 2020 (olaparib) ¹⁸¹	PBAC Olaparib 2022 ¹⁸³	PABC Niraparib ¹⁸⁷	CDA Niraparib 2021 ¹⁸⁸	Cedillo 2024 ¹⁰⁸	Yong 2024 ¹¹⁴	Zhu 2023 ¹⁷¹	Zhu 2024 ¹⁷²	Giuliani 2023 ¹⁷³		
14	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
15	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
16	N	Y	N	N	N	N	Y	Y	N	N	N	Y	Y	Y	Y	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
17	Y	Y	Y ^c	N	N	Y	Y	Y	N	Y	N	Y	Y	Y	Y	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	
18	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	
19	N	Y ^d	N	N	N	Y	N	Y	Y	N	N	N	Y	Y	Y	N	N	N	N	N	N	N	N	N	N	Y	N	Y	N	N	
20	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	
21	N	Y	N	N	N	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	Y	N	N	N	N	
Analysis and interpretation of results																															
22	Y	Y	Y	N	N	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	
23	N	Y	N	N	N	Y	N	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y	Y	N	
24	N	Y	N	N	N	N	N	Y	N	N	N	N	N	Y	Y	N	N	N	N	N	N	N	N	N	Y	Y	N	N	N	N	
25	N	N	N	N	N	N	Y	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N

Study question	26	27	28	29	30	31	32	33	34	35	36
CDA 2019 ¹⁷⁵	N	N	N	N	N	Y	Y	Y	Y	Y	Y
NICE 2019 (TA598) ¹⁰⁶	Y	Y	N	Y	Y	Y	N	Y	Y	Y	Y
SMC 2019 ¹⁷⁸	N	Y	N _j	N _f	Y	Y	N	N	Y _g	N	N
Wolford 2019 ¹⁵⁷	N	N	N	N	Y	Y	Y	Y	N	N	N
Wolford 2019 ¹¹⁵	N	N	N	N	Y	Y	Y	Y	N	N	N
Tan 2021 ¹¹³	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y
Penn 2020 ¹⁵⁸	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Moya-Alarcón 2022 ¹¹¹	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Elsea 2022 ¹⁰⁹	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y
Muston 2020 ¹⁶⁴	N	Y	Y	N	Y	Y	Y	Y	Y	Y	N
Barrington 2020 ¹⁶⁵	N	Y	N	N	Y	Y	Y	Y	Y	Y	N
Gonzalez 2020 ¹⁶⁶	Y	Y	N	N	Y	Y	Y	Y	Y	Y	N
Armeni 2020 ¹⁶⁸	N	Y	N	Y _c	Y	Y	Y	Y	Y	Y	Y
NICE. 2021 (TA693) ¹⁰⁷	N _e	Y	N	Y	Y	Y	Y	Y	Y	Y	N
NICE. 2021 (TA673) ²⁶	N _e	Y	N	Y	Y	Y	Y	Y	Y	Y	N
SMC 2021 (2368) ¹⁷⁶	N	Y	N	N	Y	Y	Y	Y	Y	Y	N
SMC 2021 (2338) ¹⁷⁷	N	Y	N	N	Y	Y	Y	Y	Y	Y	N
SMC 2019 (2209) ¹⁷⁸	N	Y	N	N	Y	Y	Y	Y	Y	Y	N
NCPE 2023 (21011) ¹⁷⁹	N	Y	N	N	Y	Y	Y	Y	Y	N	N
NCPE 2022 (21004) ¹⁸⁰	N	Y	N	N	Y	Y	Y	Y	Y	N	N
NCPE 2020 (olaparib) ¹⁸¹	N	Y	N	N	Y	Y	Y	Y	Y	Y	N
PBAC Olaparib 2022 ¹⁸³	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
PABC Niraparib ¹⁸⁷	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
CDA Niraparib 2021 ¹⁸⁸	N	N	N	N	Y	Y	N	Y	Y	Y	Y
Cedillo 2024 ¹⁰⁸	N	Y	N	N	Y	Y	Y	Y	Y	Y	N
Yong 2024 ¹¹⁴	N	Y	N	N	Y	Y	Y	Y	Y	Y	N
Zhu 2023 ¹⁷¹	N	Y	N	N	Y	Y	Y	Y	Y	Y	N
Zhu 2024 ¹⁷²	N	Y	N	N	Y	Y	Y	Y	Y	Y	N
Giuliani 2023 ¹⁷³	N	N	N	N	Y	N	N	Y	N	Y	N

N = No; NA = not applicable; NI = not included; NJ = Not justified; Y = Yes.

^a N meta-analysis given and justified.

^b Patient population, N baseline characteristics.

^c Some.

^d And method of inflation.

^e Possibly in redacted data.

^f Simply upper and lower bound.

^g Niraparib accepted for restricted use.

Notes: 1: Was the research question stated?; 2: Was the economic importance of the research question stated?; 3: Was/were the viewpoint(s) of the analysis clearly stated and justified?; 4: Was a rationale reported for the choice of the alternative programmes or interventions compared?; 5: Were the alternatives being compared clearly described?; 6:

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Was the form of economic evaluation stated?; 7: Was the choice of form of economic evaluation justified in relation to the questions addressed?; 8: Was/were the source(s) of effectiveness estimates used stated?; 9: Were details of the design and results of the effectiveness study given (if based on a single study)?; 10: Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?; 11: Were the primary outcome measure(s) for the economic evaluation clearly stated?; 12: Were the methods used to value health states and other benefits stated?; 13: Were the details of the subjects from whom valuations were obtained given?; 14: Were productivity changes (if included) reported separately?; 15: Was the relevance of productivity changes to the study question discussed?; 16: Were quantities of resources reported separately from their unit cost?; 17: Were the methods for the estimation of quantities and unit costs described?; 18: Were currency and price data recorded?; 19: Were details of price adjustments for inflation or currency conversion given?; 20: Were details of any model used given?; 21: Was there a justification for the choice of model used and the key parameters on which it was based?; 22: Was the time horizon of cost and benefits stated?; 23: Was the discount rate stated?; 24: Was the choice of rate justified?; 25: Was an explanation given if cost or benefits were not discounted?; 26: Were the details of statistical test(s) and confidence intervals given for stochastic data?; 27: Was the approach to sensitivity analysis described?; 28: Was the choice of variables for sensitivity analysis justified?; 29: Were the ranges over which the parameters were varied stated?; 30: Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?); 31: Was an incremental analysis reported?; 32: Were major outcomes presented in a disaggregated as well as aggregated form?; 33: Was the answer to the study question given?; 34: Did conclusions follow from the data reported?; 35: Were conclusions accompanied by the appropriate caveats?; 36: Were generalisability issues addressed.

Appendix F: Health-related quality-of-life studies

F1.1 Identification and selection of relevant studies

Studies reporting on HRQoL outcomes were identified in the clinical SLR (Appendix B1.1), with one additional study reporting on caregiver QoL (Shukla 2022¹²²) identified in the non-clinical SLR (Appendix E1.1 and Appendix G1.1).

The clinical SLR was conducted in March 2024, with an update in February 2025, to identify evidence on the efficacy, safety and HRQoL of niraparib and relevant comparators in adults with advanced epithelial (FIGO stages III and IV) high-grade ovarian, fallopian tube, or primary peritoneal cancer who have not progressed following first-line therapy, based on data from clinical trials and real-world evidence studies.²⁰

The non-clinical SLR was conducted in February 2019, with subsequent updates in February 2020, March 2023 and February 2025, to identify utilities and disutilities associated with relevant comparators in patients with advanced epithelial (FIGO stage III to IV) high-grade fallopian tube, or primary peritoneal cancer in the 1L maintenance setting.¹⁵³

Studies were identified using a search strategy applied across relevant platforms (via the Ovid platform as well as conference proceedings and HTA websites).^{20,153} Inclusion and exclusion criteria were applied to studies to determine those most relevant for inclusion in this submission.^{20,153}

F.1.1.1 Search strategy

The search strategies for the clinical SLR and non-clinical SLR are described in Appendix B.1.1.1 and Appendix E.1.1.1, respectively.

F.1.1.2 Study selection

The study selection methodology for the clinical SLR is described in Appendix B.1.1.1.

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

The study selection methodology for the non-clinical SLR was similar to the one described in Appendix E.1.1.1, however different PICOS criteria were applied to select studies reporting health state utility/disutility values (HSUVs).¹⁵³ The PICOS criteria used for the 2025 SLR update are presented in Table 127.¹⁵³

Table 127. PICOS selection criteria for HSUVs

Inclusion	Exclusion
Population^a	
- Adult women with advanced (stage III) or metastatic (stage IV) OC receiving 1L maintenance therapy^b - Subgroups of interest: - Bevacizumab use in 1L setting - High risk^c <i>BRCAM</i> or <i>BRCAwT</i> - HRD-positive - Homologous recombination proficient (HRD-negative) - Homologous recombination unknown (HRun) <u>High-risk subgroups</u>: high risk + <i>BRCAM</i>, high risk + HRD-positive, high risk + HRD-positive + <i>BRCAwT</i>, high risk + HRD-negative <u>HRD-positive subgroups</u>: HRD-positive + <i>BRCAwT</i> - Receipt of neoadjuvant chemotherapy (NACT) - Depth of response to 1L therapy (e.g., CR subgroup or PR subgroup)	- Patients with early disease stages (Stage I or II) - Any other indication - Patients who progressed during or following 1L treatment (i.e., second- or later-line settings)
Interventions	
No restriction	NA
Comparators	
No restriction	NA
Outcomes	
- Utilities - Disutilities	Any other outcome (data relevant to the other SLRs will be flagged to ensure all relevant information is identified). Studies with no outcomes specific for the maintenance phase will be excluded.

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Inclusion	Exclusion
Study design	
- Clinical trials (RCTs, non-RCTs, single-arm trials) - RWE (e.g., surveys, cross-sectional studies, cohort studies, vignette studies, observational studies, etc.) - Cost-utility analyses - Cost-effectiveness analyses - Economic evaluations conducted alongside clinical trials - SLRs/NMAs (to be hand-searched for relevant studies)^d	- Non-SLRs (i.e., targeted reviews) - Pharmacodynamic studies - Preclinical studies - Case reports - Case studies - Commentaries, editorials, and letters - Consensus reports
Additional limits	
Timeframe	
- Full texts: since 2023 - Conference proceedings: since 2023	- Full-text references published prior to 2023 - Conference proceedings published prior to 2023
Language	
English	Non-English language studies will be flagged for consideration in local market submissions.

1L = first-line; EORTC = European Organisation for Research and Treatment of Cancer; FACT = functional assessment of cancer therapy; HCRU = healthcare resource utilization; HRD = homologous recombination deficiency; HRR = homologous recombination repair; HSUV = health state utility/disutility value; N/A = not applicable; NMA = network meta-analysis; OC = ovarian cancer; QLQ = quality of life questionnaire; RCT = randomised controlled trial; RWE = real-world evidence; SLR = systematic literature review

^a Studies will be considered eligible if at least 80% of the study population meets the inclusion criteria or if relevant subgroup data are available. The 80% threshold is based on recommendations by IQWiG26 and is frequently applied in SLRs for HTA submission.

^b Studies in the full 1L and 1L induction settings will be flagged but not included.

^c The definition of high-risk will be recorded in the data extraction file.

^d Not included in full-text screening.

F.1.1.3 Data extraction and quality assessment

The data extraction and quality assessment procedures for the clinical SLR and non-clinical SLR are described in Appendix B.1.1.3 and Appendix E.1.1.3, respectively.

F.1.1.4 Results

Overview of search results

Study selection results for the clinical SLR and non-clinical SLR are described in Appendix B.1.1.1 and Appendix E.1.1.4, respectively.

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Overview of included studies

From the 2024 clinical SLR and 2025 SLR update, a total of 151 publications representing 45 unique studies were included following full-text screening, of which 6 RCTs (13 publications) reported on HRQoL outcomes.²⁰ No RWE studies that reported on HRQoL outcomes were identified.²⁰

A summary of study characteristics and HRQoL instruments used in each included study can be found in Table 128.²⁰

Table 128. Overview of included RCTs reporting HRQoL outcomes

Study name, NCT	Study design	Intervention	HRQoL outcome reported	Subgroup data
ATHENA-MONO Monk 2022 ¹⁴	Phase 3, double-blind RCT	Rucaparib + placebo vs placebo	• FACT-O	NA
FLAMES Wu 2023 ¹⁸⁹	Phase 3, double-blind RCT	Senaparib vs placebo	• FACT-O	NA
OVARIO Hardesty 2022 ¹³⁷	Phase 2, open- label, single- arm trial	Niraparib + bevacizumab	• FOSI	NA
PAOLA-1 Lorusso 2024 ¹⁹⁰ Ray-Coquard 2019 ⁶⁴	Phase 3, double-blind RCT	Olaparib + bevacizumab vs bevacizumab	• EORTC QLQ- C30	NA
PRIMA Chase 2022 ¹⁹¹ González-Martín 2019 ¹² Monk 2024 ¹⁶ Pothuri 2024 ⁸⁶	Phase 3, double-blind RCT	Niraparib vs placebo	• EORTC QLQ- C30 • EORTC QLQ- OV28 • EQ-5D • FOSI	• HRd • HRp
SOLO-1 Moore 2018 ¹⁵ DiSilvestro 2022 ¹⁷	Phase 3, double-blind RCT	Olaparib vs placebo	• EQ-5D • FACT-O	• BRCAm

BRCAm = BRCA mutation; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life questionnaire – Core; EORTC QLQ-OV28 = European Organisation for Research and Treatment of Cancer Quality of Life questionnaire – Ovarian Cancer module; HRd = homologous recombination deficiency; NA = not available; RCT = randomized controlled trial

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Additionally, one study reporting on caregiver HRQoL in those caring for patients with OC using the CARER-QoL-7D score (Shukla 2022¹²²) was identified in the non-clinical SLR.¹⁵³ The mean (SD) score reported was 73.8 (21.4).¹⁵³

HRQoL and utility outcomes reported in the overall population of the six RCTs are described in Table 129 and Table 130, respectively.²⁰

Table 129. HRQoL data reported in the overall population of the included studies

Study, author, year	Treatment (N)	HRQoL N	Subscale	Baseline score	Measurement at specific timepoint (SD)	CFB (95% CI)
EORTC QLQ-C30 global score						
PAOLA-1 Lorusso 2024 ¹⁹⁰ Ray-Coquard 2019 ⁶⁴	Olaparib + bevacizumab [537]	508	NA	68.6	-	-1.33 (-2.47, -0.19) ^a
	Placebo + bevacizumab [269]	249	NA	67.1	-	-2.89 (-4.52, -1.26) ^a
PRIMA Chase 2022 ¹⁹¹ Monk 2024 ¹⁶ Pothuri 2024 ⁸⁶	Niraparib [487]	212	NA	71.5	Cycle 15: 77.4 (NR)	-
	Placebo [246]	81	NA	70.2	Cycle 15: 77 (NR)	-
	Niraparib [487]	4	NA	71.5	Cycle 30: 89.6	-
	Placebo [246]	4	NA	70.2	Cycle 30: 79.2	-
EORTC-QLQ-OV28						
PRIMA Monk 2024 ¹⁶ Pothuri 2024 ⁸⁶	Niraparib [487]	185	Abdominal/GI symptoms	14.2	Cycle 15: 13.5	-
	Placebo [246]	74	Abdominal/GI symptoms	16.7	Cycle 15: 14.4	-
	Niraparib [487]	5	Abdominal/GI symptoms	14.2	Cycle 30: 4.8	-
	Placebo [246]	4	Abdominal/GI symptoms	16.7	Cycle 30: 11.9	-
	Niraparib [487]	183	Attitude toward disease/ treatment	49.3	Cycle 15: 69.8	-
	Placebo [246]	71	Attitude toward disease/ treatment	46.0	Cycle 15: 65.9	-
	Niraparib [487]	5	Attitude toward disease/ treatment	49.3	Cycle 30: 71.1	-

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Study, author, year	Treatment (N)	HRQoL N	Subscale	Baseline score	Measurement at specific timepoint (SD)	CFB (95% CI)
	Placebo [246]	4	Attitude toward disease/ treatment	46.0	Cycle 30: 69.4	-
	Niraparib [487]	185	Other chemotherapy side-effects	21.3	Cycle 15: 15.1	-
	Placebo [246]	74	Other chemotherapy side-effects	20.6	Cycle 15: 16.7	-
	Niraparib [487]	5	Other chemotherapy side-effects	21.3	Cycle 30: 8.0	-
	Placebo [246]	4	Other chemotherapy side-effects	20.6	Cycle 30: 20.0	-
FACT score						
ATHENA-MONO^b Monk 2022 ¹⁴	Rucaparib + placebo (427)	377	NA	-	Cycle 2	-4 (NR)
	Placebo (111)	103	NA	-	Cycle 2	-1.5 (NR)
	Rucaparib + placebo (427)	245	NA	-	Cycle 11	0.5 (NR)
	Placebo (111)	56	NA	-	Cycle 11	3.5 (NR)
	Rucaparib + placebo (427)	102	NA	-	Cycle 26	2.5 (NR)
	Placebo (111)	14	NA	-	Cycle 26	5 (NR)
FACT-O score						
SOLO-1 DiSilvestro 2022 ¹⁷ Moore 2018 ¹⁵	Olaparib (260)	237	NA	73.6	2 years	0.3 (-0.72, 1.32)
	Placebo (131)	125	NA	75	2 years	3.3 (1.84, 4.76)

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Study, author, year	Treatment (N)	HRQoL N	Subscale	Baseline score	Measurement at specific timepoint (SD)	CFB (95% CI)
FACT-O TOI						
FLAMES^b Wu 2024 ¹⁸⁹	Senaparib (270)	266	NA	-	Median follow-up: 23.3 months	2.4 (NR)
	Placebo (133)	133	NA	-	Median follow-up: 23.3 months	3.87 (NR)
FOSI						
OVARIO Hardesty 2022 ¹³⁷	Niraparib + bevacizumab (105)	105	NA	25.7 (3.79)	Median follow-up 27.6 months	-0.7 (-1.4, 0)
PRIMA Chase 2022 ¹⁹¹ Monk 2024 ¹⁶ Pothuri 2024 ⁸⁶	Niraparib (487)	263	NA	25.6 (NR)	Last measurement prior to progression: 25.1 (4.39)	NR (NR)
	Placebo (244)	171	NA	25.4 (NR)	Last measurement prior to progression: 25.3 (3.92)	NR (NR)
	Niraparib (487)	209	NA	25.6 (NR)	End of therapy: 23.1 (4.85)	NR (NR)
	Placebo (244)	146	NA	25.4 (NR)	End of therapy: 23.5 (4.73)	NR (NR)
	Niraparib (476)	185	NA	25.6 (NR)	Cycle 15: 26.3 (NR)	NR (NR)
	Placebo (243)	74	NA	25.4 (NR)	Cycle 15: 26.3 (NR)	NR (NR)
	Niraparib (487)	5	NA	25.6 (NR)	Cycle 30: 28.2 (NR)	NR (NR)
	Placebo (244)	4	NA	25.4 (NR)	Cycle 30: 27 (NR)	NR (NR)

CFB = change from baseline; CI = confidence interval; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life questionnaire – Core; EORTC QLQ-OV28 = European Organisation for Research and Treatment of Cancer Quality of Life questionnaire – Ovarian Cancer module; FACT-O = Functional Assessment

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

of Cancer Therapy – Ovarian; FOSI = Functional Assessment of Cancer Therapy – Ovarian Symptom Index; GI = gastrointestinal; HRQoL = health-related quality of life; NA = not applicable; NR = not reported; SD = standard deviation; TOI = trial outcome index

^a A total of 498 patients in the Olaparib + bevacizumab and 246 patients in the bevacizumab group had baseline and at least one post-baseline global health score. A minimal clinically important difference is defined as ± 10 points.

^b No baseline values were reported.

Table 130. Utility data reported in the included studies

Study, author, year	Treatment (N)	HRQoL N	Utility score (95% CI)	Timepoint
EQ-5D-5L				
SOLO-1 DiSilvestro 2022 ¹⁷ Friedlander 2021 ¹⁹²	Olaparib (260)	260	0.817 (0.807, 0.828) ^a	-
	Placebo (131)	131	0.819 (0.804, 0.835) ^a	-
PRIMA Chase 2022 ¹⁹¹ Monk 2024 ¹⁶ Pothuri 2024 ⁸⁶	Niraparib [487]	477	0.8 (NR)	Baseline
	Placebo [246]	243	0.8 (NR)	Baseline
	Niraparib [477]	183	0.9 (NR)	Cycle 15
	Placebo [242]	74	0.9 (NR)	Cycle 15
	Niraparib [487]	5	0.9 (NR)	Cycle 30
	Placebo [246]	4	0.8 (NR)	Cycle 30
EQ-5D-VAS				
Study, author, year	Treatment (N)	HRQoL N	Mean score (SD)	Timepoint
PRIMA Chase 2022 ¹⁹¹ Monk 2024 ¹⁶ Pothuri 2024 ⁸⁶	Niraparib [487]	487	75.5 (NR)	Baseline
	Placebo [244]	244	74.8 (NR)	Baseline
	Niraparib [487]	184	82.2 (NR)	Cycle 15
	Placebo [244]	74	80.2 (NR)	Cycle 15
	Niraparib [487]	30	87.9 (NR)	Cycle 24
	Placebo [244]	8	83.6 (NR)	Cycle 24

CI = confidence interval; HRQoL = health-related quality of life; NR = not reported; SD = standard deviation; VAS = visual analogue scale

^a Single-index utility score (95% CI), recorded at median follow-up (40.7 and 41.2 months, respectively). UK value set (scores ranging from -0.594 to 1.0) applied.

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

F.1.1.5 Critical appraisal of the identified studies

The critical appraisal for risk of bias of each of the studies included in the clinical SLR is presented in Appendix B1.3. No critical appraisal was reported for the study reporting on caregiver QoL (Shukla 2022¹²²) identified in the non-clinical SLR.

Appendix G: Cost and healthcare resource identification, measurement and valuation

G1.1 Identification and selection of relevant studies

A non-clinical SLR was undertaken to identify studies reporting costs and healthcare resource use in people with advanced epithelial (FIGO stages III and IV) high-grade ovarian, fallopian tube, or primary peritoneal cancer in the 1L maintenance setting.¹⁵³ Studies were identified using a search strategy across relevant platforms (via the Ovid platform as well as conference proceedings and HTA websites).¹⁵³ Inclusion and exclusion criteria were applied to studies to determine those most relevant for this submission.¹⁵³ This appendix details the objectives, methodology and findings of the SLR.¹⁵³

The SLR was originally conducted in February 2019 and was subsequently updated in February 2020, March 2023 and February 2025.

G.1.1.1 Search strategy

The search strategy is described in Appendix E.1.1.1.

G.1.1.2 Study selection

The study selection methodology was similar to the one described in Appendix E.1.1.1, however different PICOS criteria were applied to select studies reporting costs and healthcare resource use.¹⁵³ The PICOS criteria used for the 2025 SLR update are presented in Table 131.¹⁵³

Table 131. PICOS selection criteria for costs/HCRU

Inclusion	Exclusion
Population^a	
- Adult women with advanced (stage III) or metastatic (stage IV) OC receiving 1L maintenance therapy^b - Subgroups of interest: - Bevacizumab use in 1L setting - High risk^c	- Patients with early disease stages (Stage I or II) - Any other indication - Patients who progressed during or following 1L treatment (i.e., second- or later-line settings)

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Inclusion	Exclusion
○ <i>BRCAM</i> or <i>BRCAwt</i> ○ HRD-positive ○ Homologous recombination proficient (HRD-negative) ○ Homologous recombination unknown (HRun) ○ <u>High-risk subgroups</u>: high risk + <i>BRCAM</i>, high risk + HRD-positive, high risk + HRD-positive + <i>BRCAwt</i>, high risk + HRD-negative ○ <u>HRD-positive subgroups</u>: HRD-positive + <i>BRCAwt</i> ○ Receipt of neoadjuvant chemotherapy (NACT) ○ Depth of response to 1L therapy (e.g., CR subgroup or PR subgroup)	
Interventions	
No restriction	NA
Comparators	
No restriction	NA
Outcomes	
• HCRU associated with disease management • HCRU associated with caregivers • Direct costs • Indirect costs • Budget impact • Cost of illness	Any other outcome (data relevant to the other SLRs will be flagged to ensure all relevant information is identified). Studies with no outcomes specific for the maintenance phase will be excluded.
Study design	
• RWE (e.g., surveys, cross-sectional studies, cohort studies, vignette studies, observational studies, etc.) • Cost-utility analyses • Cost-effectiveness analyses • Cost-benefit analyses • Cost-minimisation analyses • Willingness-to-pay studies • Economic evaluations conducted alongside clinical trials • SLRs/NMAs (to be hand-searched for relevant studies)^d	• Non-SLRs (i.e., targeted reviews) • Case reports • Case studies • Commentaries, editorials, and letters • Consensus reports

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Inclusion	Exclusion
Additional limits	
Timeframe	
- Full texts: since 2023 - Conference proceedings: since 2023	- Full-text references published prior to 2023 - Conference proceedings published prior to 2023
Language	
English	Non-English language studies will be flagged for consideration in local market submissions.

1L = first-line; HCRU = healthcare resource utilization; HRD = homologous recombination deficiency; HRR = homologous recombination repair; NMA = network meta-analysis; OC = ovarian cancer; RWE = real-world evidence; SLR = systematic literature review

^a Studies will be considered eligible if at least 80% of the study population meets the inclusion criteria or if relevant subgroup data are available. The 80% threshold is based on recommendations by IQWiG26 and is frequently applied in SLRs for HTA submission.

^b Studies in the full 1L and 1L induction settings will be flagged but not included.

^c The definition of high-risk will be recorded in the data extraction file.

^d Not included in full-text screening.

G.1.1.3 Data extraction and quality assessment

The data extraction and quality assessment procedure is described in Appendix E.1.1.3.

G.1.1.4 Results

Overview of search results

Study selection results are described in Appendix E.1.1.4.

Overview of included studies

From the original SLR and subsequent updates, a total of 65 records were included following full-text screening. Of these, 15 records, representing 13 unique studies reported on costs/HCRU, including three NICE technology appraisals (Table 132).¹⁵³

Table 132. List of included costs/HCRU studies

SLR search	Study ID	Primary/secondary publication	Citation
Original SLR (2020)	3	Primary	Gong, H. (2019). Front-line maintenance therapy for platinum-sensitive ovarian cancer: What's next PARP inhibitors?. <i>Annals of Oncology</i> , 30, ix81.

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

SLR search	Study ID	Primary/secondary publication	Citation
Original SLR (2020)	7	Primary	Matsuo A.L., Santi C.S., Paloni E.D., Rocha M.L., Andreghetto F.M. (2017). Direct medical costs of maintenance therapy in Brazilian platinum-sensitive ovarian cancer patients of private healthcare system: Retrospective analysis of an administrative database. Value in Health
Original SLR (2020)	8	Primary	Oaknin, A., Moore, K., Colombo, N., Scambia, G., Kim, B. G., Friedlander, M., ... & DiSilvestro, P. (2019). Time to second progression (PFS2) and second subsequent therapy (TSST) for patients (pts) with newly diagnosed, advanced ovarian cancer (OC) and a BRCA mutation (BRCAm) treated with maintenance (mt) olaparib (ola): Phase III SOLO1 trial. Annals of Oncology, 30, v405.
SLR update (2023)	12	Primary	Chase, D. M., Shukla, S., de Courcy, J., Ellis, H., Piercy, J., Taylor-Whiteley, T., ... & Wethington, S. L. (2022). VOCAL (Views of Ovarian Cancer patients-how maintenance therapy Affects their Lives) study: A lens into the financial and quality of life (QoL) impact of disease burden and ethnic disparities reported directly by the patient.
SLR update (2023)	12	Secondary	Shukla, S., de Courcy, J., Ellis, H., Milligan, G., Taylor-Whitely, T., Golembesky, A., ... & Wethington, S. L. (2022). PCR211 VOCAL (Views of Ovarian Cancer Patients and Their Caregivers-How Maintenance Therapy Affects Their Lives) Study: Cancer-Related Burden and Quality of Life of Caregivers. Value in Health, 25(12), S430-S431.
SLR update (2023)	21	Primary	Rose, P. G., Yao, M., Chambers, L. M., Mei, L., & Le, P. (2021). The overtreatment and cost effectiveness of primary versus secondary maintenance therapy with poly-adenosine ribose phosphate inhibitors (PARPi) for epithelial ovarian cancer (EOC). Gynecology & obstetrics (Sunnyvale, Calif.), 11(9), 570.
SLR update (2023)	22	Primary	Simmons, D., Bhalla, J., Stone, R., Engstrom-Melnyk, J., & McLaurin, K. (2021). Clinical outcomes and cost associated with HRD biomarker guided first line maintenance therapy in advanced ovarian cancer. Gynecologic Oncology, 162, S111-S112.
SLR update (2023)	23	Primary	Hettle, R., McLaurin, K., Mihai, A., Poeton, A., Muston, D., Lopez-Acevedo, M., ... & Wynne, T. (2020). PCN107 COST COMPARISON OF ADVERSE EVENT MANAGEMENT WITH POLY (ADP-RIBOSE) POLYMERASE (PARP) INHIBITORS (PARPI) IN THE MAINTENANCE TREATMENT OF ADVANCED OVARIAN CANCER. Value in Health, 23, S42.

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

SLR search	Study ID	Primary/secondary publication	Citation
SLR update (2023)	32	Primary	Fan, L., Zhang, Y., Maguire, P., Muston, D., Monberg, M., Earla, J. R., ... & Gulati, P. (2022). Cost comparison of adverse event management among breast and ovarian cancer patients treated with poly (ADP-ribose) polymerase inhibitors: analysis based on phase 3 clinical trials. <i>Journal of Market Access & Health Policy</i> , 10(1), 2078474.
SLR update (2025)	33	Primary	Graybill, W. S., Vergote, I., Pothuri, B., Anttila, M., O'Malley, D. M., Lorusso, D., Haggerty, A. F., Fabbro, M., Chan, J. K., Heitz, F., Willmott, L. J., Bruchim, I., Zhuo, Y., Estevez-Garcia, P., Monk, B. J., Denys, H., Knudsen, A., Tinker, A. V., Sanchez, L. M., Provencher, D., Barretina-Ginesta, M. P., Hartman, J., Booth, D. V., Gonzalez-Martin, A. (2025). Use of individualized starting dose and niraparib hematologic adverse event management costs in ovarian cancer <i>Journal of comparative effectiveness research</i> , 14(1), e240133
SLR update (2025)	33	Secondary	Graybill, W., Vergote, I., Pothuri, B., Anttila, M., O'Malley, D., Lorusso, D., Haggerty, A., Fabbro, M., Chan, J., Heitz, F., Willmott, L., Bruchim, I., Zhuo, Y., Estevez-Garcia, P., Monk, B., Denys, H., Knudsen, A., Tinker, A., Sanchez, L. M., Provencher, D., Barretina-Ginesta, M. P., Hartman, J., Booth, D., Gonzalez-Martin, A. (2024). Use of individualized starting dose and niraparib hematologic adverse event management costs in ovarian cancer <i>Gynecologic Oncology</i> , 190(Supplement 1), S274 EP - S275
SLR update (2025)	39	Primary	"Mascialino, B., Lahelma, M., Salo, K., Heikkila, E., Herse, F., Idanpaan-Heikkila, J., Kakela, S., Tikka, S., Schneider, D., Hietanen, S., Loukovaara, M., Auranen, A. (2024). EE196 Has the Introduction of PARPi Changed Healthcare Resource Utilization (HCRU) and Medical Costs Among Patients With High-Grade Serous Ovarian Cancer (HGSOC) in the Real-Life Setting in Finland? <i>Value in Health</i> , 27(12 Supplement), S92
SLR update (2025)	HS-1	Primary	NICE. 2024 (TA962). Olaparib for maintenance treatment of BRCA mutation-positive advanced ovarian, fallopian tube or peritoneal cancer after response to first-line platinum-based chemotherapy
SLR update (2025)	HS-16	Primary	NICE. 2024 (TA1055). Rucaparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

SLR search	Study ID	Primary/secondary publication	Citation
SLR update (2025)	HS-3	Primary	NICE. 2024 (TA946). Olaparib with bevacizumab for maintenance treatment of advanced high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer

Thirteen records representing 12 primary studies reported on cost outcomes,^{27,28,70,122,193-200} while five studies reported on HCRU outcomes.^{27,28,70,89,200} Six of the included studies reported direct costs,^{27,28,70,122,194,201} but none reported on indirect costs. Adverse event costs were reported in six studies,^{27,28,70,197-199} total costs in four studies,^{70,195,199,200} and other costs in four studies.^{27,28,70,196}

A summary of costs and resource use as reported by the included studies can be found in Table 133 and Table 134, respectively.¹⁵³

Table 133. Costs outcomes reported in the included studies

Source	Region, currency	Interventions	Direct costs	Drug costs
Gong 2019 ¹⁹³	USA, USD (\$)	PARPis	NR	Olaparib maintenance: \$260.57 per unit of NHB
Matsuo 2017 ²⁰¹	Brazil, USD (\$)	N/A	Direct medical costs of maintenance therapy: \$63,060.51/ person Total maintenance direct medical costs: \$4,035,872.72	NR
Chase 2022 ¹⁹⁴	USA, USD (\$)	N/A	Medical costs, mean: \$396.60 (SD: 996.10) Tests/labs, mean: \$133.50 (SD: 483.89)	NR
Shukla 2022 ¹²²	USA, USD (\$)	N/A	Mean monthly household medical costs: \$263.0 (SD: 442.7) Patient medical costs: \$213.4 (SD: 277.4)	NR
Rose 2021 ¹⁹⁵	USA, USD (\$)	PARPis	NR	Annual cost for olaparib: \$123,200 Annual cost for niraparib: \$138,000 Annual cost for observation: \$1,200

Source	Region, currency	Interventions	Direct costs	Drug costs
Simmons 2021 ¹⁹⁶	USA, USD (\$)	PARPis vs bevacizumab	NR	Patients receiving HRD biomarker-guided prescribing: PARP: \$0 (n=0) PARP + bevacizumab: \$17,051,865 (n=31) Bevacizumab: \$3,378,881 (n=10) Routine surveillance: \$5,710,694 (n=24) Patients receiving non-biomarker guided prescribing: PARP: \$28,202,808 (n=65) PARP + bevacizumab: \$0 (n=0) Bevacizumab: \$0 (n=0) Routine surveillance: \$0 (n=0)
Hettle 2020 ¹⁹⁷	USA, USD (\$)	PARPis	NR	NR
Fan 2022 ¹⁹⁸	USA, USD (\$)	PARPis	NR	NR
Graybill 2025 ¹⁹⁹ (PRIMA trial)	USA, USD (\$)	Niraparib	NR	NR
Mascialino 2024 ²⁰⁰	Finland, Euro (€)	PARPis	NR	

Source	Region, currency	Interventions	Direct costs	Drug costs
NICE (TA 962) 2024 ²⁷	England, GBP (£)	Olaparib	Outpatient visit (consultant oncologist): £164.92 Blood count unit cost: £2.39 CT scan unit cost: £106.22	Olaparib Unit cost/pack: £4,635 Unit cost/unit: £82.77 Niraparib Unit cost/pack: £4,500 Unit cost/unit: £80.36 Initial infusion chemotherapy administration Unit cost: £207.59 Subsequent chemotherapy administration Unit cost: £326.46

Source	Region, currency	Interventions	Direct costs	Drug costs
NICE (TA 946) 2024 ⁷⁰	England, GBP (£)	Olaparib with bevacizumab	Oncology consultation cost: £224.55 CT scan cost: £3.63 Complete blood count cost: £83.25	Olaparib 100mg for 28-day cycle: £4,635.00 Olaparib 100mg for 3.44-day cycle: £5,038.90 Bevacizumab 400 mg/16 ml solution for infusion vials (25 mg per 1 ml): £924.40 Bevacizumab 15 mg/kg per model cycle: £2,105.64 Bevacizumab 7.5 mg/kg: £1,110.27 Olaparib (tablet) unit cost: £2,317.50 Olaparib average cost per mg: £0.28 Niraparib (tablet) unit cost: £6,750.00 Niraparib average cost per mg: £0.80 Rucaparib (tablet) unit cost: £3,562.00 Rucaparib average cost per mg: £0.20

Source	Region, currency	Interventions	Direct costs	Drug costs
NICE (TA 1055) 2024 ²⁸	England, GBP (£)	Rucaparib, placebo; Olaparib + bevacizumab; bevacizumab	Outpatient visit (consultant oncologist): £240.97 CT scan: £93.00 Blood test: £3.22	Rucaparib List price (per pack of 60 tablets): £3,562.00 Average cost per year: £105,869 Total drug acquisition cost: £7,227.89 per month Administration cost: £137.00 Bevacizumab List price (400 mg/16mL): £810.00 Total drug acquisition cost: £2,971.29 per month Administration costs (initial infusion): £172.00 Olaparib List price (per pack of 56 tablets): £2,317.50 Total drug acquisition cost: £4,836.95. per month Administration cost: £137.00

AE = adverse event; CT = computed tomography; FSD = fixed starting dose; HGSOc = high-grade serous ovarian cancer; HRD = homologous recombination deficiency; ISD = individualised starting dose; IV = intravenous; N/A = not applicable; NICE = National Institute for Health and Care Excellence; NR = not reported; SD = standard deviation; TA = technology appraisal

Table 134. HCRU outcomes reported in the included studies

Source	Interventions	Inpatient HCRU	Outpatient HCRU	Other HCRU
Oaknin 2019 ⁸⁹ (SOLO-1)	N/A	NR	NR	Subsequent therapy or therapies in the 198 patients who progressed, Olaparib: 91/102 Placebo: 94/96 Most common therapies were: - Platinum-based chemotherapy - (n=58 [64%] vs n=50 [53%]) - Platinum-based chemotherapy with bevacizumab - (n=22 [24%] vs n=15 [16%]) -Platinum-based chemotherapy followed by PARPi - (n=20 [22%] vs n=49 [52%]) -Non-platinum-based chemotherapy (excluding regimens with bevacizumab) - (n=35 [38%] vs n=26 [28%])
Mascialino 2024 ²⁰⁰	PARPis	Bevacizumab monotherapy: 1.3 average visits during first year	Outpatient visits PARPi monotherapy: 10.0 average visits during first year	NR

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Source	Interventions	Inpatient HCRU	Outpatient HCRU	Other HCRU
		PARPi monotherapy: 1.1 average visits during first year	PARPi plus bevacizumab: 18.1 average visits during first year ER visits Bevacizumab monotherapy: 2.5 average visits during first year PARPi monotherapy: 1.2 average visits during first year	
NICE (TA 962) 2024 ²⁷	Olaparib	Patients who receive end-of-life care: 51.8%	NR	Drug utilization rate Olaparib: 65% Niraparib: 35%
NICE (TA 946) 2024 ⁷⁰	Olaparib with bevacizumab	NR	Olaparib + bevacizumab PF on treatment (2 years) Consultation (office visit): 16 Blood count: 16 Chest CT: 2 PF: follow-up to 5 years after treatment Consultation (office visit): 4 Blood count: 4 Chest CT: 1	Drug utilization rate Olaparib: 100% Niraparib: 100% Rucaparib: 100%

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Source	Interventions	Inpatient HCRU	Outpatient HCRU	Other HCRU
			Placebo + bevacizumab PF on treatment (1 year) Consultation (office visit): 16 Blood count: 16 Chest CT: 2 PF: follow-up to 6 years after treatment Consultation (office visit): 4 Blood count: 4 Chest CT: 1 Both treatments PD Consultation (office visit): 16 Blood count: 16 Chest CT: 4	
NICE (TA 1055) 2025 ²⁸	Rucaparib	NR	Outpatient visit (consultant oncologist) (per cycle) Progression-free on maintenance: 1.333 Progression-free off maintenance: 0.333 Progressed: 1.333	CT scan (per cycle) Progression-free on maintenance: 0.167 Progression-free off maintenance: 0.083 Progressed: 0.333 Blood test (per cycle)

Source	Interventions	Inpatient HCRU	Outpatient HCRU	Other HCRU
				Progression-free on maintenance: 1.333 Progression-free off maintenance: 0.333 Progressed: 1.333

ER = emergency room; HCRU = healthcare resource utilisation; N/A = not applicable; NICE = National Institute for Health and Care Excellence; NR = not reported; PF = progression-free

G.1.1.5 Critical appraisal of the identified studies

Quality assessments of the economic evaluations and cost-effectiveness studies with full-text publications which reported on costs/HCRU, performed using the Drummond checklist,¹⁵⁴ are presented in Appendix E.1.1.5.¹⁵³ No quality assessments were reported for the other studies reporting on costs/HCRU.¹⁵³

Appendix H: Clinical outcomes and disaggregated results from the model

H1.1 Clinical outcomes from the model

Table 135. Observed survival and model estimated survival for niraparib (BRCAm)

Comparators	Median (months)	1-year	2-years	3-years	4-years	5-years	6-years
Niraparib PRIMA Trial PFS	30.1	75.3%	56.2%	47.4%	41.0%	37.5%	36.5%
Niraparib Model PFS Estimate	████	████	████	████	████	████	████
Niraparib PRIMA Trial OS	79.4	98.0%	88.5%	76.8%	63.5%	57.9%	51.9%
Niraparib Model OS Estimate	████	████	████	████	████	████	████

Table 136. Observed survival and model estimated survival for niraparib (BRCAwt)

Comparators	Median (months)	1-year	2-years	3-years	4-years	5-years	6-years
Niraparib PRIMA Trial PFS	10.9	44.3%	25.1%	19.2%	16.1%	14.8%	12.7%
Niraparib Model PFS Estimate	████	████	████	████	████	████	████
Niraparib PRIMA Trial OS	41.8	92.4%	76.4%	56.6%	41.5%	33.7%	28.5%
Niraparib Model OS Estimate	████	████	████	████	████	████	████

H1.2 Disaggregated results of the base-case incremental cost-effectiveness analysis

Table 137. Disaggregated Health Outcomes (BRCAm)

Health State	QALY niraparib	QALY olaparib	Incremental
Progression Free	██████	4.94443	██████
Progressed	██████	1.32754	██████
AE QALY Loss	██████	-0.00055	██████
Total	██████	6.27142	██████

Table 138. Disaggregated Cost Outcomes (BRCAm)

Cost Categories	Cost niraparib	Cost olaparib	Incremental
Drug Acquisition Cost	██████	£ 106,501	██████
Drug Administration Cost	█	£ 0	█
Adverse Event Management Cost	████	£ 235	████
Follow-up and Monitoring Cost	██████	£ 14,008	████
Terminal Care Cost	██████	£ 3,467	█
Subsequent Treatment Cost	██████	£ 3,527	█
Total	██████	£ 127,738	██████

Table 139. Disaggregated Health Outcomes (BRCAwt)

Health State	QALY niraparib	QALY rucaparib	Incremental
Progression Free	██████	1.98651	██████
Progressed	██████	1.51388	██████
AE QALY Loss	██████	-0.00123	██████

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Total	██████	3.49916	██████

Table 140. Disaggregated Cost Outcomes (BRCAwt)

Cost Categories	Cost niraparib	Cost rucaparib	Incremental
Drug Acquisition Cost	██████	£ 95,360	██████
Drug Administration Cost	██	£ 0	██
Adverse Event Management Cost	████	£ 378	████
Follow-up and Monitoring Cost	██████	£ 12,001	████
Terminal Care Cost	██████	£ 4,031	██
Subsequent Treatment Cost	██████	£ 5,612	██
Total	██████	£ 117,381	██████

H1.3 Detailed results of the Scenario Analysis

Table 141. Detailed results of the Scenario Analysis (BRCAm)

Scenario	Cost niraparib	Cost olaparib	Incremental cost	QALY niraparib	QALY olaparib	Incremental QALY
Base case	██████	£ 127,738	██████	██████	6.27142	██████
Time horizon (20 years)	██████	£ 126,135	██████	██████	5.61936	██████
Discount Rate (1.5%)	██████	£ 132,952	██████	██████	7.37813	██████
Median age from SACT data: 65 years	██████	£ 127,200	██████	██████	5.60317	██████
Alternative cure point (8 years)	██████	£ 127,928	██████	██████	6.38413	██████
Alternative cure point (12 years)	██████	£ 127,650	██████	██████	6.20306	██████
PFS distribution (lognormal)	██████	£ 130,838	██████	██████	6.05918	██████
PFS distribution (1-knot normal spline)	██████	£ 127,369	██████	██████	6.32801	██████
PFS HR =0.8	██████	£ 132,853	██████	██████	6.75343	██████
OS distributions (lognormal)	██████	£ 127,177	██████	██████	6.11882	██████
OS distributions (Gen. gamma)	██████	£ 128,198	██████	██████	6.35819	██████
Excess mortality vs general population HR=1	██████	£ 127,901	██████	██████	6.37372	██████
Nira SACT TTDD - 90% discontinuing at 36 months	██████	£ 127,738	██████	██████	6.27142	██████
SACT TTDD until 42 months and 38 months for NIRA and OLA	██████	£ 121,885	██████	██████	6.27142	██████
100% Label-based stopping rules	██████	£ 111,545	██████	██████	6.27142	██████

TTDD curves using PFS curve combined with trial-based AE discontinuation	<u>x xxxxxx</u>	£ 118,766	██████	██████	6.27142	██████
Detailed NIRA dosing based on PRIMA	<u>x xxxxxx</u>	£ 127,738	██████	██████	6.27142	██████
Population specific mean dose from PRIMA data	<u>x xxxxxx</u>	£ 127,738	██████	██████	6.27142	██████
Proportion of patients starting at 200 vs. 300mg based on PRIMA	<u>x xxxxxx</u>	£ 127,738	██████	██████	6.27142	██████
Proportion of patients starting at 200 vs. 300mg based on MONITOR-UK	<u>x xxxxxx</u>	£ 127,738	██████	██████	6.27142	██████
Inclusion of RDI for OLA	<u>x xxxxxx</u>	£ 123,478	██████	██████	6.27142	██████
Excludes stopping rule for follow-up and monitoring costs applied to patients who remain progression free for at least 7 years	<u>x xxxxxx</u>	£ 130,412	██████	██████	6.27142	██████
Use Grade 3+ incidence AEs from PRIMA	<u>x xxxxxx</u>	£ 127,738	██████	██████	6.27142	██████
Alternative health state utility (0.81 for progression-free and 0.76 for progressed)	<u>x xxxxxx</u>	£ 127,738	██████	██████	6.18550	██████
Exclude AE disutility	<u>x xxxxxx</u>	£ 127,738	██████	██████	6.27197	██████

Table 142. Detailed results of the Scenario Analysis (BRCAwt)

Scenario	Cost niraparib	Cost rucaparib	Incremental cost	QALY niraparib	QALY rucaparib	Incremental QALY
Base case	██████	£ 117,381	██████	██████	3.49916	██████
Time horizon (20 years)	██████	£ 117,124	██████	██████	3.36765	██████
Discount Rate (1.5%)	██████	£ 119,689	██████	██████	3.84712	██████
Median age from SACT data: 70 years	██████	£ 117,179	██████	██████	3.23270	██████
Alternative cure point (8 years)	██████	£ 117,455	██████	██████	3.55198	██████
Alternative cure point (12 years)	██████	£ 117,339	██████	██████	3.46618	██████
PFS distribution (2-knot normal spline)	██████	£ 116,489	██████	██████	3.55253	██████
OS distributions (lognormal)	██████	£ 117,267	██████	██████	3.46593	██████
OS distributions (Gen. gamma)	██████	£ 117,560	██████	██████	3.53268	██████
Nira SACT TTDD - 90% discontinuing at 36 months	██████	£ 117,381	██████	██████	3.49916	██████
SACT TTDD until 42 months for NIRA	██████	£ 117,381	██████	██████	3.49916	██████
100% Label-based stopping rules	██████	£ 111,353	██████	██████	3.49916	██████
TTDD curves using PFS curve combined with trial-based AE discontinuation	██████	£ 119,926	██████	██████	3.49916	██████
Detailed NIRA dosing based on PRIMA	██████	£ 117,381	██████	██████	3.49916	██████
Population specific mean dose from PRIMA data	██████	£ 117,381	██████	██████	3.49916	██████
Proportion of patients starting at 200 vs. 300mg based on PRIMA	██████	£ 117,381	██████	██████	3.49916	██████
Proportion of patients starting at 200 vs. 300mg based on MONITOR-UK	██████	£ 117,381	██████	██████	3.49916	██████

Inclusion of RDI for RUCA	██████	£ 105,938	██████	██████	3.49916	██████
Excludes stopping rule for follow-up and monitoring costs applied to patients who remain progression free for at least 7 years	██████	£ 118,123	██████	██████	3.49916	██████
Use Grade 3+ incidence AEs from PRIMA	██████	£ 117,381	██████	██████	3.49916	██████
Alternative health state utility (0.81 for progression-free and 0.76 for progressed)	██████	£ 117,381	██████	██████	3.47501	██████
Exclude AE disutility	██████	£ 117,381	██████	██████	3.50039	██████

Appendix I: Price details of treatments included in the submission

I1.1 Price of intervention, comparators and subsequent treatments

Table 143. Unit Costs per package for 1L maintenance and subsequent treatments

Drugs	Unit size 1 (mg)	Pack size 1	List price per pack for pack size 1 (£)	Unit size 2 (mg)	Pack size 2	List price per pack for pack size 2 (£)	Source
1L maintenance treatment							
Niraparib	100.0 mg	56	£ 4,500.00	100.0 mg	84	£ 6,750.00	BNF ⁴¹
Rucaparib	200.0 mg	60	£ 3,562.00	300.0 mg	60	£ 3,562.00	BNF ⁴¹
Olaparib	100.0 mg	56	£ 2,317.50	150.0 mg	56	£ 2,317.50	BNF ⁴¹
Subsequent treatment							
Carboplatin	450.0 mg	1	£ 23.18	50.0 mg	1	£ 6.71	eMIT ₁₂₄
Cisplatin	50.0 mg	1	£ 19.69	10.0 mg	1	£ 3.67	eMIT ₁₂₄
Cyclophosphamide	50.0 mg	100	£ 46.74	---	---	---	eMIT ₁₂₄
Paclitaxel	100.0 mg	1	£ 12.89	30.0 mg	1	£ 4.79	eMIT ₁₂₄
Doxorubin (PLD)	50.0 mg	1	£ 396.10	20.0 mg	1	£ 189.46	eMIT ₁₂₄
Gemcitabine	1800.0 mg	1	£ 41.96	200.0 mg	1	£ 3.59	eMIT ₁₂₄

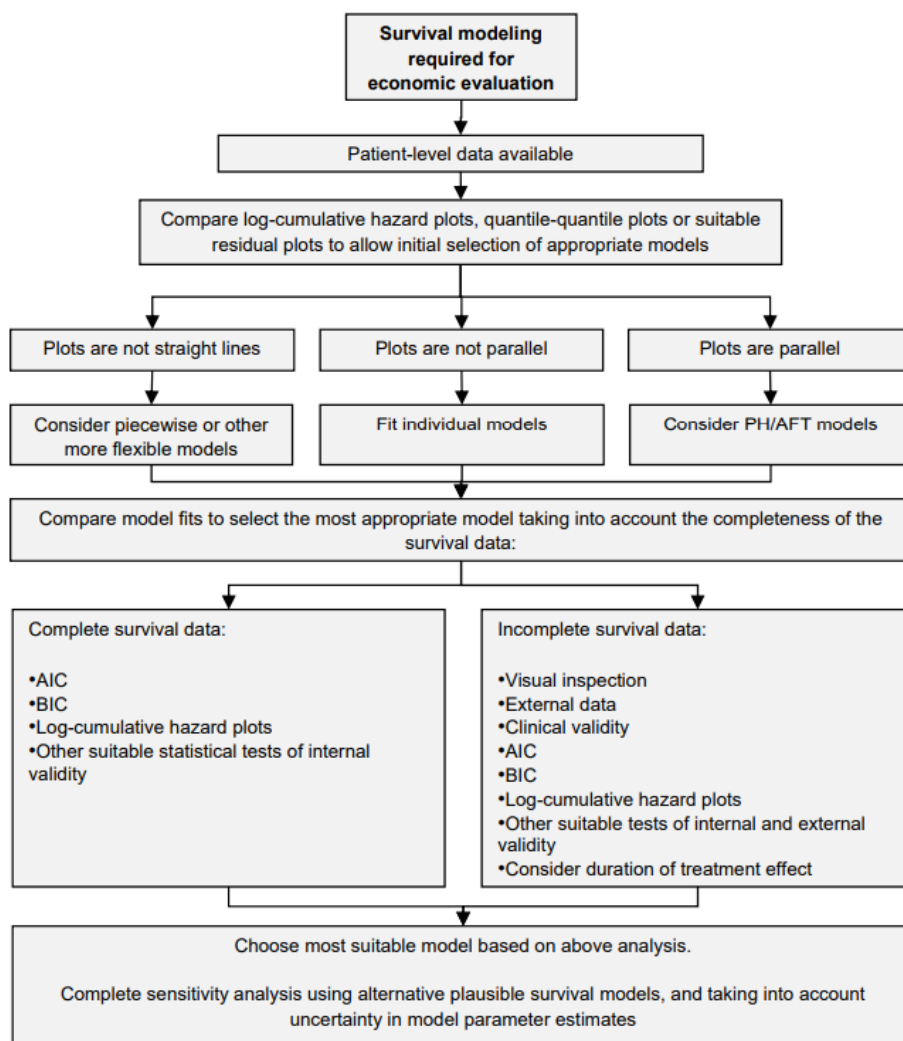
Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Appendix J: Clinical Inputs: Survival Analysis

Approach to Curve Selection Process:

Parametric survival analysis assumes that time to the event of interest follows a parametric distribution. Among the models fitted for each outcome, the most plausible parametric models for the base case and for scenario analysis were chosen for niraparib in line with NICE DSU TSD14 guidance⁹⁹, outlined in Figure 47. The analytical process involves evaluating the fit of each distribution over the observed data period and assessing the face validity beyond the observed period.

Figure 47. NICE DSU TSD14 guidance for parametric survival model selection



Abbreviations: AFT = accelerated failure time; AIC = Akaike information criterion; BIC = Bayesian information criterion; PH = proportional hazard

The analytical process involves evaluating the fit of each distribution over the observed data period and assessing the face validity beyond the observed period. For each population and survival outcome, parametric survival model selection was based on the following four broad categories:

- Statistical fit:

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

- Statistical fit was assessed using Akaike information criterion (AIC) and Bayesian information criterion (BIC), with the lowest AIC and BIC indicating the model with the best statistical fit to the observed data.
- While prior application of AIC and BIC rules of thumb in NICE oncology TA appears inconsistent,²⁰² it can be useful in classifying relative statistical fit for remaining models compared to the distribution with the lowest AIC or BIC. Statistical fit was categorized using modified Burnham/Anderson^{203,204} (for AIC) and Kass/Raftery²⁰⁵ (for BIC) rules of thumb to check the appropriateness of the remaining distributions relative to the best fitting one, with statistical fit classifications from the original papers adapted to ensure completeness, as well as consistency in categorization and interpretation, across rule of thumb categories between measures. The modified rules of thumb for assessing statistical goodness-of-fit are summarized in the table below.

Table 144. AIC-BIC rules of thumb

Rule of thumb category	Difference from fit with lowest AIC	Difference from fit with lowest BIC
Reasonable	0-7 points	0-7 points
Inferior	7-10 points	7-10 points
Poor	>10 points	>10 points

Abbreviations: AIC = Akaike information criterion; BIC = Bayesian information criterion

- Visual fit:
 - Visual inspection of the fitted parametric models was performed in relation to the observed K-M curves.
 - Particular attention may be given to visual fit at the tail, where larger differences between parametric fits are anticipated, but where sudden drops or long plateaus in the K-M curves may be present and associated with low numbers of patients at risk, and therefore must be interpreted with caution.

- Hazard profiles:
 - Smoothed hazard and average hazard rate over time plots for the observed K-M data were compared to hazard plots for each of the parametric distributions to assess which parametric curves provide broad hazard profiles most similar to that implied by the observed data.
- Clinical plausibility/face validity:
 - Internal validity
 - Combinations of chosen parametric survival models were reviewed across outcomes (PFS, OS, TTDD) for each comparator, to ensure plausible combinations of parametric fits are applied (e.g., avoiding implausible overlapping of curves).
 - Consideration was also given to consistency between population subgroups where relevant. For example, choice of OS extrapolations was reviewed to avoid prediction of higher long-term survival for the BRCAwt subgroup, who are expected to have worse survival prognosis compared to BRCAm patients.
 - External validity
 - Comparing fitted models with long-term data from other RCTs or identified RWE or relevant clinical expert feedback from prior HTA appraisals, where relevant. However, given the focus on the PRIMA trial on high-risk patients and focus on niraparib, a lack of external study data or prior clinical expert feedback was available to help inform long-term niraparib extrapolations.
 - Elicitation of UK clinical expert opinion to assess plausibility (e.g., expectations of the proportion of patients without an event at 10, 15 or 20 years).

- General plausibility of combined PFS and OS extrapolations, with PFS and OS anticipated to cross within the modelled time horizon given the lack of expected cure in patients not receiving PARPi maintenance therapy in subsequent treatment lines.

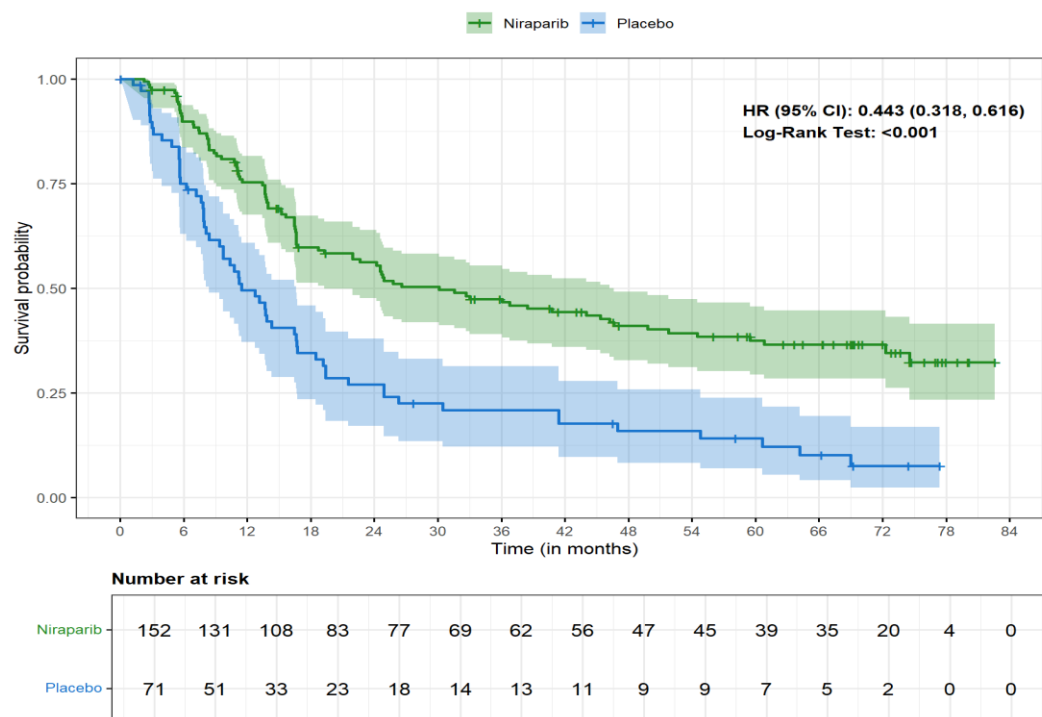
As assessments of statistical fit, visual fit and hazard profiles only relate to the observed period of available follow-up for the K-M curves, weight given to these criteria in determining the most appropriate model was considered lower than the clinical plausibility of long-term survival extrapolations based on UK clinical expert feedback, given the observed PFS and OS data are not complete and extrapolation beyond the duration of observed data was required.

J1.1 Survival in the BRCAm population

J1.1.1 Progression free survival

Progression free survival (investigator-assessed) KM plots for the BRCAm population in the PRIMA study are shown in Figure 48.

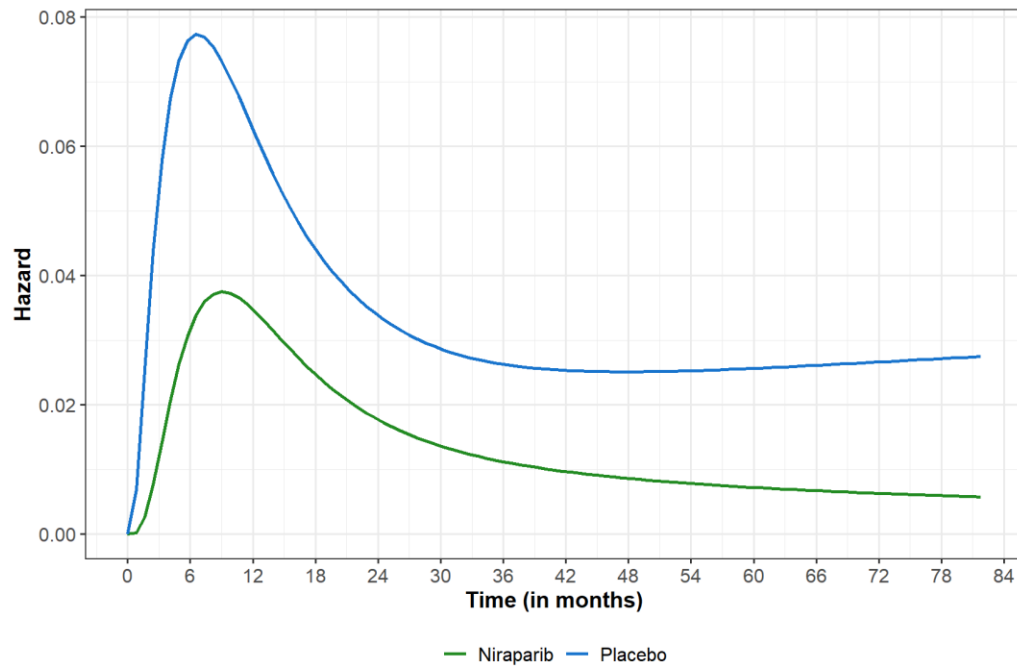
Figure 48. KM plots for PFS (INV) for the BRCAm population in PRIMA



Abbreviations: CI = confidence interval; HR = hazard ratio

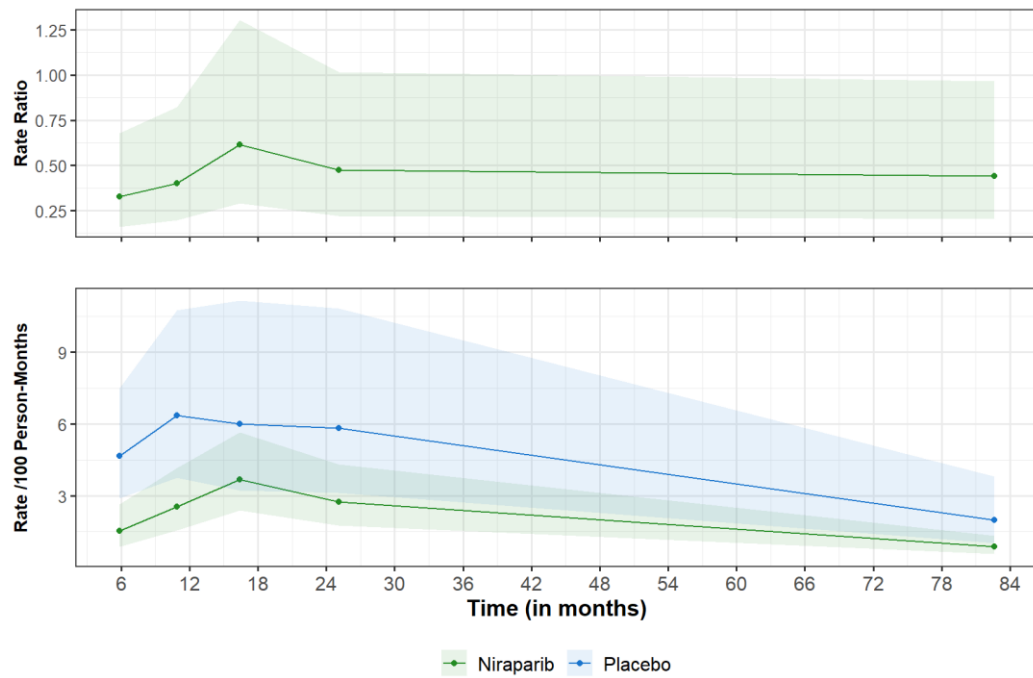
The smoothed hazard plots for the observed PFS KM data are displayed in Figure 49. The plot is indicative of an increasing then decreasing hazard profile, broadly in line those produced by the non-monotonic standard distributions (log-logistic, log-normal and generalised gamma) and by each of the spline models.

Figure 49. Smoothed PFS hazard for BRCAm population in PRIMA



The average hazard plots for the observed PFS KM data are displayed in Figure 50. Again, the plots indicated an increasing then decreasing hazard profile for niraparib.

Figure 50. Average PFS hazard for BRCAm population in PRIMA



AIC and BIC estimates for the niraparib PFS standard and spline parametric survival distributions are shown in Table 145.

Table 145. AIC and BIC Estimates for niraparib PFS distributions (BRCam)

Distribution	AIC	BIC
Exponential	909.8	912.8
Weibull (PH)	910.5	916.5
Gompertz	899.4	905.5
Log-logistic	897.3	903.3
Log-normal	891.0	897.0
Gamma	911.6	917.6
Generalised Gamma	879.2	888.3
1-knot hazard spline	878.6	887.6
2-knot hazard spline	880.0	892.1
3-knot hazard spline	881.7	896.8
1-knot odds spline	878.1	887.1
2-knot odds spline	879.9	892.0
3-knot odds spline	881.8	896.9
1-knot normal spline	877.6	886.7
2-knot normal spline	879.4	891.5
3-knot normal spline	881.5	896.6

Abbreviations: AIC = Akaike information criterion; BIC = Bayesian information criterion

AIC and BIC classifications of relative fit, including both standard and flexible (spline) parametric models, is outlined in Table 146. The 1-knot normal-based spline model produced the best statistical fit with the lowest AIC and lowest BIC. The 1-knot normal spline model produced the best statistical fit, with the other 1-knot based hazard and odds models also within 1 AIC and BIC point of the 1-knot normal spline model, while 2-knot models produced reasonable relative fits according to both AIC and BIC. However, while 3-knot models were reasonable relative fits according to AIC (i.e. within 7 points), they produced inferior (7-10 point difference) or poor (>10 point difference) relative fits for BIC compared to the 1-knot normal spline model. From the standard parametric models, the generalised gamma distribution produced the best

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

statistical fit and was considered to be reasonable fit with less than a 2-point difference from the 1-knot normal-based spline, while other standard models all produced poor relative fits for both AIC and BIC (i.e. >10-point differences).

Table 146. AIC and BIC Goodness-of-Fit relative to the distribution with the lowest AIC and BIC for niraparib PFS (BRCAm)

Distribution	Difference from lowest AIC	AIC relative goodness-of-fit classification	Difference from lowest BIC	BIC relative goodness-of-fit classification
Exponential	32.2	Poor (>10 difference)	26.1	Poor (>10 difference)
Weibull (PH)	32.9	Poor (>10 difference)	29.8	Poor (>10 difference)
Gompertz	21.8	Poor (>10 difference)	18.8	Poor (>10 difference)
Log-logistic	19.7	Poor (>10 difference)	16.6	Poor (>10 difference)
Log-normal	13.4	Poor (>10 difference)	10.3	Poor (>10 difference)
Gamma	34.0	Poor (>10 difference)	30.9	Poor (>10 difference)
Generalised Gamma	1.6	Reasonable (0-7 difference)	1.6	Reasonable (0-7 difference)
1-knot hazard spline	1.0	Reasonable (0-7 difference)	0.9	Reasonable (0-7 difference)
2-knot hazard spline	2.4	Reasonable (0-7 difference)	5.4	Reasonable (0-7 difference)
3-knot hazard spline	4.1	Reasonable (0-7 difference)	10.1	Poor (>10 difference)
1-knot odds spline	0.5	Reasonable (0-7 difference)	0.4	Reasonable (0-7 difference)

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Distribution	Difference from lowest AIC	AIC relative goodness-of-fit classification	Difference from lowest BIC	BIC relative goodness-of-fit classification
2-knot odds spline	2.3	Reasonable (0-7 difference)	5.3	Reasonable (0-7 difference)
3-knot odds spline	4.2	Reasonable (0-7 difference)	10.2	Inferior (7-10 difference)
1-knot normal spline	Lowest AIC	Reference	Lowest BIC	Reference
2-knot normal spline	1.8	Reasonable (0-7 difference)	4.8	Reasonable (0-7 difference)
3-knot normal spline	3.9	Reasonable (0-7 difference)	9.9	Inferior (7-10 difference)

Abbreviations: AIC = Akaike information criterion; BIC = Bayesian information criterion

To assess the visual fit, each of the standard survival parametric curves were overlaid on the PFS curve as shown in



Time (in months)

— Exponential — Gompertz — Log-normal — Generalized Gamma
— Weibull(PH) — Log-logistic — Gamma

Fitted flexible parametric spline curves were also overlaid on the KM PFS curve as shown in [REDACTED]. Excluding the 0-knot models (which correspond to Weibull, log-logistic and log-normal models for hazard, odds and normal type splines, respectively), all spline models provided a broadly good visual fit to the observed data.

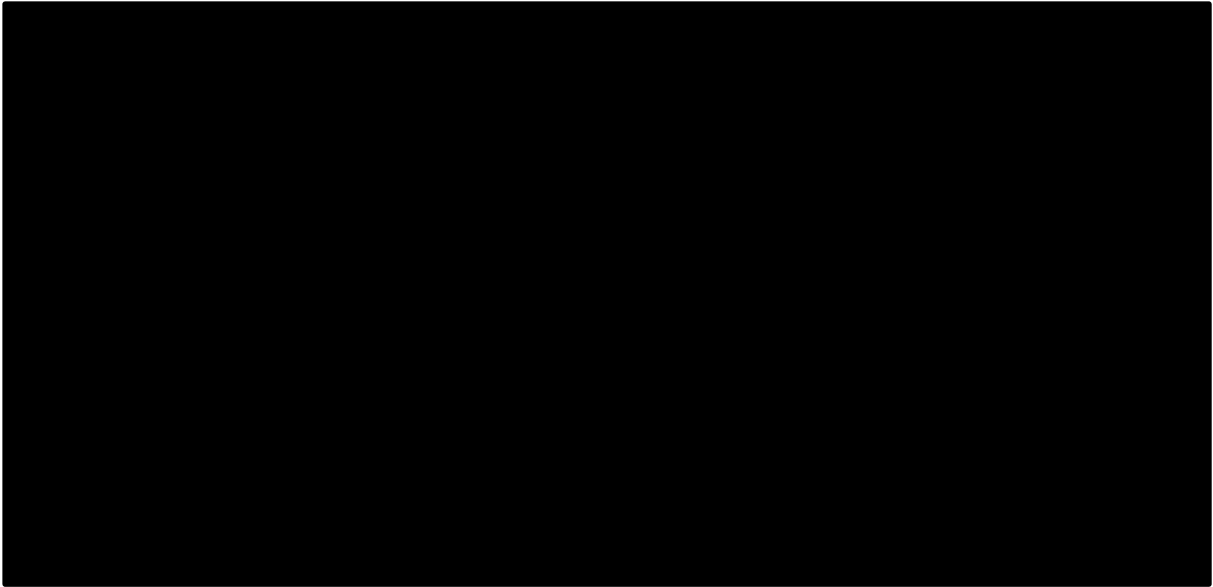
. The generalised gamma and the Gompertz distributions produced the best overall visual fits to the KM curves among standard models including close fits to the tails. Log-logistic and log-normal models slightly overestimated the KM curve between approximately 15-30 months before notably underestimating the tail, while exponential, Weibull and gamma distributions had a generally poor visual fit to the data.



Time (in months)

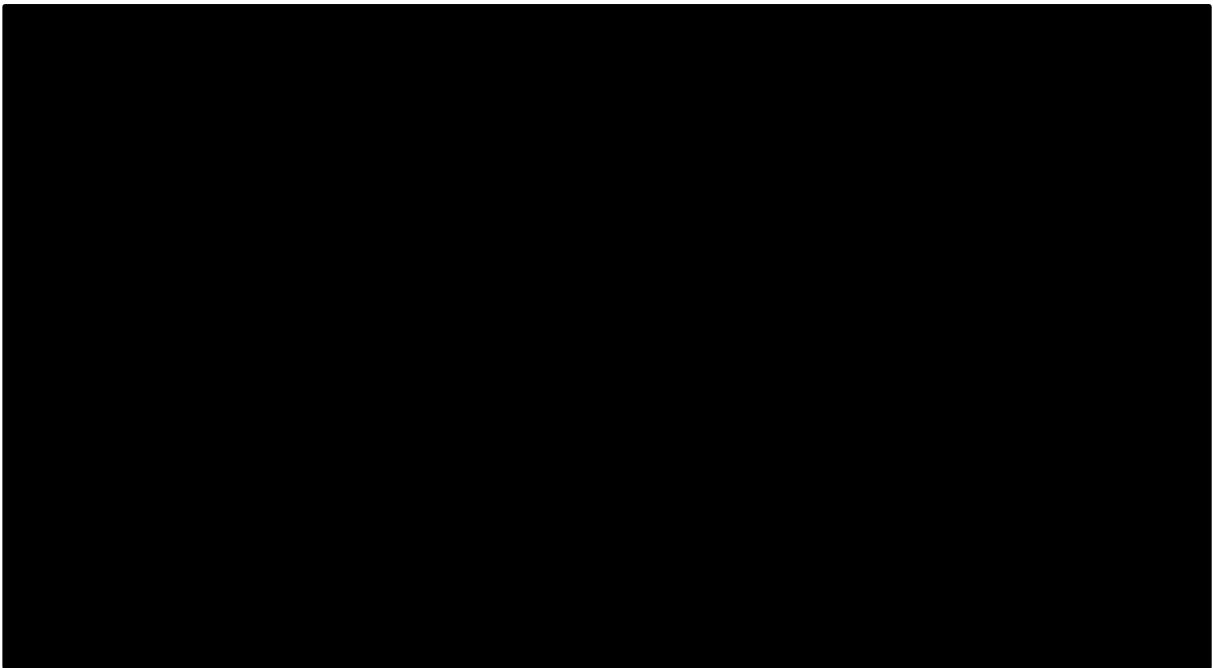
— Exponential — Gompertz — Log-normal — Generalized Gamma
— Weibull(PH) — Log-logistic — Gamma

Fitted flexible parametric spline curves were also overlaid on the KM PFS curve as shown in [REDACTED]. Excluding the 0-knot models (which correspond to Weibull, log-logistic and log-normal models for hazard, odds and normal type splines, respectively), all spline models provided a broadly good visual fit to the observed data.



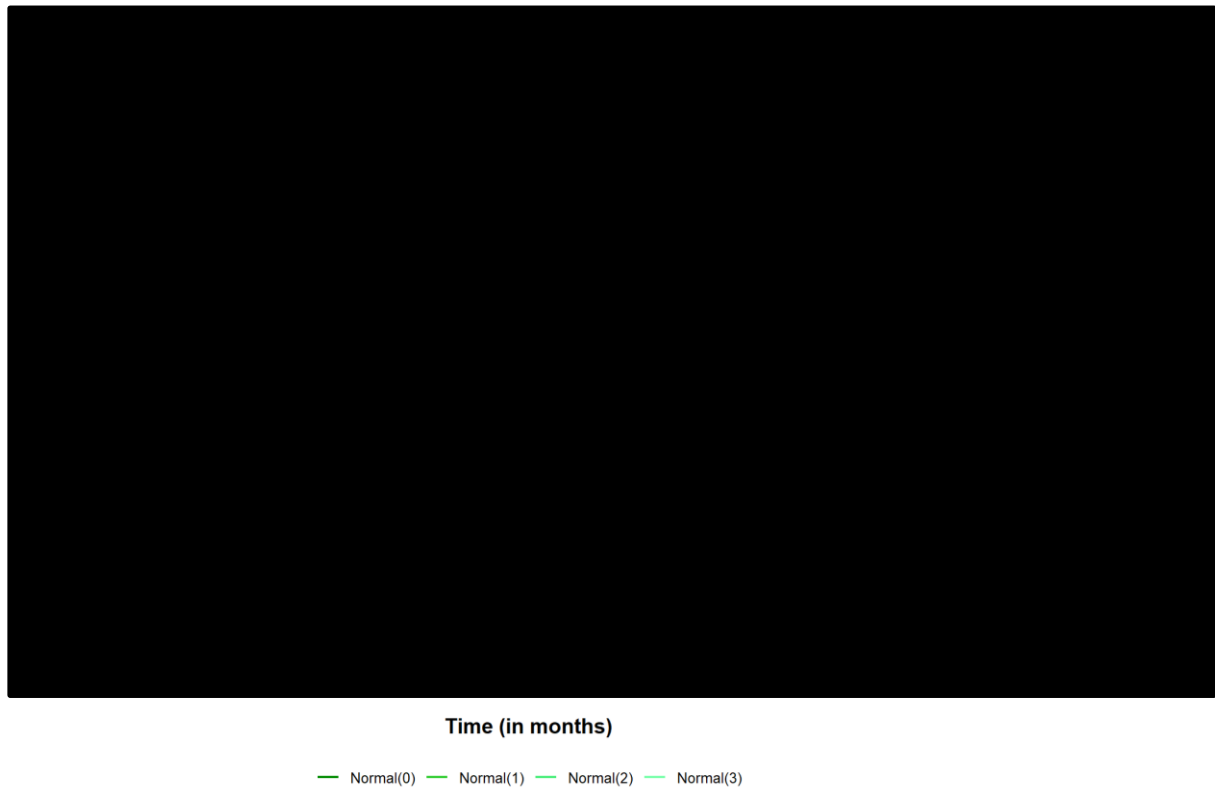
Time (in months)

— Hazard(0) — Hazard(1) — Hazard(2) — Hazard(3)



Time (in months)

— Odds(0) — Odds(1) — Odds(2) — Odds(3)



Long-term extrapolations of PFS are shown in xxxxxx ■ and xxxxxx ■ for standard parametric and flexible parametric models, respectively, including a 10-year cure timepoint (after which adjusted general population mortality is applied). The curves from the Gompertz and generalised gamma distributions for niraparib provided the most optimistic PFS extrapolations among standard models, with all flexible spline parametric models providing fairly similar long-term extrapolations to the estimates from Gompertz and generalised gamma distributions.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Table 147 presents milestone estimates for the observed PFS in the PRIMA trial for niraparib in BRCAm population.

Table 147. PFS observed survival estimates for niraparib (BRCAm)

Comparators	Median PFS (months)	1-year	2-years	3-years	4-years	5-years	6-years
Niraparib	30.1	75.3%	56.2%	47.4%	41.0%	37.5%	36.5%

Abbreviations: PFS = progression-free survival

The expected percentage of progression-free patients at 1 to 40-years were extracted in Table 148 across all parametric survival models, considering a 10-year cure landmark. After the end of the observed data in PRIMA, the estimated proportion of patients who are alive and progression-free ranged from [REDACTED]% (exponential) to [REDACTED]%

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

(1-knot odds spline) at 10 years, with estimates varying between 10% (exponential) to 20% (1-knot odds spline) at 15 years and 20% (exponential) to 30% (1-knot odds spline) at 20 years.

Table 148. Expected PFS per parametric distribution for niraparib (BRCAm)

Distribution	1-year PFS prediction	3-year PFS prediction	5-year PFS prediction	10-year PFS prediction	15-year PFS prediction	20-year PFS prediction	30-year PFS prediction	40-year PFS prediction
	(with 10-year cure landmark)							
Exponential	10%	20%	30%	10%	20%	30%	40%	50%
Weibull (PH)	10%	20%	30%	10%	20%	30%	40%	50%
Gompertz	10%	20%	30%	10%	20%	30%	40%	50%
Log-logistic	10%	20%	30%	10%	20%	30%	40%	50%
Log-normal	10%	20%	30%	10%	20%	30%	40%	50%
Gamma	10%	20%	30%	10%	20%	30%	40%	50%
Generalised Gamma	10%	20%	30%	10%	20%	30%	40%	50%
1-knot hazard spline	10%	20%	30%	10%	20%	30%	40%	50%
2-knot hazard spline	10%	20%	30%	10%	20%	30%	40%	50%
3-knot hazard spline	10%	20%	30%	10%	20%	30%	40%	50%
1-knot odds spline	10%	20%	30%	10%	20%	30%	40%	50%
2-knot odds spline	10%	20%	30%	10%	20%	30%	40%	50%
3-knot odds spline	10%	20%	30%	10%	20%	30%	40%	50%
1-knot normal spline	10%	20%	30%	10%	20%	30%	40%	50%
2-knot normal spline	10%	20%	30%	10%	20%	30%	40%	50%

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Distribution	1-year PFS prediction	3-year PFS prediction	5-year PFS prediction	10-year PFS prediction	15-year PFS prediction	20-year PFS prediction	30-year PFS prediction	40-year PFS prediction
				(with 10-year cure landmark)				
3-knot normal spline	████	████	████	████	████	████	████	████

Abbreviations: PFS = progression-free survival

To validate the plausibility of long-term survival predictions, PFS BRCam extrapolations for niraparib were discussed during one-to-one interviews with four UK clinical experts:

- The first clinical expert indicated an expectation of approximately 24% PFS at 15 years
- The second clinical expert indicated an expectation of a 10% drop in PFS between 5 to 10 years and expected PFS to be between estimates produced by the log-normal and generalised gamma models at 10 and 20 years (i.e. █████% at 10 years and █████% at 20 years)
- The third clinical expert indicated survival expectations similar to those produced by the generalised gamma model based on 10 and 20 year predictions (████% and █████%, respectively)
- The fourth clinical expert noted an expectation of an additional 5% drop in PFS between 5 and 10 years, resulting in ~████% PFS at 10 years. The clinical expert therefore stated a preferred for the generalised gamma and spline models as they better reflected the expected drop in PFS between 5 and 10 years, followed by smaller declines between 10 and 15 years.

For the base case analysis, the generalised gamma model was selected to model niraparib PFS for the BRCam population. This model provided the best statistical fit among models aligning most closely with the overall range of UK clinical expert feedback at 10 (████%), 15 (████%), and 20 (████%) years, whilst also producing a good visual fit and an appropriate hazard profile compared to that implied by the observed data (increasing then decreasing).

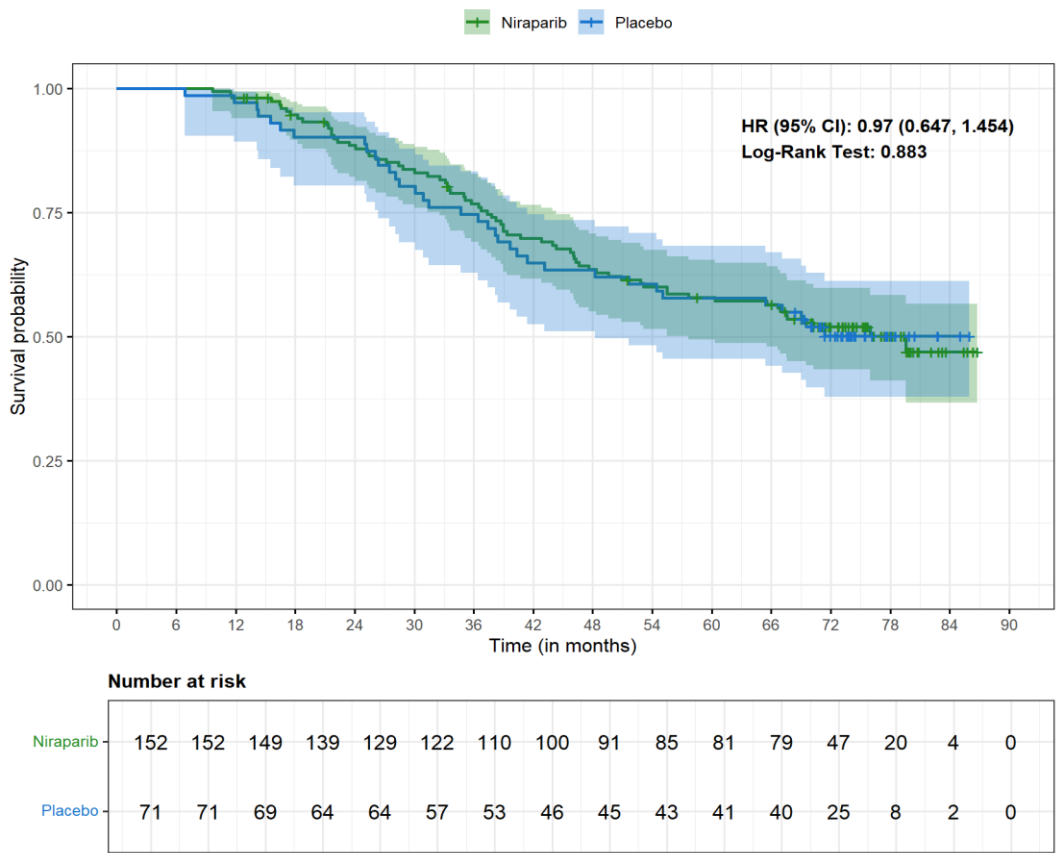
Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Despite being a poor statistical (13.4 AIC difference and 10.3 BIC difference vs. the lowest) and fairly poor visual fit to the observed KM curve, the log-normal model was explored in a scenario analysis as a more conservative projection given it was suggested by one of the clinical experts as a plausible lower bound for 10-year (████%) and 20-year (████%) PFS for niraparib. A second scenario analysis was also conducted using the 1-knot normal spline, which had the best statistical fit with the lowest AIC and BIC estimates, and provided a slightly more optimistic projection (████%, █████%, and █████% at 10, 15, and 20 years, respectively) compared to the generalised gamma model (████%, █████%, and █████% at 10, 15, and 20 years, respectively) while still providing a good visual and hazard profile fit to the observed data.

J1.1.2 Overall survival

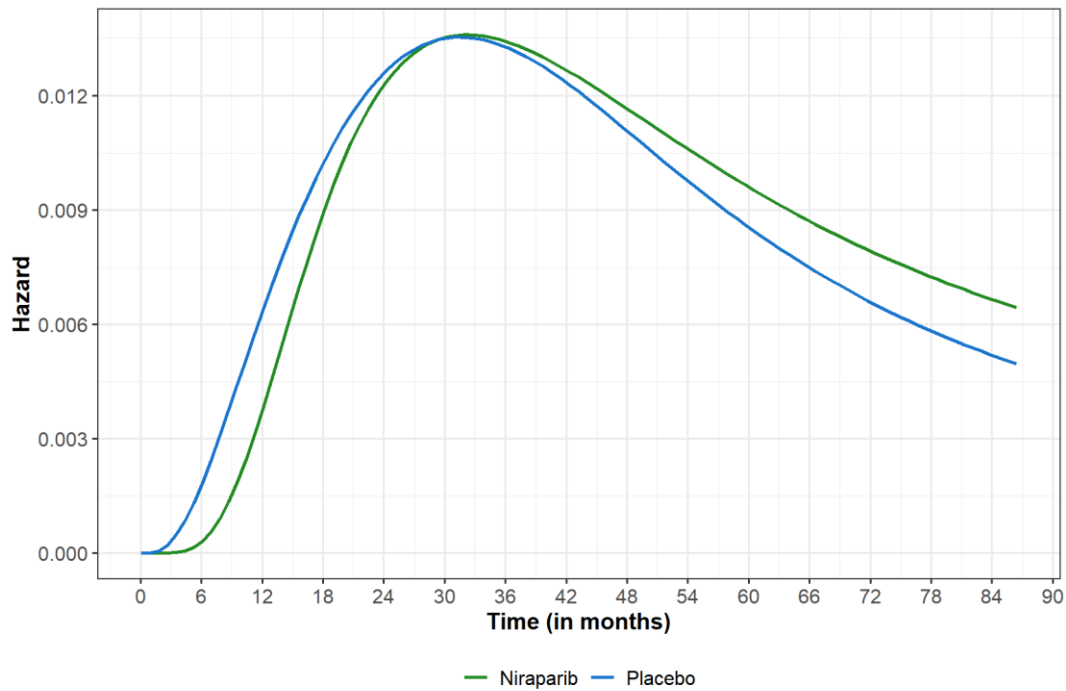
Overall survival KM plots for the BRCAm population in the PRIMA study are shown in Figure 55.

Figure 55. KM plots for OS for the BRCAm population in PRIMA



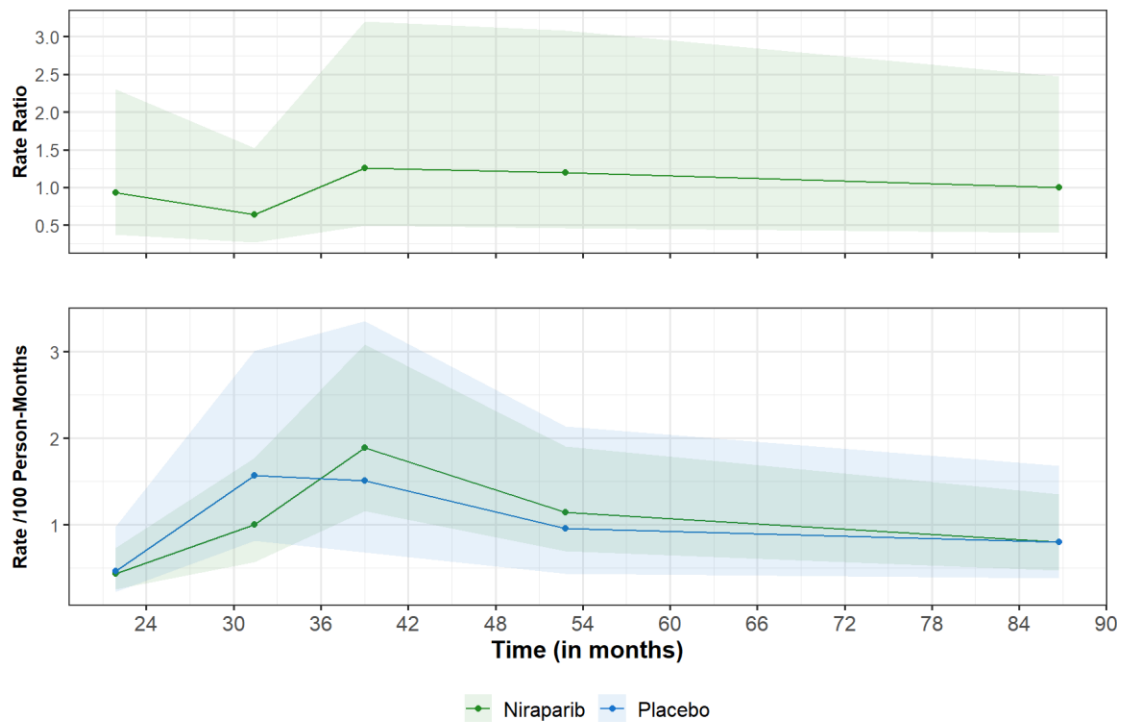
Smoothed hazard plots for the observed OS KM data are displayed in Figure 56. The plot is indicative of an increasing then decreasing hazard profile. The models most aligned with the broad hazard profile implied by the KM data were the non-monotonic standard fit models (log-logistic, log-normal, generalised gamma) and spline models.

Figure 56. Smoothed OS hazard for BRCAm population in PRIMA



The average hazard plots for the observed OS KM data are displayed in Figure 57, which also implied an increasing then decreasing hazard profile for niraparib.

Figure 57. Average OS hazard for BRCAm population in PRIMA



AIC and BIC estimates for the OS distributions are shown in Table 149.

Table 149. AIC and BIC Estimates for niraparib OS distributions (BRCAm)

Distribution	AIC	BIC
Exponential	820.5	823.6
Weibull (PH)	807.1	813.1
Gompertz	816.6	822.7
Log-logistic	801.9	808.0
Log-normal	797.2	803.2
Gamma	803.9	809.9
Generalised Gamma	794.3	803.4
1-knot hazard spline	794.6	803.7
2-knot hazard spline	796.5	808.6
3-knot hazard spline	797.9	813.1
1-knot odds spline	794.7	803.7

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Distribution	AIC	BIC
2-knot odds spline	796.6	808.6
3-knot odds spline	797.8	812.9
1-knot normal spline	794.3	803.4
2-knot normal spline	795.9	808.0
3-knot normal spline	797.4	812.5

Abbreviations: AIC = Akaike information criterion; BIC = Bayesian information criterion

AIC and BIC classifications of relative fit are outlined in Table 150, including both standard and flexible spline parametric models. The 1-knot normal spline model and the standard parametric generalised gamma produced the best statistical fit according to AIC, with the log-normal model associated with the lowest BIC. Log-normal and remaining spline models were reasonable relative fits for AIC, with log-logistic and gamma inferior fits and remaining standard fits poor relative fits. For BIC, generalised gamma and 1-2 knot splines were reasonable relative fits compared to the log-normal distribution. Log-logistic, gamma, Weibull and 3-knot splines were classed as inferior, while exponential and Gompertz were determined to be poor relative BIC fits.

Table 150. AIC and BIC Goodness-of-Fit relative to the distribution with the lowest AIC and BIC for niraparib OS (BRCAm)

Distribution	Difference from lowest AIC	AIC relative goodness-of-fit classification	Difference from lowest BIC	BIC relative goodness-of-fit classification
Exponential	26.2	Poor (>10 difference)	20.4	Poor (>10 difference)
Weibull (PH)	12.8	Poor (>10 difference)	9.9	Inferior (7-10 difference)
Gompertz	22.3	Poor (>10 difference)	19.5	Poor (>10 difference)
Log-logistic	7.6	Inferior (7-10 difference)	4.8	Reasonable (0-7 difference)

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

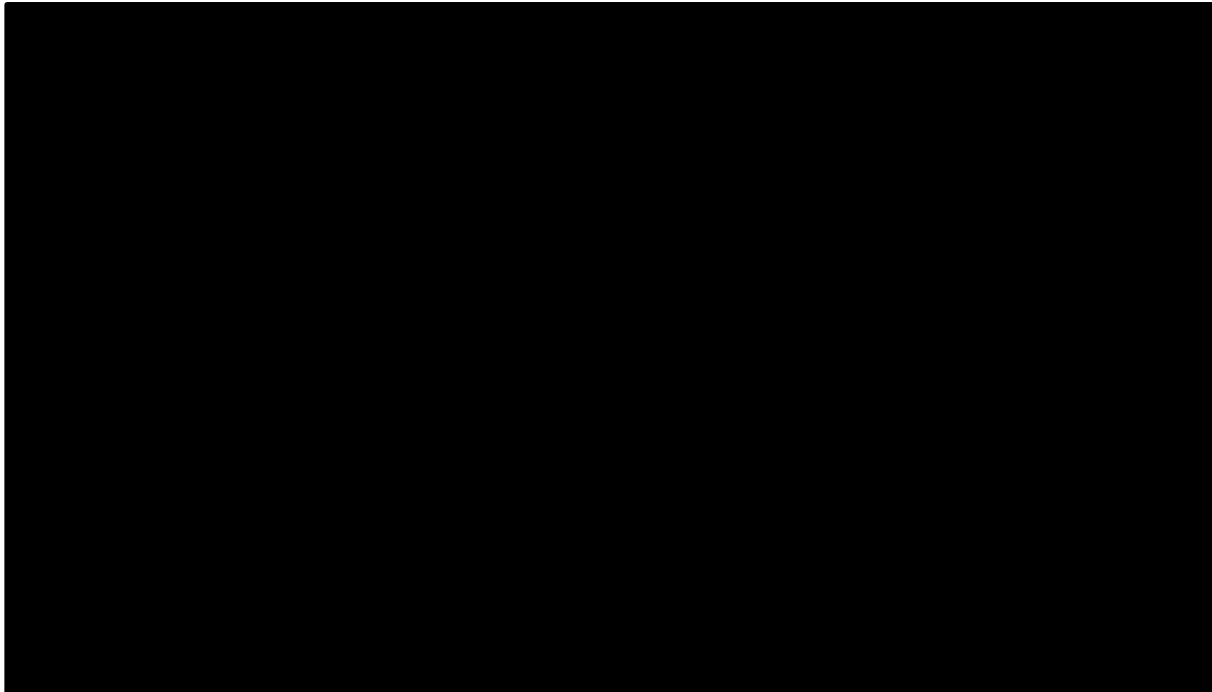
Distribution	Difference from lowest AIC	AIC relative goodness-of-fit classification	Difference from lowest BIC	BIC relative goodness-of-fit classification
Log-normal	2.9	Reasonable (0-7 difference)	Lowest BIC	Reference
Gamma	9.6	Inferior (7-10 difference)	6.7	Reasonable (0-7 difference)
Generalised Gamma	Lowest AIC	Reference	0.2	Reasonable (0-7 difference)
1-knot hazard spline	0.3	Reasonable (0-7 difference)	0.5	Reasonable (0-7 difference)
2-knot hazard spline	2.2	Reasonable (0-7 difference)	5.4	Reasonable (0-7 difference)
3-knot hazard spline	3.6	Reasonable (0-7 difference)	9.9	Inferior (7-10 difference)
1-knot odds spline	0.4	Reasonable (0-7 difference)	0.5	Reasonable (0-7 difference)
2-knot odds spline	2.3	Reasonable (0-7 difference)	5.4	Reasonable (0-7 difference)
3-knot odds spline	3.5	Reasonable (0-7 difference)	9.7	Inferior (7-10 difference)
1-knot normal spline	Lowest AIC	Reference	0.2	Reasonable (0-7 difference)

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Distribution	Difference from lowest AIC	AIC relative goodness-of-fit classification	Difference from lowest BIC	BIC relative goodness-of-fit classification
2-knot normal spline	1.6	Reasonable (0-7 difference)	4.8	Reasonable (0-7 difference)
3-knot normal spline	3.1	Reasonable (0-7 difference)	9.3	Inferior (7-10 difference)

Abbreviations: AIC = Akaike information criterion; BIC = Bayesian information criterion; RS = treatment of physician's choice

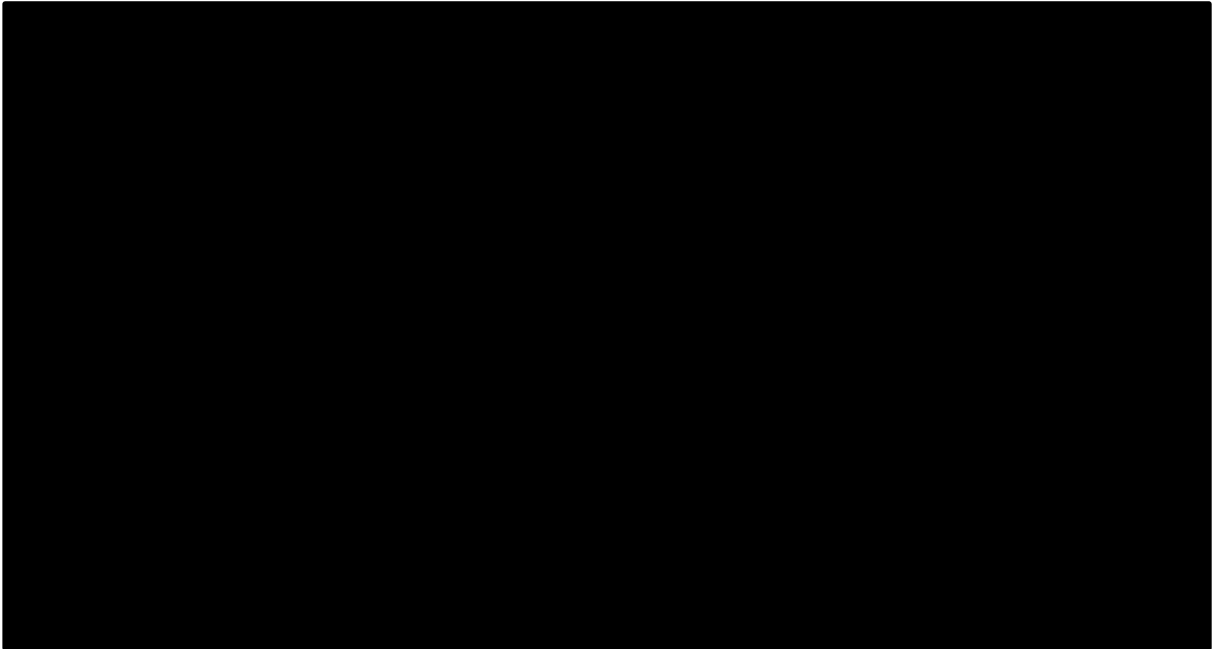
Standard survival parametric curves were fitted and overlaid on the KM OS curve as presented in xxxxxx ■ to assess visual fit to the observed data. For niraparib, the generalised gamma was the best overall visual fit among standard models. Weibull, log-logistic, gamma and log-normal appear to over predict the KM curve between approximately 40-50 months while under predicting the tail. Exponential and Gompertz both had generally bad visual fits to the KM curve, albeit with the exponential fit providing a better fit to the second half of the observed data.



— Exponential — Gompertz — Log-normal — Generalized Gamma
— Weibull(PH) — Log-logistic — Gamma

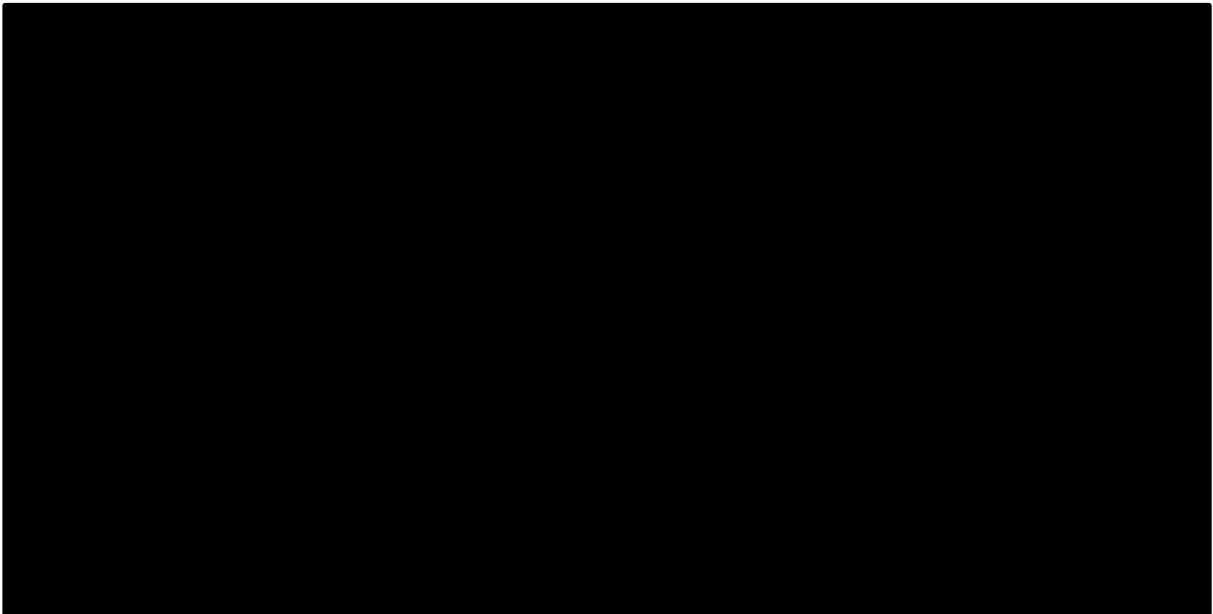
Fitted flexible parametric spline curves were also overlaid on the KM OS curves and are shown in xxxxxx ■. Excluding the 0-knot models, all splines provided generally good visual fits to the observed data, with fairly negligible differences in visual fit across different spline types and 1-3 knot models.

[Redacted text block]



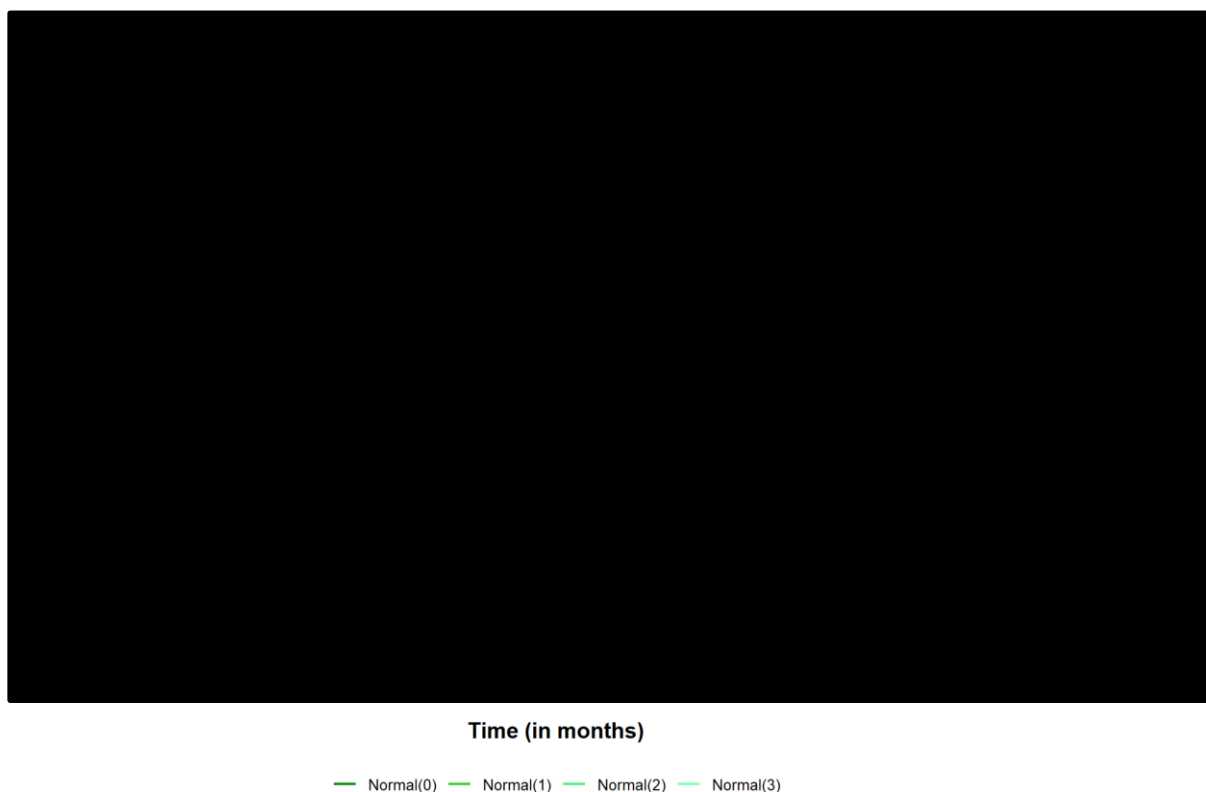
Time (in months)

— Hazard(0) — Hazard(1) — Hazard(2) — Hazard(3)



Time (in months)

— Odds(0) — Odds(1) — Odds(2) — Odds(3)



Long-term extrapolations of OS are shown in xxxxxx ■ and xxxxxx ■ for standard parametric and flexible parametric models, respectively, accounting for the selected base case PFS distribution (generalised gamma) for the BRCAm population. Among the standard parametric models, the exponential and generalised gamma provided the most optimistic OS extrapolations. All flexible parametric models were mostly overlapping up to the end of the KM curve, however diverged thereafter, with increasing numbers of knots associated with more optimistic survival projections.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Table 151 presents milestone estimates for observed OS for niraparib in PRIMA.

Table 151. OS survival estimates

Comparators	Median OS (months)	1-year	2-years	3-years	4-years	5-years	6-years
Niraparib	79.4	98.0%	88.5%	76.8%	63.5%	57.9%	51.9%

Abbreviations: OS = overall survival

The expected percentage of alive patients at 1 to 40-years is outlined in Table 152, considering general population background mortality and capped from below by the selected PFS base case model (generalised gamma) including a 10-year cure landmark point. The estimated proportion of niraparib patients alive at 10 years ranged from [REDACTED]% (Weibull, Gompertz and gamma) to [REDACTED]% (3-knot odds spline). At 15 Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

years, predicted OS estimates were between of ████% (all standard models excluding generalised gamma and 1-knot hazard spline) to ████% (3-knot odds spline). By 20 years, all OS models had hit the selected PFS curve (████%), with the exception of the generalised gamma (████%) and 3-knot odds spline (████%).

Table 152. Expected OS per parametric distribution for niraparib curves (BRCAm)

Distribu tion	1-year OS predict ion	3-year OS predict ion	5-year OS predict ion	10- year OS predict ion	15- year OS predict ion	20- year OS predict ion	30- year OS predict ion	40- year OS predict ion
Expone ntial	████	████	████	████	████	████	████	████
Weibull (PH)	████	████	████	████	████	████	████	████
Gompert z	████	████	████	████	████	████	████	████
Log- logistic	████	████	████	████	████	████	████	████
Log- normal	████	████	████	████	████	████	████	████
Gamma	████	████	████	████	████	████	████	████
Generali sed Gamma	████	████	████	████	████	████	████	████
1-knot hazard spline	████	████	████	████	████	████	████	████
2-knot hazard spline	████	████	████	████	████	████	████	████

Distribution	1-year OS prediction	3-year OS prediction	5-year OS prediction	10-year OS prediction	15-year OS prediction	20-year OS prediction	30-year OS prediction	40-year OS prediction
3-knot hazard spline								
1-knot odds spline								
2-knot odds spline								
3-knot odds spline								
1-knot normal spline								
2-knot normal spline								
3-knot normal spline								

Abbreviations: OS = overall survival

As for PFS, feedback from UK clinical experts was sought on long-term OS expectations for niraparib. Feedback provided varied slightly between clinical experts:

- The first expert indicated OS expectations of around 28% for niraparib at 15 years

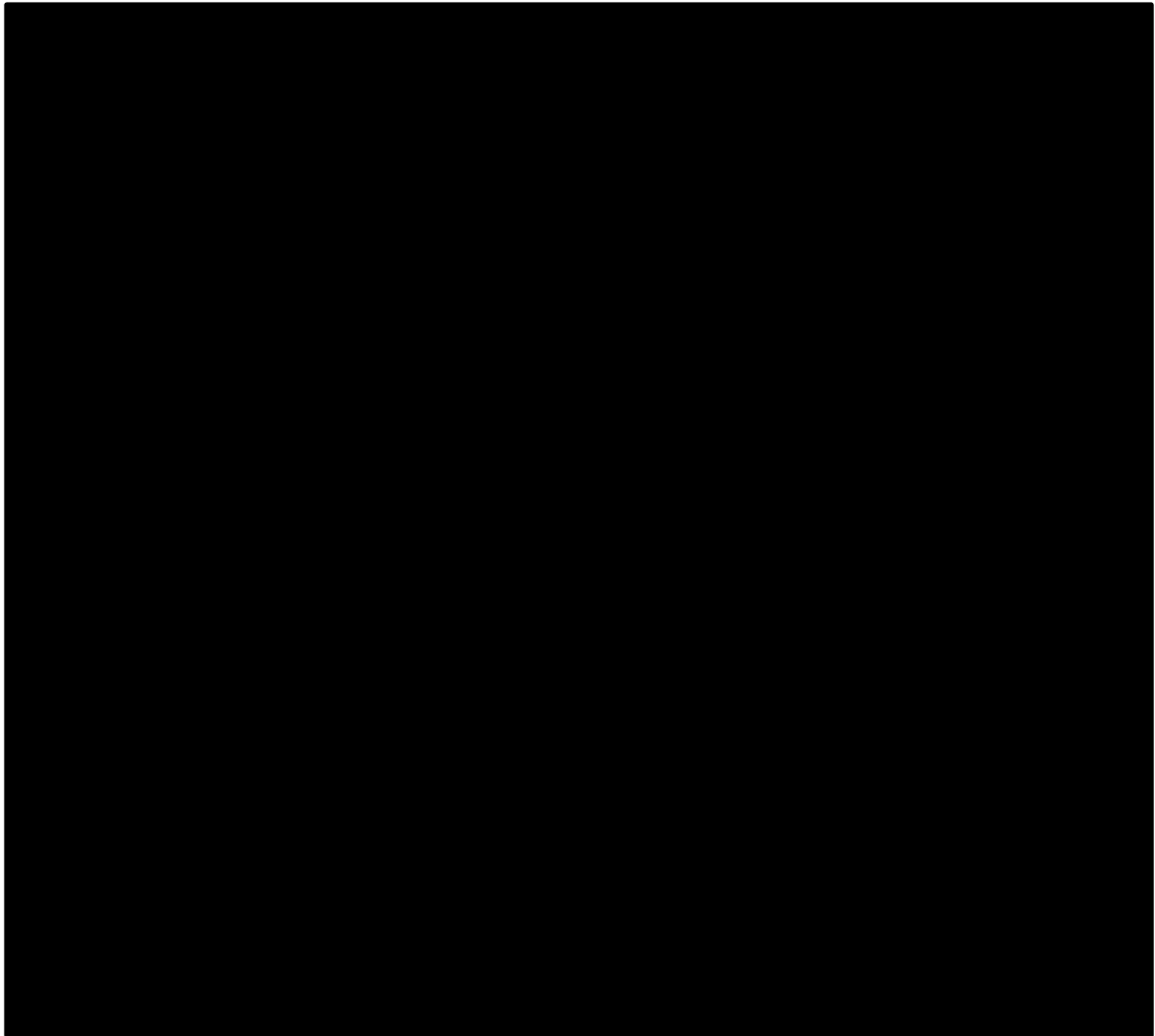
Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

- The second expert suggested survival would be somewhere between log-normal and generalised gamma at 10 years (~■%-■%) and 20 years (~■%-■%), with a preference towards the log-normal model due to the PFS/OS crossing point at ~11 years, and suggesting OS may be closer to ■% at 10 years and ■% at 20 years.
- Although estimates presented for each parametric model were capped by adjusted general population mortality, the third clinical expert struggled to recommend a parametric model suggesting that 30-year OS predictions may be too optimistic in general due to the underlying age of the patient population.
- The fourth expert noted an expectation of 35-40% OS at 10 years, suggesting that OS of around 36% at 10 years and around 20% at 20 years would be reasonable, and stating a preference for spline models due to the PFS crossing point

Although the second clinical expert suggested a range between log-normal and generalised gamma, only 1-knot hazard, 2-knot hazard and 1-knot normal spline models provided values within this range and were generally closer to the generalised gamma model, with a drop off in survival predictions for all other standard models compared to generalised gamma and spline models at 10, 15 and 20 years. For the base case analysis, the 1-knot normal model was selected as this model produced the joint best overall statistical fit alongside the generalised gamma model, a slightly better visual and statistical fit compared to the log-normal model, and provided the best overall reflection of feedback across clinical experts. Log-normal and generalised gamma were then explored in scenario analyses as potential lower and upper bound OS scenarios for niraparib.

J1.1.3 Time to treatment discontinuation

The time to treatment discontinuation or death (TTDD) niraparib KM curve for the BRCAm population in the PRIMA study is shown in xxxxxx ■.



Abbreviations: CI = confidence interval; HR = hazard ratio

AIC and BIC estimates for the standard parametric model TTDD distributions are shown in Table 153.

Table 153. AIC and BIC Estimates for TTDD distribution fits for the BRCam population - PRIMA

Distribution	AIC	BIC
Exponential	1256.0	1259.0
Weibull (PH)	1258.0	1264.0

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Distribution	AIC	BIC
Gompertz	1257.2	1263.2
Log-logistic	1272.9	1278.9
Log-normal	1277.3	1283.4
Gamma	1258.0	1264.0
Generalised Gamma	1259.1	1268.1

Abbreviations: AIC = Akaike information criterion; BIC = Bayesian information criterion

AIC and BIC classifications of relative fit are shown in Table 154. Among the standard parametric fits explored, the exponential distribution produced the best statistical fit with both the lowest AIC and lowest BIC. The Weibull, Gompertz, gamma and generalised gamma distributions all produced a reasonable statistical fits on the basis of AIC, with the generalised gamma showing an inferior fit based on BIC, being 9 points away from the reference distribution (exponential). The other standard models (log-logistic and log-normal) produced poor relative fits for both AIC and BIC.

Table 154. AIC and BIC Goodness-of-Fit per standard parametric distribution relative to the distribution with the lowest AIC and BIC for niraparib TTDD (BRCAm) – PRIMA

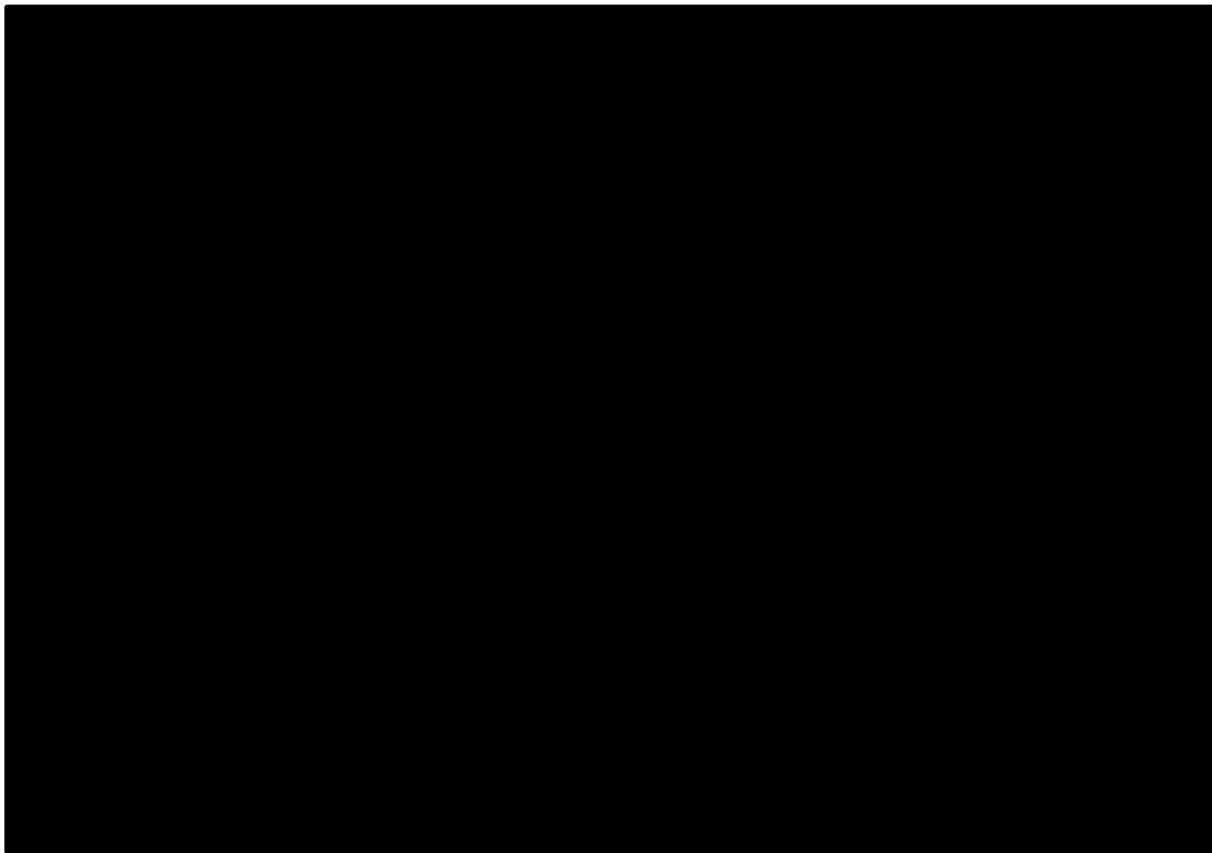
Distribution	Difference from lowest AIC	AIC relative goodness-of-fit classification	Difference from lowest BIC		BIC relative goodness-of-fit classification
Exponential	Lowest AIC		Reference	Lowest AIC	Reference
Weibull (PH)	2.0		Reasonable (0-7 difference)	5.0	Reasonable (0-7 difference)
Gompertz	1.2		Reasonable (0-7 difference)	4.2	Reasonable (0-7 difference)
Log-logistic	16.9		Poor (>10 difference)	19.9	Poor (>10 difference)

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Distribution	Difference from lowest AIC	AIC relative goodness-of-fit classification	Difference from lowest BIC		BIC relative goodness-of-fit classification
Log-normal	21.3		Poor (>10 difference)	24.4	Poor (>10 difference)
Gamma	2.0		Reasonable (0-7 difference)	5.0	Reasonable (0-7 difference)
Generalised Gamma	3.1		Reasonable (0-7 difference)	9.1	Inferior (7-10 difference)

Abbreviations: AIC = Akaike information criterion; BIC = Bayesian information criterion; RS = treatment of physician's choice

Standard survival parametric curves overlaid on the niraparib BRCaM TTDD KM curve are shown in [REDACTED]. Excluding the log-logistic and log-normal models, which provided poor visual fits to most of the observed data, the remaining models produced reasonable and similar visual fits to most of the KM curve, although underpredicted the curve between 40-60 months and clearly overpredicted the drop at the end of the KM curve to [REDACTED]% at around 76-77 months.



Time (in months)

— Exponential — Gompertz — Log-normal — Generalized Gamma
— Weibull(PH) — Log-logistic — Gamma

Although the PRIMA trial showed patients continuing on niraparib beyond the maximum treatment duration of 36 months specified within the label, when discussing expectations of time on treatment for niraparib with a UK clinical expert during a one-to-one interview as well as during an advisory board with three UK clinical experts, all of the clinical experts indicated that they expected only a small proportion of patients to continue on niraparib after 36 months in UK clinical practice. Clinicians highlighted that only patients with visible disease would continue on niraparib beyond 36 months, which was rare among patients remaining progression-free who were responding to treatment. Although there was limited evidence to make a strong judgement on whether continued use of niraparib beyond 36 months would have additional benefit,

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

clinical experts indicated that results of the PRIMA trial suggest that the benefit of the third year of treatment is much less than the first two years, and as such they would be unlikely to prescribe it beyond 36 months.

During the one-to-one interview, one of the UK clinical experts also stated that they expected no one to remain on niraparib in UK clinical practice at the time of the end of observed follow-up in the PRIMA trial (~78 months).

Due to the expectation of discontinuation of niraparib by at least 78 months, and the lack of need to extrapolate beyond the observed data, statistical fit and visual fit of the parametric models for niraparib TTDD ⁹⁹ was used as the primary selection criteria, in line with NICE DSU TSD14 guidance on selection criteria in the presence of complete survival data. However, given that none of the models produced particularly strong visual fits to the data, TTDD was modeled in the base case analysis using the available KM data up to 78 months following by exponential model for any extrapolation required beyond 78 months as the best statistical fit (given the relatively limited differences in visual fit between models with better statistical fits).

As part of the scenario analyses outlined in Section 3.4.7, niraparib and olaparib TTDD data from SACT were considered for scenario analyses, with available summary-level KM data digitized and pseudo-IPD produced using the Guyot algorithm, and fitted using standard parametric models. Based on AIC/BIC (Table 153), the log-normal model and Gompertz models provided the best statistical fits to the niraparib and Olaparib SACT TTDD KM curves, respectively.

Table 155. AIC and BIC estimates for TTDD distribution fits for the BRCAm population for niraparib and olaparib - SACT

Distribution	Niraparib SACT		Olaparib SACT	
	AIC	BIC	AIC	BIC
Exponential	455.3	457.8	3471.8	3476.4
Weibull (PH)	456.8	461.8	3371.0	3380.2
Gompertz	456.4	461.4	3326.8	3335.9

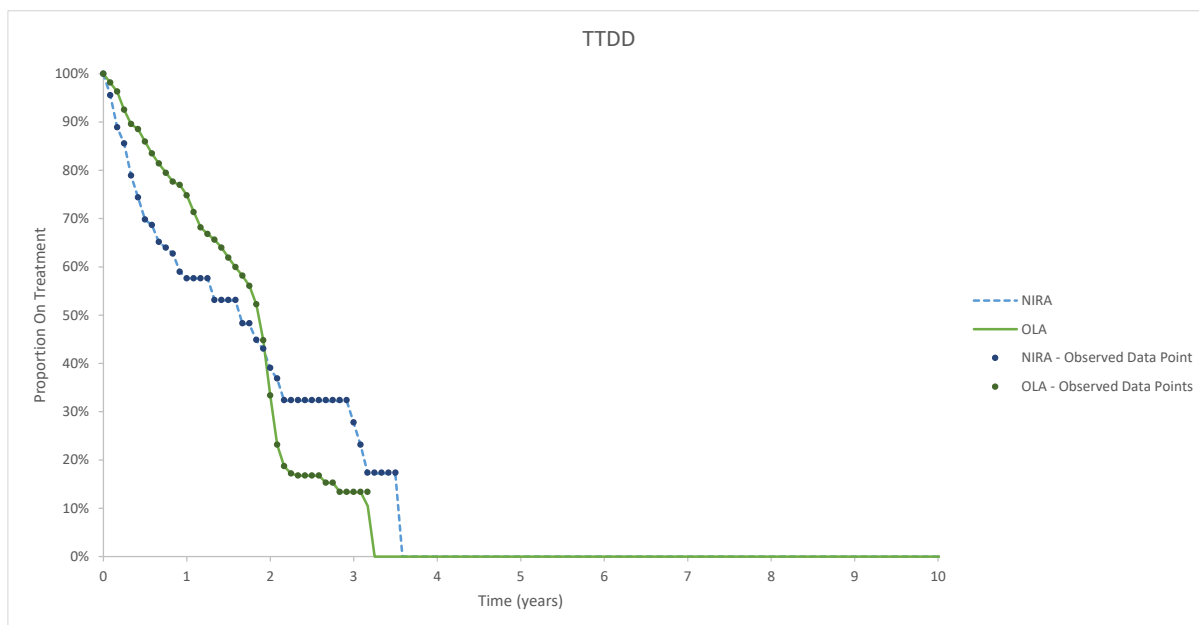
Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer



Based on the statistical fit indicated by AIC/BIC (Table 153), the fairly poor visual fit to the observed data (particularly for olaparib), fairly complete nature of the KM curves, and in line with the approach adopted in the base case analysis for the niraparib PRIMA TTDD data, the KM curves combined with the best statistically fitting distributions (log-normal for niraparib, Gompertz for olaparib) were used for SACT-based TTDD scenario analyses.

The following figures (xxxxxx ■■■, Figure 67, xxxxxx 68, and ■■■■■) outline TTDD extrapolations of niraparib and olaparib for various scenario analyses in the BRCAm population (see Section 3.4.7).

Figure 67. SACT TTDD KM data to the approximate end of available follow-up (42 months for NIRA and 38 months for OLA), then assume all patients discontinue



Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

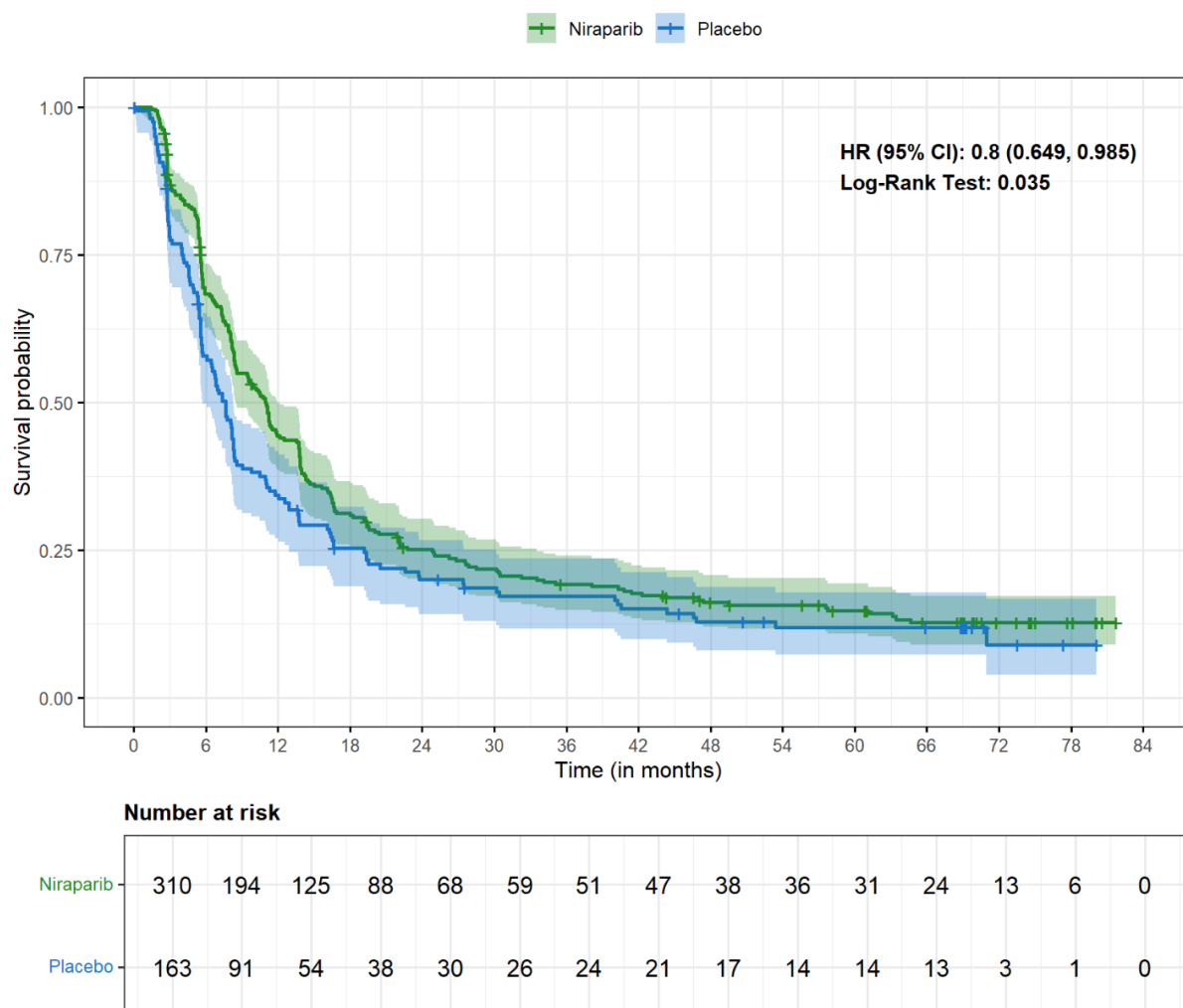
[REDACTED]

J1.2 Survival in the BRCAwt population

J1.2.1 Progression free survival

Figure 70 illustrates the KM plots for investigator-assessed progression-free survival in the BRCAwt population of the PRIMA study.

Figure 70. KM plots for PFS (INV) for the BRCAwt population in PRIMA



Abbreviations: CI = confidence interval; HR = hazard ratio

Figure displays the smoothed hazard plots for the observed PFS Kaplan-Meier data. These plots indicate a hazard profile that initially increases and then decreases, which aligns with the profiles generated by non-monotonic Figure displays the smoothed hazard plots for the observed PFS KM data. These plots

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

indicate a hazard profile that initially increases and then decreases, which aligns with the profiles generated by non-monotonic standard distributions (log-logistic, log-normal, and generalised gamma) as well as by each of the spline models.

Figure 71. Smoothed PFS hazard for BRCAwt population in PRIMA

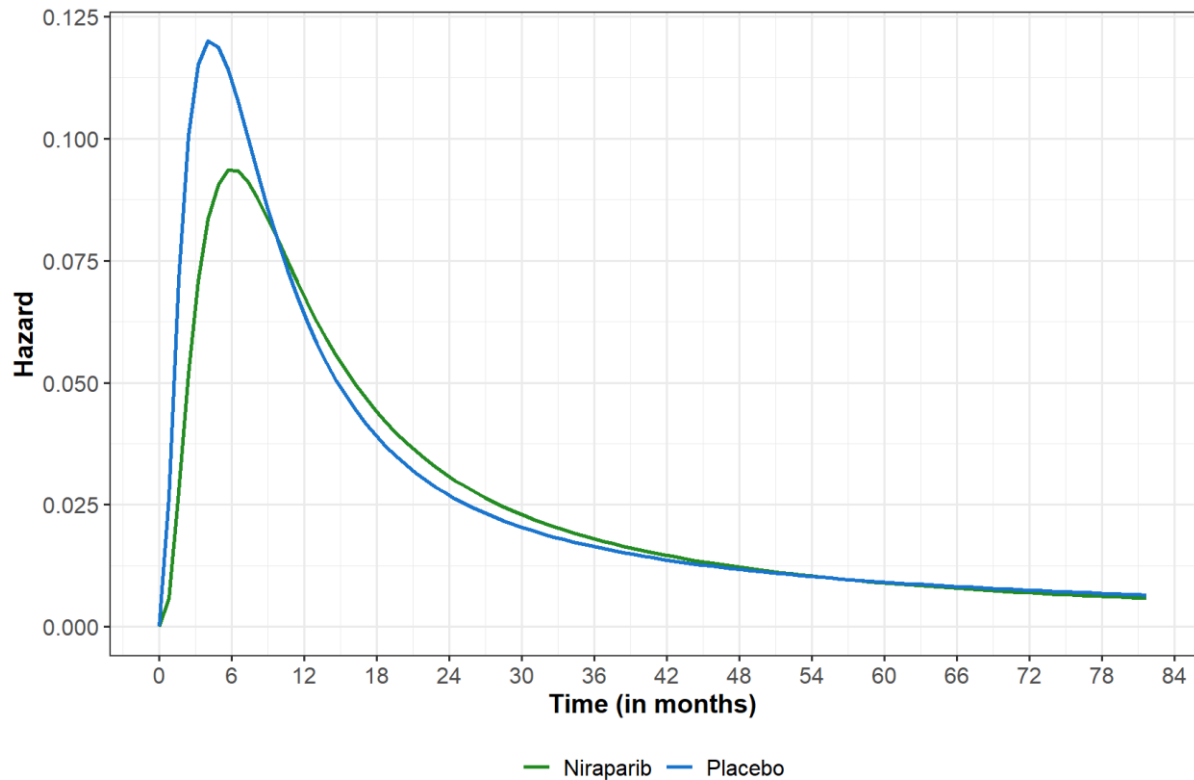
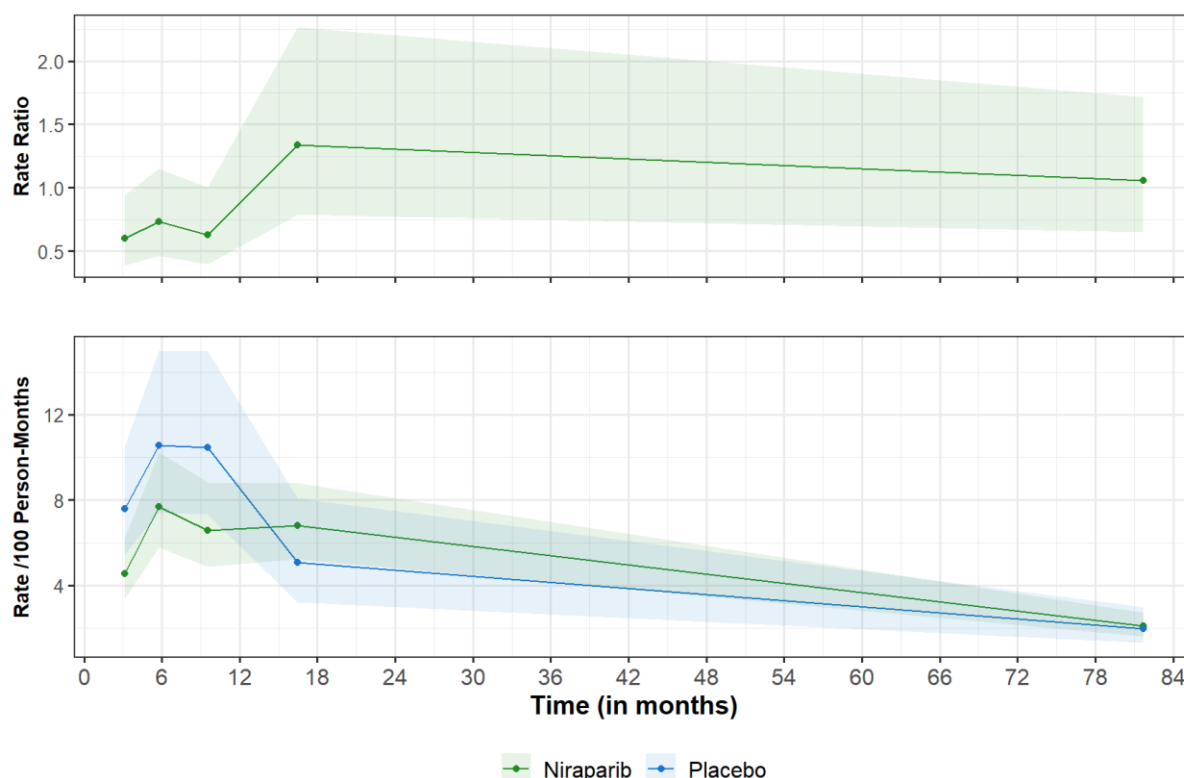


Figure 72 presents the average hazard plots for the observed PFS KM data. Again, the plots shown an initial increase followed by a decrease in hazard profiles for niraparib.

Figure 72. Average PFS hazard for BRCAwt population in PRIMA



AIC and BIC estimates for the niraparib PFS distributions are shown in Table 156.

Table 156. AIC and BIC estimates for niraparib PFS distribution fits (BRCAwt)

Distribution	AIC	BIC
Exponential	2023.3	2027.1
Weibull (PH)	2015.9	2023.4
Gompertz	1965.0	1972.5
Log-logistic	1940.7	1948.1
Log-normal	1939.0	1946.5
Gamma	2023.8	2031.3
Generalised Gamma	1895.1	1906.3
1-knot hazard spline	1901.2	1912.4
2-knot hazard spline	1901.7	1916.6
3-knot hazard spline	1902.0	1920.7

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Distribution	AIC	BIC
1-knot odds spline	1900.7	1911.9
2-knot odds spline	1902.1	1917.1
3-knot odds spline	1901.6	1920.3
1-knot normal spline	1896.9	1908.1
2-knot normal spline	1897.7	1912.6
3-knot normal spline	1897.6	1916.2

Abbreviations: AIC = Akaike information criterion; BIC = Bayesian information criterion

AIC and BIC classifications of relative fit are outlined in Table 157, including both standard and flexible (spline) parametric models. Overall, the generalised gamma model produced the best statistical fit with the lowest AIC and lowest BIC. Based on AIC, all of the flexible parametric spline models produced a reasonable fit, however according to BIC, the 2- and -3 knot models were generally considered a poor relative fit. All other standard parametric models were also considered to be poor relative fits based on both AIC and BIC, with substantial increases in AIC and BIC compared to the generalised gamma model (>40 point differences).

Table 157. AIC and BIC Goodness-of-Fit relative to the distribution with the lowest AIC and BIC for niraparib PFS (BRCAwt)

Distribution	Difference from lowest AIC	AIC relative goodness-of-fit classification	Difference from lowest BIC	BIC relative goodness-of-fit classification
Exponential	128.2	Poor (>10 difference)	120.8	Poor (>10 difference)
Weibull (PH)	120.8	Poor (>10 difference)	117.1	Poor (>10 difference)
Gompertz	69.9	Poor (>10 difference)	66.2	Poor (>10 difference)
Log-logistic	45.6	Poor (>10 difference)	41.8	Poor (>10 difference)

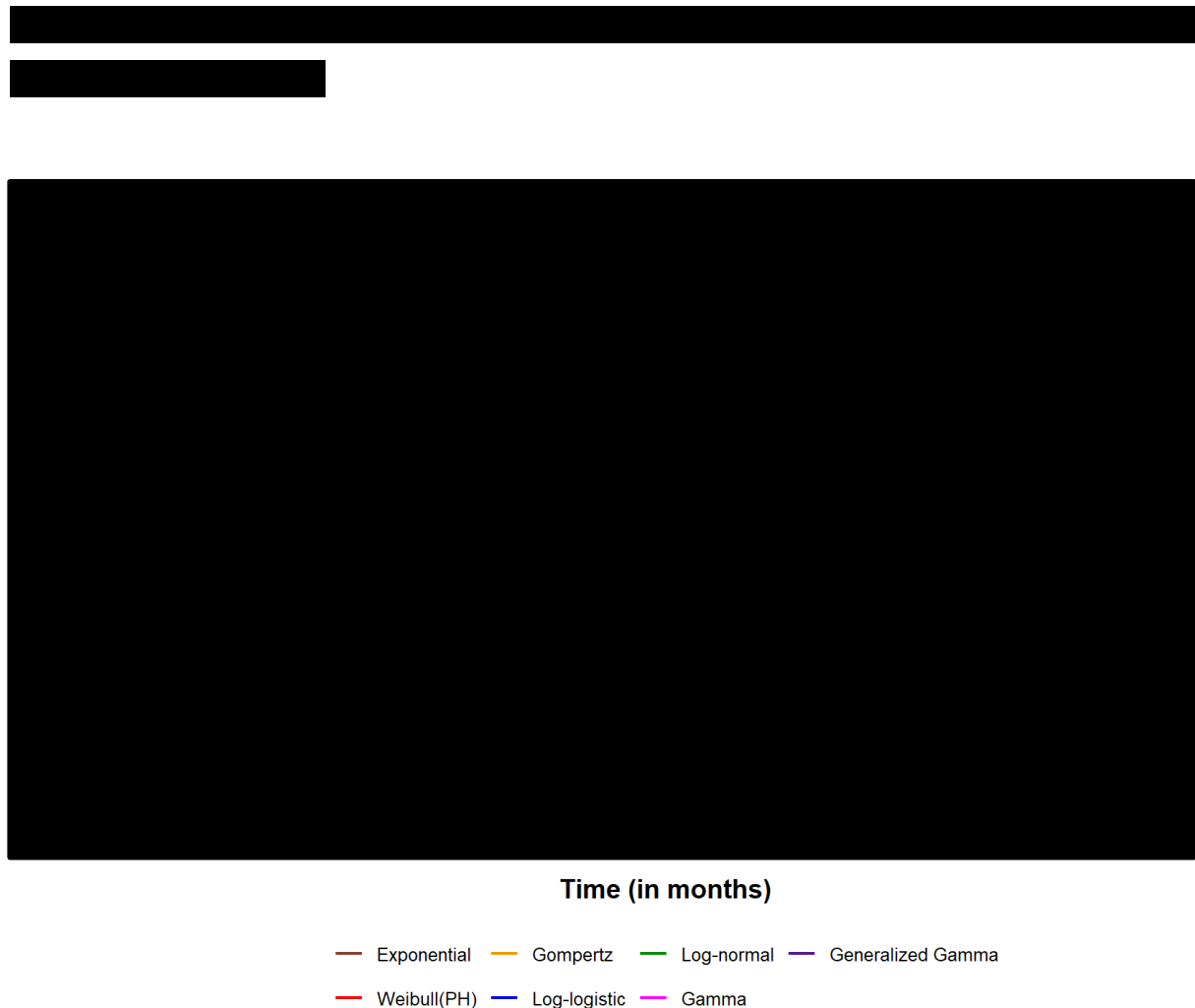
Distribution	Difference from lowest AIC	AIC relative goodness-of-fit classification	Difference from lowest BIC	BIC relative goodness-of-fit classification
Log-normal	43.9	Poor (>10 difference)	40.2	Poor (>10 difference)
Gamma	128.7	Poor (>10 difference)	125.0	Poor (>10 difference)
Generalised Gamma	Lowest AIC	Reference	Lowest BIC	Reference
1-knot hazard spline	6.1	Reasonable (0-7 difference)	6.1	Reasonable (0-7 difference)
2-knot hazard spline	6.6	Reasonable (0-7 difference)	10.3	Poor (>10 difference)
3-knot hazard spline	6.9	Reasonable (0-7 difference)	14.4	Poor (>10 difference)
1-knot odds spline	5.6	Reasonable (0-7 difference)	5.6	Reasonable (0-7 difference)
2-knot odds spline	7.0	Reasonable (0-7 difference)	10.8	Poor (>10 difference)
3-knot odds spline	6.5	Reasonable (0-7 difference)	14.0	Poor (>10 difference)
1-knot normal spline	1.8	Reasonable (0-7 difference)	1.8	Reasonable (0-7 difference)
2-knot normal spline	2.6	Reasonable (0-7 difference)	6.3	Reasonable (0-7 difference)
3-knot normal spline	2.5	Reasonable (0-7 difference)	9.9	Inferior (7-10 difference)

Abbreviations: AIC = Akaike information criterion; BIC = Bayesian information criterion; RS = treatment of physician's choice

Standard survival parametric curves were fitted and overlaid on the KM PFS curve as shown in [REDACTED]. The generalised gamma and Gompertz distributions provided the best overall visual fits to the KM curve. The log-logistic distribution showed a reasonable

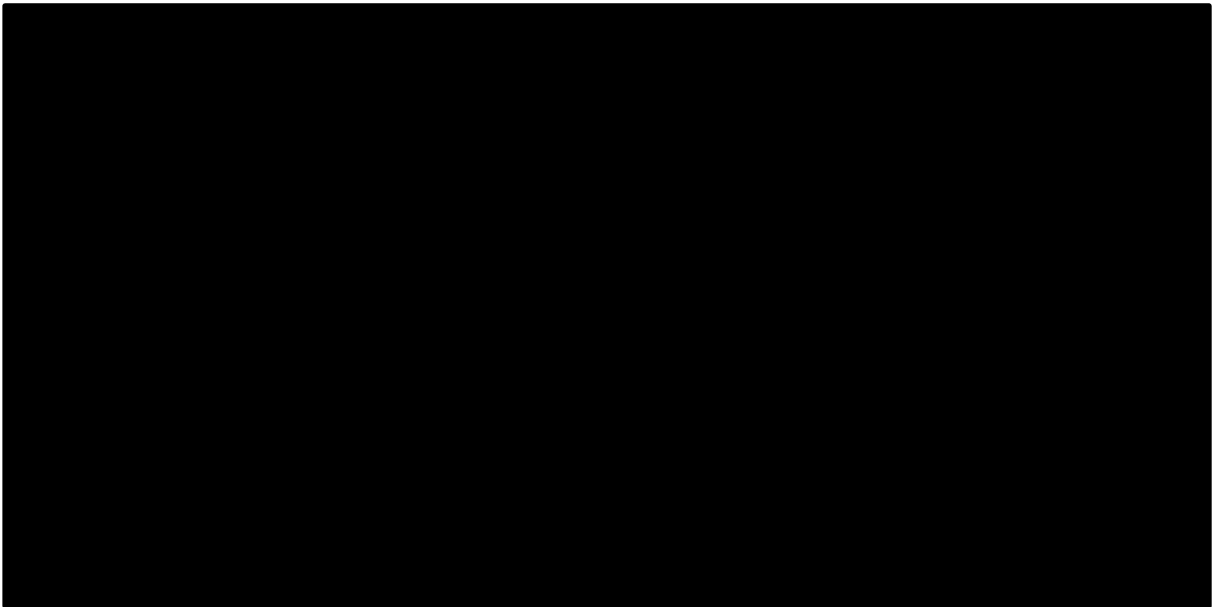
Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

visual fit up to around 30 months before clearly underestimating the remainder of the KM curve. The log-normal model slightly overestimated the KM curve between approximately 10-30 months but before also substantially underestimating the tail. Exponential, Weibull, and gamma distributions generally exhibited poor visual fits to the data.



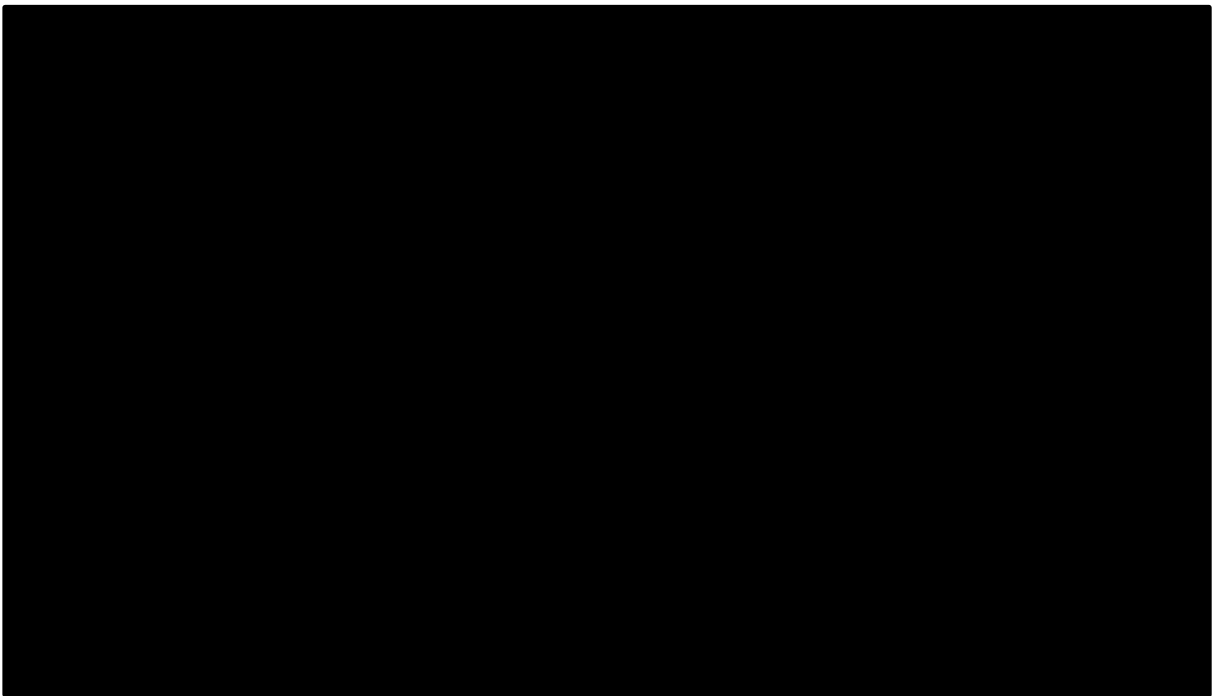
Similarly to above, the flexible parametric spline curves for niraparib were also overlaid on the KM PFS curves and shown in xxxxxx 74x. Excluding the 0-knot models, all spline models provided a broadly good visual fit to the observed data, irrespective of the type of spline model and number of internal knots.

[Redacted text block]



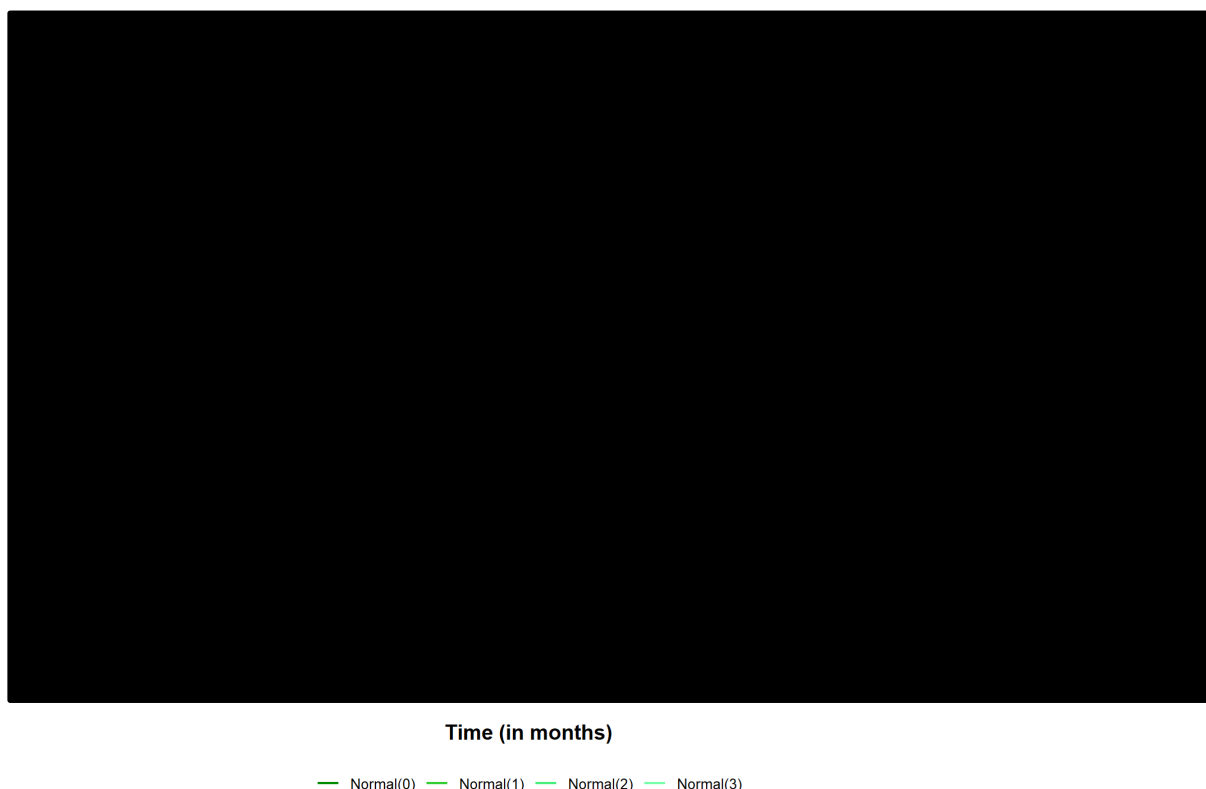
Time (in months)

— Hazard(0) — Hazard(1) — Hazard(2) — Hazard(3)



Time (in months)

— Odds(0) — Odds(1) — Odds(2) — Odds(3)



Long-term extrapolations of PFS are shown in [REDACTED] and [REDACTED], for standard parametric and flexible parametric models, respectively, including a 10-year cure timepoint after which general population mortality is applied. The curves from the Gompertz and generalised gamma distributions provided the most optimistic PFS extrapolations among standard models with all remaining parametric model providing much more pessimistic extrapolations. All flexible parametric models provided fairly similar long-term extrapolations.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Table 158 presents the observed PFS milestone estimates for niraparib in PRIMA for the BRCAwt population.

Table 158. PFS observed survival estimates for niraparib (BRCAwt)

Comparators	Median PFS (months)	1-year	2-years	3-years	4-years	5-years	6-years
NIRA	10.9	44.3%	25.1%	19.2%	16.1%	14.8%	12.7%

Abbreviations: PFS = progression Free Survival; NIRA = niraparib

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

The expected percentage of progression-free patients at 1 to 40-years are displayed in Table 159, considering a 10-year cure landmark. The estimated proportion of patients who alive and progression-free at 10 years ranged from █% (exponential) to █% (Gompertz). At 15 years, values ranges between █% (exponential) and █% (Gompertz), with estimates varying between █% (exponential) and █% (Gompertz) at 20 years.

Table 159. Expected PFS per parametric distribution for niraparib (BRCAwt)

Distribution	1-year PFS predicti on	3-year PFS predicti on	5-year PFS predicti on	10-year PFS predicti on	15-year PFS predicti on	20-year PFS predicti on	30-year PFS predicti on	40-year PFS predicti on
	(with 10-year cure landmark)							
Exponential	█	█	█	█	█	█	█	█
Weibull (PH)	█	█	█	█	█	█	█	█
Gompertz	█	█	█	█	█	█	█	█
Log-logistic	█	█	█	█	█	█	█	█
Log-normal	█	█	█	█	█	█	█	█
Gamma	█	█	█	█	█	█	█	█
Generalised Gamma	█	█	█	█	█	█	█	█
1-knot hazard spline	█	█	█	█	█	█	█	█
2-knot hazard spline	█	█	█	█	█	█	█	█
3-knot hazard spline	█	█	█	█	█	█	█	█
1-knot odds spline	█	█	█	█	█	█	█	█

Distribution	1-year PFS prediction	3-year PFS prediction	5-year PFS prediction	10-year PFS prediction	15-year PFS prediction	20-year PFS prediction	30-year PFS prediction	40-year PFS prediction
	(with 10-year cure landmark)							
2-knot odds spline	████	████	████	████	████	████	████	████
3-knot odds spline	████	████	████	████	████	████	████	████
1-knot normal spline	████	████	████	████	████	████	████	████
2-knot normal spline	████	████	████	████	████	████	████	████
3-knot normal spline	████	████	████	████	████	████	████	████

Abbreviations: PFS = progression-free survival

To validate the plausibility of long-term survival extrapolations, niraparib PFS BRCAwt extrapolations from PRIMA were discussed with UK clinical experts. As the first clinical expert provided feedback on PFS expectations for subpopulations within BRCAwt, feedback from the one-to-one interviews conducted with the remaining three clinical experts (those included in the advisory board) for the overall BRCAwt population was utilised to validate PFS expectations:

- The second clinical expert indicated that estimates between log-normal and generalised gamma models were plausible (approximately █████% at 10 years)
- The third clinical expert stated expectations of █████% PFS at 10 years, suggesting that the generalised gamma or Gompertz models seem appropriate as the PFS curve appears to flatten out

- The fourth clinical expert stated that estimates produced by the spline models and generalised gamma models provided the closest fits to their long-term PFS expectations, suggesting █% or █% PFS at 10 years to be reasonable

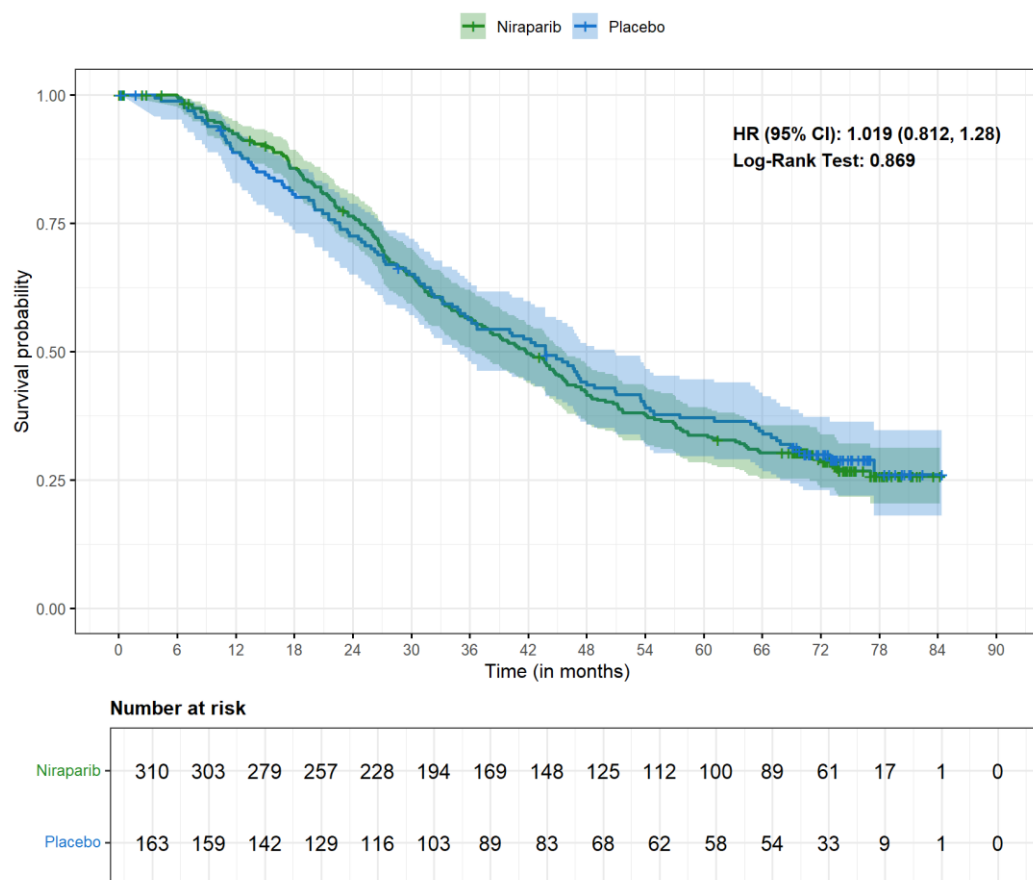
The generalised gamma model, which estimated █% PFS at 10 years, was chosen as the base case since it overlapped with the ranges of estimates from all three clinical experts, whilst also providing the best statistical fit along with a good visual and hazard profile fit to the observed data.

Scenario analysis was conducted using the 2-knot normal spline joint fit model, which provided the best statistical fit among models closer to the upper bound implied by two of the clinical experts (i.e. between █% PFS at 10 years). Although one of the clinical experts suggested <8.0% PFS at 10 years for niraparib may be plausible, all models predicting less than █% PFS at 10 years were substantially lower than 8% (█% or lower) and had very poor statistical and visual fits to the observed data (>40 AIC/BIC point differences compared to generalised gamma), and therefore were not considered for scenario analysis.

J1.2.2 Overall survival

Figure 77 shows the OS KM plots for the BRCAwt population in the PRIMA study.

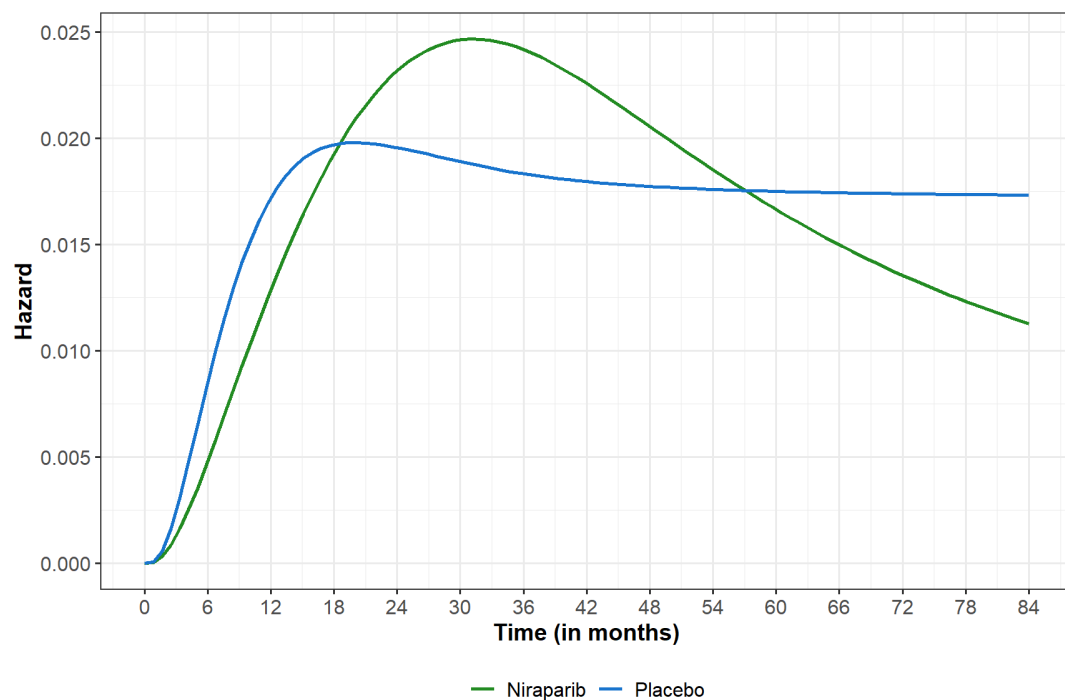
Figure 77. KM plots for OS for the BRCAwt population in PRIMA



Abbreviations: CI = confidence interval; HR = hazard ratio

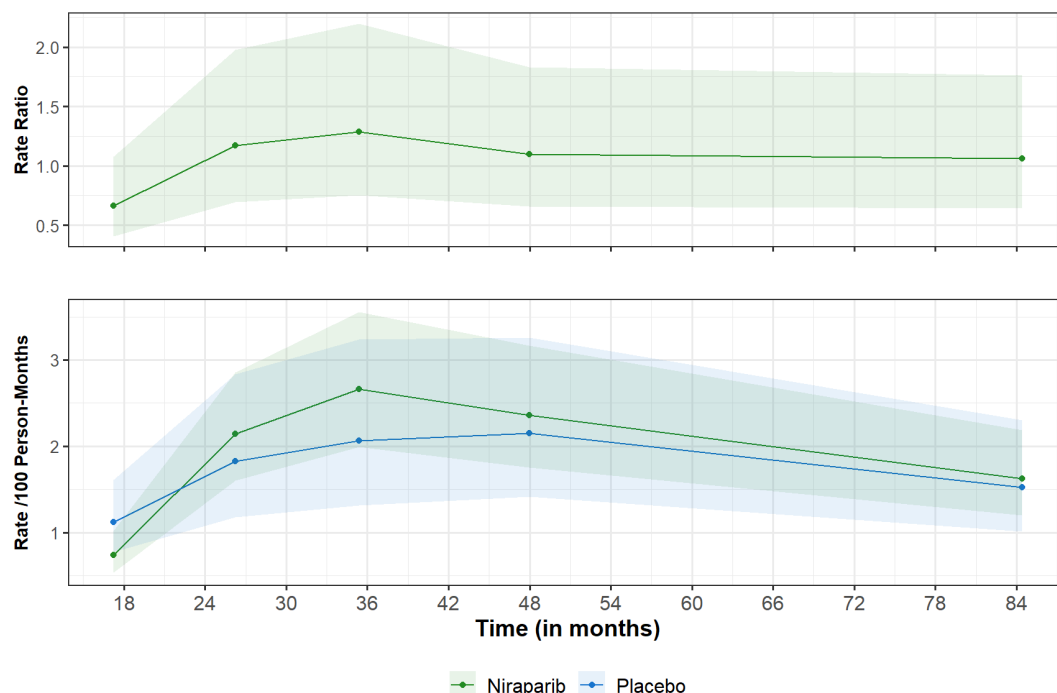
Smoothed hazard plots for the observed OS KM data are displayed in Figure 78. These plots were indicative of an increasing then decreasing hazard profile. The models that most closely aligned with the broad hazard profile implied by the KM data were the log-logistic, log-normal, generalised gamma standard models and spline models.

Figure 78. Smoothed OS hazard for BRCAwt population in PRIMA



The average hazard plots for the observed OS KM data are displayed in Figure 79. Again, these plots suggest an increasing then decreasing hazard profile for niraparib.

Figure 79. Average OS hazard for BRCAwt population in PRIMA



AIC and BIC estimates for the niraparib OS distributions are shown in Table 160.

Table 160. AIC and BIC Estimates for niraparib OS distribution fits (BRCAwt)

Distribution	NIRA	
	AIC	BIC
Exponential	2217.0	2220.7
Weibull (PH)	2182.3	2189.8
Gompertz	2206.8	2214.3
Log-logistic	2161.3	2168.8
Log-normal	2156.3	2163.8
Gamma	2172.9	2180.3
Generalised Gamma	2156.1	2167.3
1-knot hazard spline	2157.3	2168.5
2-knot hazard spline	2158.1	2173.1
3-knot hazard spline	2159.8	2178.5

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Distribution	NIRA	
	AIC	BIC
1-knot odds spline	2156.8	2168.0
2-knot odds spline	2158.2	2173.1
3-knot odds spline	2159.9	2178.6
1-knot normal spline	2156.8	2168.0
2-knot normal spline	2156.4	2171.4
3-knot normal spline	2158.2	2176.9

Abbreviations: AIC = Akaike information criterion; BIC = Bayesian information criterion

AIC and BIC classifications of relative fit is outlined in Table 161, including both standard and flexible (spline) parametric models. The generalised gamma model produced the best statistical fit according to AIC, while the log-normal model was associated with the lowest BIC. The log-normal, log-logistic, and all spline models were considered reasonable relative fits according to AIC, whereas the remaining standard parametric models were poor fits. For BIC, the generalised gamma and log-logistic models, as well as the 1-knot splines, were reasonable relative fits compared to log-normal. The 2-knot spline models were classified as inferior, while all other fits were determined to be poor relative BIC fits.

Table 161. AIC and BIC Goodness-of-Fit relative to the distribution with the lowest AIC and BIC for niraparib OS distribution fits (BRCAwt)

Distribution	Difference from lowest AIC	AIC relative goodness-of-fit classification	Difference from lowest BIC	BIC relative goodness-of-fit classification
Exponential	60.9	Poor (>10 difference)	56.9	Poor (>10 difference)
Weibull (PH)	26.2	Poor (>10 difference)	26.0	Poor (>10 difference)
Gompertz	50.7	Poor (>10 difference)	50.5	Poor (>10 difference)

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Distribution	Difference from lowest AIC	AIC relative goodness-of-fit classification	Difference from lowest BIC	BIC relative goodness-of-fit classification
Log-logistic	5.2	Reasonable (0-7 difference)	5.0	Reasonable (0-7 difference)
Log-normal	0.2	Reasonable (0-7 difference)	Lowest BIC	Reference
Gamma	16.8	Poor (>10 difference)	16.5	Poor (>10 difference)
Generalised Gamma	Lowest AIC	Reference	3.5	Reasonable (0-7 difference)
1-knot hazard spline	1.2	Reasonable (0-7 difference)	4.7	Reasonable (0-7 difference)
2-knot hazard spline	2.0	Reasonable (0-7 difference)	9.3	Inferior (7-10 difference)
3-knot hazard spline	3.7	Reasonable (0-7 difference)	14.7	Poor (>10 difference)
1-knot odds spline	0.7	Reasonable (0-7 difference)	4.2	Reasonable (0-7 difference)
2-knot odds spline	2.1	Reasonable (0-7 difference)	9.3	Inferior (7-10 difference)
3-knot odds spline	3.8	Reasonable (0-7 difference)	14.8	Poor (>10 difference)
1-knot normal spline	0.7	Reasonable (0-7 difference)	4.2	Reasonable (0-7 difference)
2-knot normal spline	0.3	Reasonable (0-7 difference)	7.6	Inferior (7-10 difference)
3-knot normal spline	2.1	Reasonable (0-7 difference)	13.1	Poor (>10 difference)

Abbreviations: AIC = Akaike information criterion; BIC = Bayesian information criterion

Standard survival parametric curves were fitted and overlaid on the KM OS curve as presented in xxxxxx 80x The generalised gamma model provided the best overall

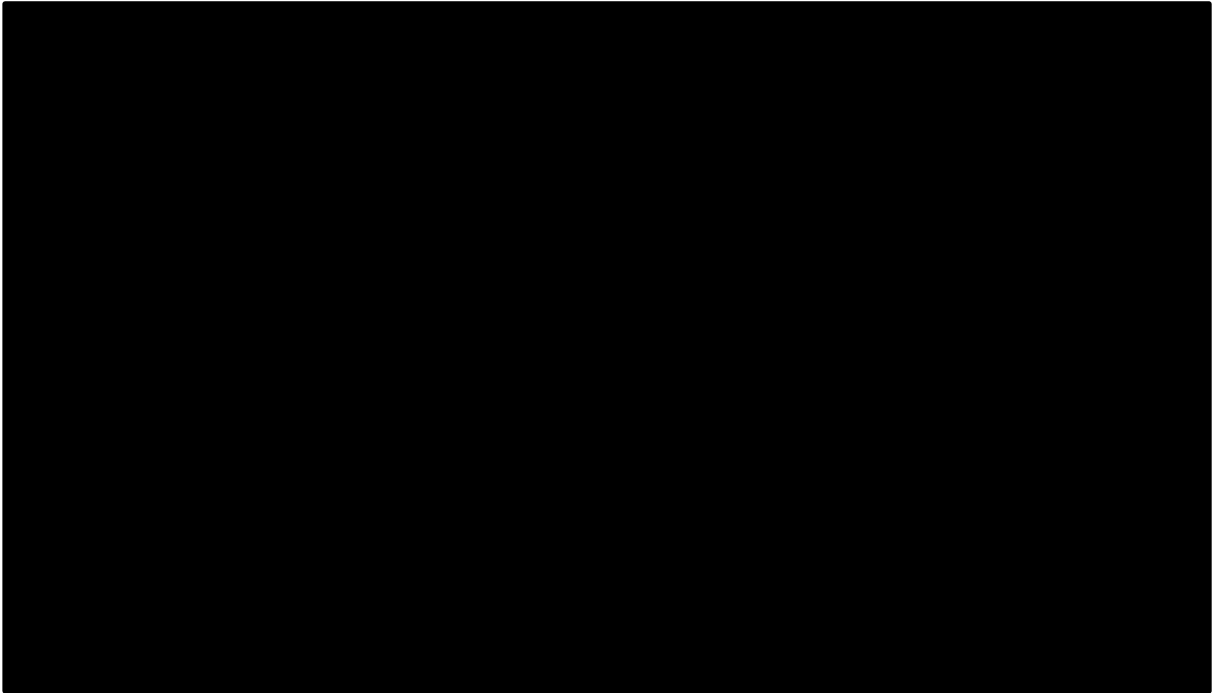
Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

visual fit to the observed data. The Gompertz and exponential models both fairly poor overall visual fits, notably underpredicting survival for approximately the first 25-35 months. Other models tended to underpredict the tail of the survival curve, with gamma and Weibull models also slightly overpredicting the middle section of the KM curve.



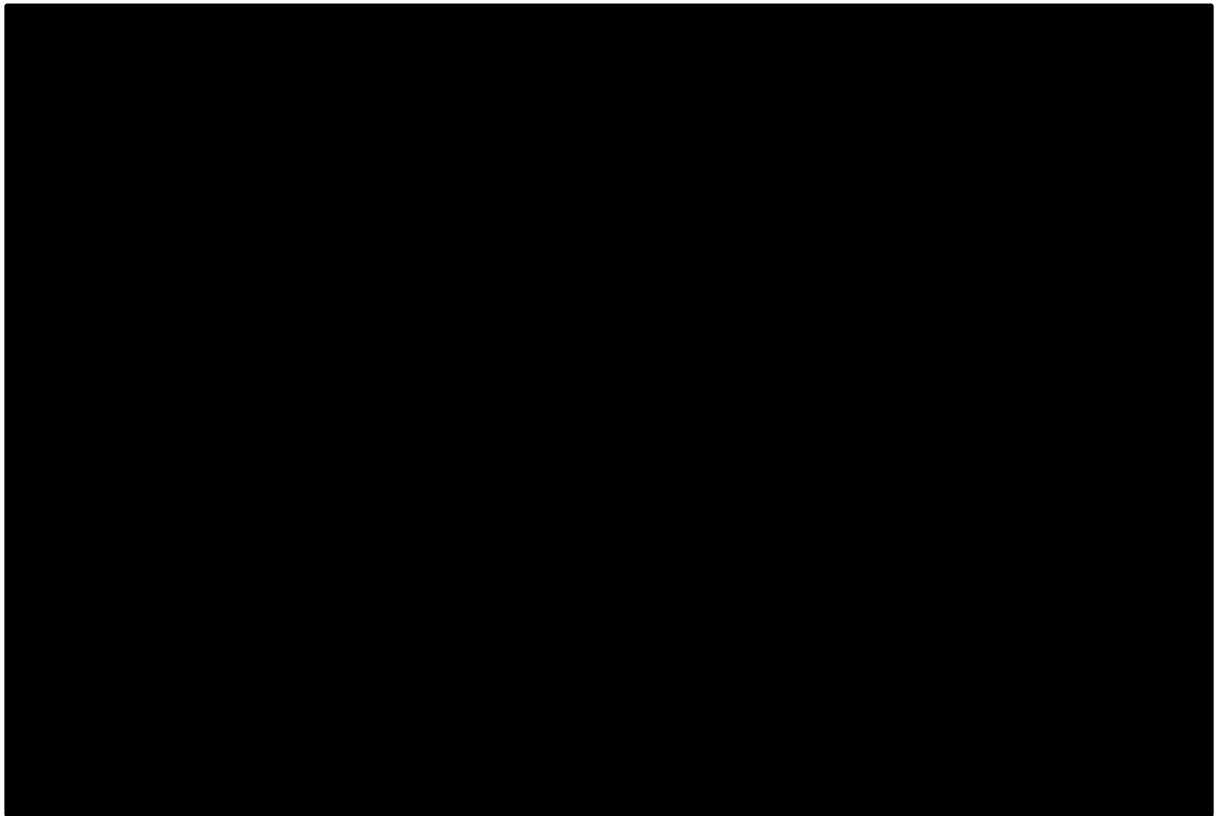
The fitted flexible parametric spline curves for niraparib were also overlaid on the KM OS curves and are shown in [REDACTED]. Excluding the 0-knot models, all splines provided good (and similar) visual fits to the observed data.

[Redacted text block]



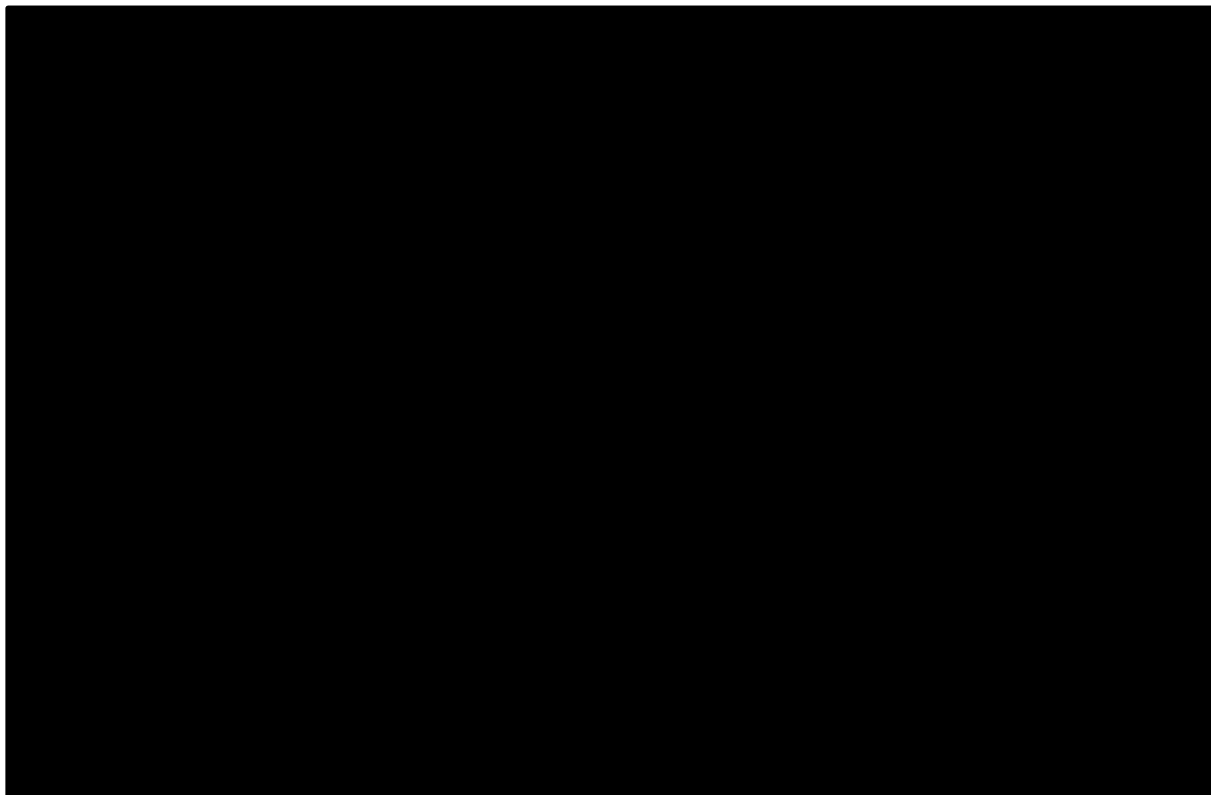
Time (in months)

— Hazard(0) — Hazard(1) — Hazard(2) — Hazard(3)



Time (in months)

— Odds(0) — Odds(1) — Odds(2) — Odds(3)



Time (in months)

— Normal(0) — Normal(1) — Normal(2) — Normal(3)

Long-term extrapolations of OS are shown in xxxxxx ■ and xxxxxx ■ for standard parametric and flexible parametric models, respectively, accounting for the selected PFS distribution (generalised gamma) for the BRCAwt population with a 10-year cure point. From the standard parametric models, the exponential and generalised gamma distributions provided the most optimistic OS extrapolations. All flexible parametric models were mostly overlapping up to the end of the KM curve, however diverged thereafter. The 3-knot odds model provided the most optimistic scenario while the 1-knot hazard provided the most pessimistic predictions.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Table 162 presents milestone estimates for the observed OS for niraparib for the BRCAwt population in PRIMA.

Table 162. OS survival estimates

Comparators	Median OS (months)	1-year	2-years	3-years	4-years	5-years	6-years
Niraparib	41.8	92.4%	76.4%	56.6%	41.5%	33.7%	28.5%

Abbreviations: OS = overall survival

The expected percentage of alive patients at 1 to 40-years are outlined in Table 163, considering general population background mortality and a 10-year cure landmark. The estimated proportion of patients remaining alive at 10 years ranged between [REDACTED]% (Weibull and Gompertz) to [REDACTED]% (3-knot odds spline). At 15 years, most standard parametric models (excluding generalised gamma), 1-knot hazard and 2-knot hazard Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

spline models had met the base case PFS model (generalised gamma) with ███% survival, with the most optimistic projection provided by the 3-knot odds model (████%). At 20 years, only 2 and 3-knot spline odds models remained above the generalised gamma PFS curve (████%), with 20-year OS of ███% and ███% respectively.

Table 163. Expected OS per parametric distribution for niraparib (BRCAwt)

Distribu tion	1-year OS predict ion	3-year OS predict ion	5-year OS predict ion	10- year OS predict ion	15- year OS predict ion	20- year OS predict ion	30- year OS predict ion	40- year OS predict ion
Expone ntial	████	████	████	████	████	████	████	████
Weibull (PH)	████	████	████	████	████	████	████	████
Gompert z	████	████	████	████	████	████	████	████
Log- logistic	████	████	████	████	████	████	████	████
Log- normal	████	████	████	████	████	████	████	████
Gamma	████	████	████	████	████	████	████	████
Generali sed Gamma	████	████	████	████	████	████	████	████
1-knot hazard spline	████	████	████	████	████	████	████	████
2-knot hazard spline	████	████	████	████	████	████	████	████

Distribution	1-year OS prediction	3-year OS prediction	5-year OS prediction	10-year OS prediction	15-year OS prediction	20-year OS prediction	30-year OS prediction	40-year OS prediction
3-knot hazard spline								
1-knot odds spline								
2-knot odds spline								
3-knot odds spline								
1-knot normal spline								
2-knot normal spline								
3-knot normal spline								

Abbreviations: OS = overall survival

OS expectations for BRCAwt patients on niraparib were also sought from UK clinical experts. As for PFS, feedback from one-to-one interviews with the latter three clinical experts (those also included in the advisory board) was utilised due to provision of OS expectations for subgroups within BRCAwt from the first UK clinical expert:

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

- The second clinical expert stated OS expectations of ~■% at 10 years and ~5% at 20 years, although noted a preference for log-normal and log-logistic models based on the PFS crossing point
- The third clinical expert indicated that ■% OS at 10 years was clinically plausible
- The fourth clinical expert also noted an expectation of approximately ■% OS at 10 years. In addition, the clinical expert stated that they expected PFS and OS to cross between 15 and 20 years, suggesting that estimates produced by the 3-knot spline hazards model were most appropriate

For the base case analysis, the 1-knot hazard spline model was selected as it represented a reasonable balance of OS expectations between clinical experts, and producing the closest value to ■% at 10 years stated by the first clinical expert. It also provided a fairly good overall relative statistical fit (1 AIC point difference from the lowest, 4.7 BIC point difference from the lowest) and a slightly better visual fit to the observed data compared to the log-normal distribution (which appeared to slightly underpredict the tail of the observed data), in addition to producing an appropriate hazard profile in relation to that implied by the observed data. Similar to the BRCaM population, scenario analyses were then conducted using models that provided the best statistical fits among models representative of the approximate lower and upper bound expectations across the clinical expert feedback collected (log-normal and generalised gamma, respectively).

J1.2.3 Time to treatment discontinuation

The time to treatment discontinuation or death (TTDD) niraparib KM curve for the BRCAwt population in PRIMA is shown in xxxxxx ■.

[REDACTED]

[REDACTED]

Abbreviations: CI = confidence interval; HR = hazard ratio

AIC and BIC estimates for the niraparib TTDD distributions are shown in Table 164.

Table 164. AIC and BIC Estimates for niraparib TTDD distribution fits for the BRCAwt population

Distribution	NIRA	
	AIC	BIC
Exponential	2276.5	2280.3
Weibull (PH)	2267.0	2274.5

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Distribution	NIRA	
	AIC	BIC
Gompertz	2246.0	2253.4
Log-logistic	2228.7	2236.1
Log-normal	2230.0	2237.4
Gamma	2274.2	2281.7
Generalised Gamma	2231.8	2243.0

Abbreviations: AIC = Akaike information criterion; BIC = Bayesian information criterion; NIRA = niraparib

Classifications of relative AIC and BIC statistical fit are presented in Table 165.

Among the standard parametric models explored, the log-logistic distribution produced the best statistical fit with the lowest AIC and BIC values. The log-normal and generalised gamma distributions also provided a reasonable statistical fit based on both AIC and BIC criteria. All other distributions showed a poor statistical fit, with their AIC and BIC values differing by more than 10 from the log-logistic distribution.

Table 165. AIC and BIC Goodness-of-Fit per standard parametric distribution relative to the distribution with the lowest AIC and BIC for niraparib TTDD (BRCAwt) - PRIMA

Distribution	Difference from lowest AIC	AIC relative goodness-of-fit classification	Difference from lowest BIC	BIC relative goodness-of-fit classification
Exponential	47.8	Poor (>10 difference)	44.2	Poor (>10 difference)
Weibull (PH)	38.3	Poor (>10 difference)	38.4	Poor (>10 difference)
Gompertz	17.3	Poor (>10 difference)	17.3	Poor (>10 difference)
Log-logistic	Lowest AIC	Reference	Lowest AIC	Reference
Log-normal	1.3	Reasonable (0-7 difference)	1.3	Reasonable (0-7 difference)

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Distribution	Difference from lowest AIC	AIC relative goodness-of-fit classification	Difference from lowest BIC	BIC relative goodness-of-fit classification
Gamma	45.5	Poor (>10 difference)	45.6	Poor (>10 difference)
Generalised Gamma	3.1	Reasonable (0-7 difference)	6.9	Reasonable (0-7 difference)

Abbreviations: AIC = Akaike information criterion; BIC = Bayesian information criterion

The fitted independent standard survival parametric curves were overlaid on the NIRA BRCAwt KM TTDD curve and are shown in xxxxxx . The Gompertz, log-logistic, log-normal, and generalised gamma models all produced fairly reasonable and similar visual fits to most of the KM curve. In contrast, the Weibull, exponential, and gamma models produced poor visual fits, generally overpredicting the KM curve between 10-25 months while underpredicting from around the 40th month onwards.



Time (in months)

— Exponential — Gompertz — Log-normal — Generalized Gamma
— Weibull(PH) — Log-logistic — Gamma

Although the PRIMA trial showed that some patients continued on NIRA beyond the maximum treatment duration of 36 months specified within the label, UK clinical experts indicated that they expected only a small proportion of patients to continue on NIRA after 36 months in UK clinical practice. Therefore, as for the BRCAm population, 90% of patients were assumed to discontinue niraparib after 36 months, with the remainder continuing on the selected TTDD extrapolation. Further details on this topic are discussed in Section 3.4.7.

Due to the expectation of discontinuation of NIRA by at least 83 months, and the lack of need to extrapolate beyond the observed data, statistical fit and visual fit of the parametric models for NIRA TTDD was used as the primary selection criteria, in line with NICE DSU TSD14 guidance⁹⁹ on selection criteria in the presence of complete Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

survival data. However, given that none of the models produced particularly strong visual fits to the data (with all models slightly underpredicting parts of the middle of the KM curve), TTDD was modeled using the available KM data combined with the best statistically fitting parametric model (exponential) where required for scenarios requiring extrapolation beyond the available 83 months of follow-up data from PRIMA.

As part of scenario analyses and similar to the BRCAm population, niraparib TTDD for BRCAwt patients was also modeled using the available KM data from SACT. Based on the AIC/BIC estimates (Table 166), the generalised gamma model provided the best statistical fit to the data.

Table 166. AIC and BIC Estimates for TTDD distribution fits for the BRCAwt population for niraparib - SACT

Distribution	AIC	BIC
Exponential	14159.0	14164.9
Weibull (PH)	14157.9	14169.7
Gompertz	14147.0	14158.8
Log-logistic	14014.5	14026.3
Log-normal	13927.1	13938.9
Gamma	14144.0	14155.8
Generalised Gamma	13917.6	13935.3

Abbreviations: AIC = Akaike information criterion; BIC = Bayesian information criterion

Fitted independent standard survival parametric curve are overlaid on the NIRA SACT BRCAwt KM TTDD curve in xxxxxx . Although log-normal, log-logistic and generalised gamma models provided reasonable visual fits to most of the observed data, they also provided clear overpredictions of the tail of the KM curve after approximately 36 months. Remaining models tended to slightly overpredict the KM curve between approximately 5 and 15 months before underpredicting the KM curve between approximately 25 to 35 months.

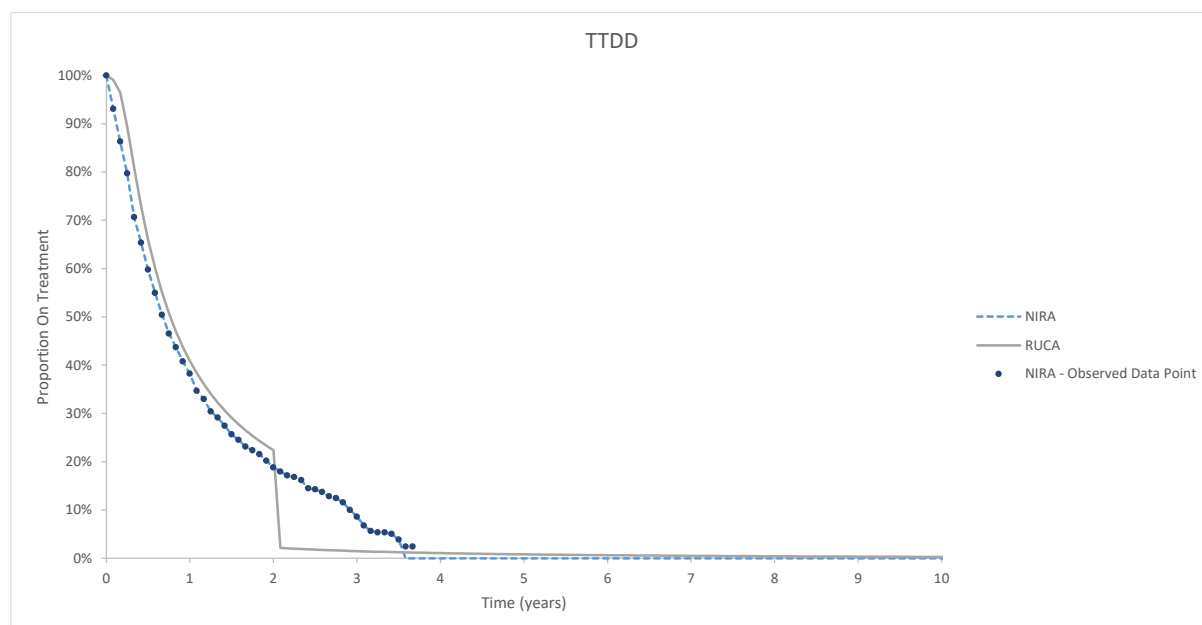


In line with the approaches adopted for other TTDD extrapolations, and given that none of the standard models provided particularly strong visual fits to the observed data, the available KM data was used in combination with the best statistically fitting parametric model (generalised gamma model) where required for extrapolation for the SACT TTDD scenarios for the BRCAwt population.

The following figures (xxxxxx ■■■, Figure 88, ■■■■■■■■■■, xxxxxx 90x) outline the TTDD extrapolations for the various scenarios of niraparib and rucaparib in the BRCAwt population (as outlined in Section 3.4.7).



Figure 88. Niraparib SACT TTDD curve until 42 months, then assume all patients discontinue



Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Appendix K: Detailed niraparib dosing approach used in scenario analyses

K1.1 BRCAm Population

xxxxxx [REDACTED] and Table 167 outline the detailed dosing distribution for the BRCAm population from PRIMA for the detailed cycle dosing scenario analysis.

[REDACTED]

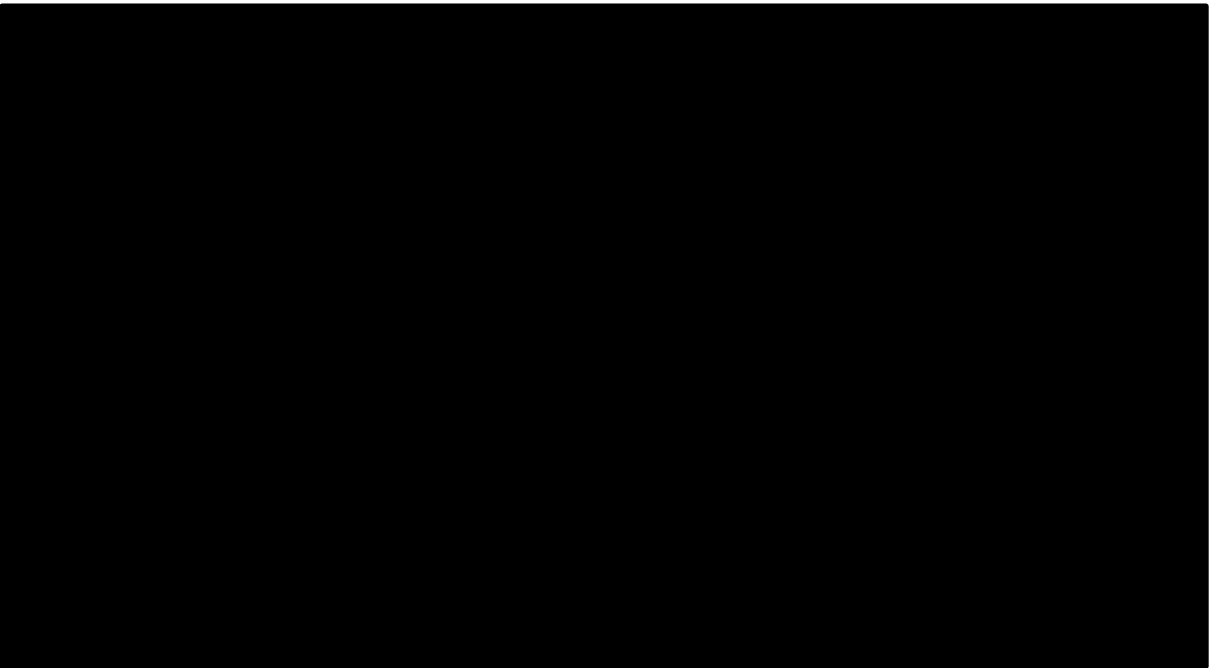


Table 167. Detailed niraparib dosing distribution for BRCAm population

	Proportion receiving alternate doses		
Month	100.00 mg dose	200.00 mg dose	300.00 mg dose
0	[REDACTED]	[REDACTED]	[REDACTED]
1	[REDACTED]	[REDACTED]	[REDACTED]
2	[REDACTED]	[REDACTED]	[REDACTED]
3	[REDACTED]	[REDACTED]	[REDACTED]
4	[REDACTED]	[REDACTED]	[REDACTED]
5	[REDACTED]	[REDACTED]	[REDACTED]
6	[REDACTED]	[REDACTED]	[REDACTED]
7	[REDACTED]	[REDACTED]	[REDACTED]
8	[REDACTED]	[REDACTED]	[REDACTED]

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

	Proportion receiving alternate doses		
Month	100.00 mg dose	200.00 mg dose	300.00 mg dose
9			
10			
11			
12			
13			
14			
15			
16			
17			
18			
19			
20			
21			
22			
23			
24			
25			
26			
27			
28			
29			
30			
31			
32			
33			
34			
35			
36			
37			
38			
39			
40			
41			
42			
43			
44			
45			
46			

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

	Proportion receiving alternate doses		
Month	100.00 mg dose	200.00 mg dose	300.00 mg dose
47			
48			
49			
50			
51			
52			
53			
54			
55			
56			
57			
58			
59			
60			
61			
62			
63			
64			
65			
66			
67			
68			
69			
70			
71			
72			
73			
74			
75			
76			
77			
78			
79			
80			
81			
82			
83			
84			

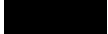
Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

	Proportion receiving alternate doses		
Month	100.00 mg dose	200.00 mg dose	300.00 mg dose
8			
9			
10			
11			
12			
13			
14			
15			
16			
17			
18			
19			
20			
21			
22			
23			
24			
25			
26			
27			
28			
29			
30			
31			
32			
33			
34			
35			
36			
37			
38			
39			
40			
41			
42			
43			
44			
45			

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

	Proportion receiving alternate doses		
Month	100.00 mg dose	200.00 mg dose	300.00 mg dose
46			
47			
48			
49			
50			
51			
52			
53			
54			
55			
56			
57			
58			
59			
60			
61			
62			
63			
64			
65			
66			
67			
68			
69			
70			
71			
72			
73			
74			
75			
76			
77			
78			
79			
80			
81			
82			
83			

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

	Proportion receiving alternate doses		
Month	100.00 mg dose	200.00 mg dose	300.00 mg dose
84			
85			
86			

Appendix L: Base case inputs and assumptions

Table 169 Summary of variables applied in the economic model

Variable	Base case value	Measurement of uncertainty and distribution: confidence interval (distribution)	Justification / source	Reference to section in submission
Model settings				
Perspective	NHS and PSS	---	NICE reference case ¹²⁵	3.3.2
Time horizon	BRCAm: lifetime (■ years) BRCAwt: lifetime (■ years)	---	NICE reference case ¹²⁵	3.3.2
Cycle length	1 month	---		3.3.2
Discount rate for costs	3.5%	---	NICE reference case ¹²⁵	3.3.2
Discount rate for benefits	3.5%	---	NICE reference case ¹²⁵	3.3.2
Population characteristics				
Patients' age at baseline (mean)	BRCAm: ■ years BRCAwt: ■ years	BRCAm: SE= ■ BRCAwt: SE= ■	PRIMA data ^{12,16}	3.4.1
Patients' weight (mean)	BRCAm: ■ kg BRCAwt: ■ kg	BRCAm: SE= ■ BRCAwt: SE= ■	PRIMA data ¹²	3.4.1
BSA (mean)	BRCAm: ■ m ² BRCAwt: ■ m ²	BRCAm: SE= ■ BRCAwt: SE= ■	PRIMA data ^{12,16}	3.4.1
Glomerular Filtration Rate (GFR) (mean)	93.00 mL/min/1.73 m ²	SE= 9.30 (assumption)	NICE TA962 ²⁷ Used for AUC-based dosing calculations	3.4.1
Clinical inputs – BRCAm and BRCAwt populations				

Variable	Base case value	Measurement of uncertainty and distribution: confidence interval (distribution)	Justification / source	Reference to section in submission
PFS cure landmark (% cured)	10 years (100% cured)	---	Clinical expert feedback ¹⁰	3.4.2
Background mortality	UK general population lifetables	---	UK Office National Statistics ²⁰⁶	3.4.2
Clinical inputs – BRCAm population				
PFS parametric fit - niraparib	Generalised gamma	Multivariate normal / Cholesky	PRIMA data ¹⁶ Appropriate fit in terms of AIC/BIC, validated with clinical experts	3.4.4
PFS HR - olaparib	HR: 1.00 (i.e. equivalence)	Log-normal	Bucher ITC of PRIMA data ¹⁶ vs SOLO-1 ¹⁷	3.4.6
OS parametric fit - niraparib	1-knot normal spline	Multivariate normal / Cholesky	PRIMA data ^{12,16} Appropriate fit in terms of AIC/BIC, validated with clinical experts	3.4.5
OS HR - olaparib	HR: 1.00 (i.e. equivalence)	Log-normal	Supported by SACT OS Olaparib data comparison	3.4.6
OS HR (vs age-sex general population mortality) cured patients	1.26	Log-normal	Mai 2009 ²⁰⁷ , in line with NICE TA946 ⁷⁰ and TA962 ²⁷	3.4.2
TTDD modelling - niraparib	KM + exponential	Multivariate normal / Cholesky	PRIMA data ¹⁶ . Expected shorter-term cut off point for niraparib; best AIC/BIC distribution; extrapolation beyond observed data may not be used.	3.4.7
TTDD niraparib: maximum treatment duration	36 months	---	Clinical expert feedback ¹⁰	3.4.7
TTDD niraparib: proportion patients discontinuing at stopping rule	90.0%	---	Clinical expert feedback ¹⁰	3.4.7

Variable	Base case value	Measurement of uncertainty and distribution: confidence interval (distribution)	Justification / source	Reference to section in submission
TTDD modelling - olaparib	Generated via PFS and AE discontinuation	---	SOLO-1 data (DiSilvestro 2023) ¹⁷	3.4.7
TTDD olaparib: maximum treatment duration	24 months	---	Based on product labels and prior NICE TA962 ²⁷	3.4.7
TTDD olaparib: proportion patients discontinuing at stopping rule	90.0%	---	Clinical expert feedback ¹⁰	3.4.7
AE olaparib discontinuation probability	11.92%	Beta (based on n = 260)	SOLO-1 data (DiSilvestro 2023) ¹⁷	3.4.10
AE incidence – niraparib	Anaemia: 9.80% Hypertension: 15.20% Neutrophil count decrease: 7.70% Platelet count decrease: 10.95%	Beta distributions	NIRA RWE (MONITOR-UK). ²⁵ Grade 3+ AEs with at least 5% incidence. MONITOR-UK reflective of NIRA toxicity observed in UK practice.	3.4.10
AE incidence - olaparib	Anaemia: 21.92% Neutropenia: 8.46% Thrombocytopenia: 0.77%	Beta distributions	SOLO-1 data (DiSilvestro 2023). ¹⁷ Grade 3+ AEs with at least 5% incidence.	3.4.10
Clinical inputs – BRCAwt population				
PFS parametric fit - niraparib	Generalised gamma	Multivariate normal / Cholesky	PRIMA data ¹⁶ . Appropriate fit in terms of AIC/BIC, validated with clinical experts	3.4.4
PFS HR - rucaparib	HR: 1.00 (i.e. equivalence)	Log-normal	Bucher ITC of PRIME data ¹⁶ vs ATHENA-MONO ¹⁴	3.4.6
OS parametric fit - niraparib	1-knot hazard spline	Multivariate normal / Cholesky	PRIMA data ¹⁶ . Appropriate fit in terms of AIC/BIC, validated with clinical experts	3.4.5

Variable	Base case value	Measurement of uncertainty and distribution: confidence interval (distribution)	Justification / source	Reference to section in submission
OS HR - rucaparib	HR: 1.00 (i.e. equivalence)	Log-normal	Bucher ITC of PRIME data ¹⁶ vs ATHENA-MONO ¹⁴	3.4.6
OS HR (vs age-sex general population mortality) cured patients	1.00	Log-normal	Aligned with TA1055 ²⁸ . Absence of data of excess mortality in BRCAwt population.	3.4.2
TTDD modelling - niraparib	KM + log-logistic	Multivariate normal / Cholesky	PRIMA data ¹⁶ . Expected shorter-term cut off point for niraparib; best AIC/BIC distribution; extrapolation beyond observed data may not be used.	3.4.7
TTDD niraparib: maximum treatment duration	36 months	---	Clinical expert feedback ¹⁰	3.4.7
TTDD niraparib: proportion patients discontinuing at stopping rule	90.0%	---	Clinical expert feedback ¹⁰	3.4.7
TTDD modelling - rucaparib	Generated via PFS and AE discontinuation	---	ATHENA-MONO data (Monk et al 2022) ¹⁴	3.4.7
TTDD rucaparib: maximum treatment duration	24 months	---	Based on product labels and prior NICE TA1055 ²⁸	3.4.7
TTDD rucaparib: proportion patients discontinuing at stopping rule	90.0%	---	Clinical expert feedback ¹⁰	3.4.7
AE rucaparib discontinuation probability	11.76%	Beta (based on n = 425)	ATHENA-MONO data (Monk et al 2022) ¹⁴	3.4.10
AE incidence – niraparib	Anaemia: 9.80% Hypertension: 15.20%	Beta distributions	NIRA RWE (MONITOR-UK). Grade 3+ AEs with at least 5% incidence. MONITOR-UK	3.4.10

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Variable	Base case value	Measurement of uncertainty and distribution: confidence interval (distribution)	Justification / source	Reference to section in submission
	Neutrophil count decrease: 7.70% Platelet count decrease: 10.95%		reflective of NIRA toxicity observed in UK practice.	
AE incidence - rucaparib	Anaemia: 28.71% Increased ALT/AST: 10.59% Neutropenia: 14.59% Thrombocytopenia: 7.06%	Beta distributions	ATHENA-MONO data (Monk et al 2022) ¹⁴ Grade 3+ AEs with at least 5% incidence.	3.4.10
Cost inputs – BRCam and BRCAwt populations				
Drug wastage (initial and subsequent treatment)	100%	---	Assumption	3.6.1
Drug administration costs (initial and subsequent treatment)	Deliver simple parenteral chemo at first attendance (SB12Z): £133.00 Deliver more complex parenteral chemo at first attendance (SB13Z): £184.00 Deliver complex chemo, including prolonged infusional treatment, at first attendance (SB14Z): £337.00 Deliver subsequent elements of a chemo cycle (SB15Z): £198.00	SE assumption (10% of mean)	NHS reference costs 2023/24. Cost codes aligned with TA946 ⁷⁰ , TA962 ²⁷ and TA1055 ²⁸	3.6.1
AE unit cost	Anaemia: £802.00 Fatigue: £873.32 Hypertension: £759.00 Increased ALT/AST: £15.00 Lymphopenia: £636.47 Neutropenia: £636.47 Neutrophil count decreased: £636.47 Platelet count decreased: £752.58	Gamma SE assumption (10% of mean)	NHS reference costs 2023/24 ¹²⁵	3.6.3

Variable	Base case value	Measurement of uncertainty and distribution: confidence interval (distribution)	Justification / source	Reference to section in submission
	Thrombocytopenia: £752.58			
Follow-up and monitoring costs: unit costs	Outpatient specialist visits (WF01A): £191.00 Complete blood counts (PATH05): £7.66 CT-scans (RD20A – RD27Z): £110.42	---	NHS reference costs 2023/24 ¹²⁵ Cost codes aligned with prior NICE appraisals.	3.6.2
Follow-up and monitoring costs: Health care resource use – additional one-off monitoring - niraparib	Complete blood count: 2.67 Summary additional one-off monitoring cost (1 st cycle): £20.43	Gamma SE assumption (10% of mean)	UK SMPC ^{24,71}	3.6.2
Follow-up and monitoring costs: Health care resource use – progression free on treatment	Outpatient specialist visits: 1.33 monthly Complete blood counts: 1.33 monthly CT-scans: 0.17 monthly Summary progression free - on treatment: £283.32	Gamma SE assumption (10% of mean)	NICE TA1055 ²⁸ and NICE TA946 ⁷⁰	3.6.2
Follow-up and monitoring costs: Health care resource use – progression free off treatment	Outpatient specialist visits: 0.33 monthly Complete blood counts: 0.33 monthly CT-scans: 0.08 monthly Summary progression free - off treatment: £75.39	Gamma SE assumption (10% of mean)	NICE TA1055 ²⁸ and NICE TA946 ⁷⁰	3.6.2
Follow-up and monitoring costs: Health care resource use – progressed	Outpatient specialist visits: 1.33 monthly Complete blood counts: 1.33 monthly CT-scans: 0.33 monthly	Gamma SE assumption (10% of mean)	NICE TA1055 ²⁸ and NICE TA946 ⁷⁰	3.6.2

Variable	Base case value	Measurement of uncertainty and distribution: confidence interval (distribution)	Justification / source	Reference to section in submission
	Summary progression free - on treatment: £301.65			
Follow-up and monitoring costs: Progression free on treatment stopping rule	7 years	Gamma SE assumption (10% of mean)	NICE TA962 ²⁷ and NICE TA946 ⁷⁰	3.6.2
Terminal care costs: unit cost	£9,248.28	Gamma SE assumption (10% of mean)	Guest 2006 ¹²⁸ inflated to 2024 costs from value used in NICE TA946/TA962 ^{27,70}	3.6.5
Terminal care costs: proportion of patients receiving end-of-life care	51.3%	Beta SE assumption (10% of mean)	Gao 2013 ¹²⁹ . Aligned with all recent NICE PARPi re-appraisals ^{27,28,70}	3.6.5
Cost inputs – BRCa population				
Relative dose intensity - niraparib	200mg: █████% 300mg: █████%	---	PRIMA data ¹⁶	3.6.1
Proportion receiving - niraparib	200mg: 86.67% 300mg: 13.33%	---	SACT ¹⁹	3.6.1
Relative dose intensity - olaparib	100%	---	Assumption based on flat pricing for olaparib	3.6.1
Distribution subsequent treatment costs (duration in months)	2L+: Carboplatin: █████ (5.0) Cisplatin: █████ (5.0) Cyclophosphamide: █████ (5.0) Paclitaxel: █████ (5.0) Doxorubicin (PLD): █████ (6.0) Gemcitabine: █████ (5.0) 3L+:	Gamma SE assumption (10% of mean)	PRIMA data ¹⁶ and UK clinical experts. NICE TA946 ⁷⁰ and TA1055 ²⁸ and UK clinical experts.	3.6.4

Variable	Base case value	Measurement of uncertainty and distribution: confidence interval (distribution)	Justification / source	Reference to section in submission
	Carboplatin: [REDACTED] (4.14) Cisplatin: [REDACTED] (5.0) Cyclophosphamide: [REDACTED] (5.0) Paclitaxel: [REDACTED] (5.0) Doxorubicin (PLD): [REDACTED] Gemcitabine: [REDACTED] (5.0) Total cost of subsequent treatment 2L first progression: £5,444.25 3L+ second progression: £4,646.92			
Distribution subsequent treatment costs – proportion 2L patients with 3L+ treatment	Niraparib: [REDACTED]% Olaparib: [REDACTED]%	Beta SE assumption (10% of mean)	PRIMA data ¹⁶ Calculated as the proportion of first progression patients with a second progression. Olaparib assumed equal to niraparib.	3.6.4
Cost inputs – BRCAwt population				
Relative dose intensity - niraparib	200mg: [REDACTED]% 300mg: [REDACTED]%	---	PRIMA data ¹⁶	3.6.1
Proportion receiving - niraparib	200mg: 83.25% 300mg: 16.75%	---	SACT ¹⁹	3.6.1
Relative dose intensity - rucaparib	100%	---	Assumption based on flat pricing for olaparib	3.6.1
Distribution subsequent treatment costs (duration in months)	2L+: Carboplatin: [REDACTED] (5.0) Cisplatin: [REDACTED] Cyclophosphamide: [REDACTED] (5.0)	Gamma SE assumption (10% of mean)	PRIMA data ¹⁶ and UK clinical experts. NICE TA946 ⁷⁰ and TA1055 ²⁸ and UK clinical experts.	3.6.4

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

Variable	Base case value	Measurement of uncertainty and distribution: confidence interval (distribution)	Justification / source	Reference to section in submission
	Paclitaxel: [REDACTED] (5.0) Doxorubicin (PLD): [REDACTED] (6.0) Gemcitabine: [REDACTED] (5.0) 3L+: Carboplatin: [REDACTED] (4.14) Cisplatin: [REDACTED]% (5.0) Cyclophosphamide: [REDACTED] (5.0) Paclitaxel: [REDACTED] (5.0) Doxorubicin (PLD): [REDACTED] (6.0) Gemcitabine: [REDACTED] (5.0) Total cost of subsequent treatment 2L first progression: £4,4713.10 3L+ second progression: £5,026.01			
Distribution subsequent treatment costs – proportion 2L patients with 3L+ treatment	Niraparib: [REDACTED]% Rucaparib: [REDACTED]%	Beta SE assumption (10% of mean)	PRIMA data ¹⁶ . Calculated as the proportion of first progression patients with a second progression. Rucaparib assumed equal to niraparib.	3.6.4
Utility inputs – BRCAm and BRCAwt population				
Utility: Progression free	[REDACTED]	SE = 0.0044	PRIMA data ¹⁶ . EQ-5D-5L responses cross-walked to EQ-5D-3L health state specific utilities. NICE reference case ¹²⁵ Age- adjusted. Reference age: 61.15 years	3.5.5
Utility: Progressed disease	[REDACTED]	SE = 0.0069		3.5.5

Variable	Base case value	Measurement of uncertainty and distribution: confidence interval (distribution)	Justification / source	Reference to section in submission
AE disutility (duration in weeks)	Anaemia: -0.0800 (1.00) Fatigue: -0.1000 (1.31) Hypertension: -0.1300 (1.57) Increased ALT/AST: -0.0900 (1.60) Lymphopenia: -0.1500 (2.29) Neutropenia: -0.0900 (1.33) Neutrophil count decreased: -0.0900 (1.33) Platelet count decreased: -0.0900 (1.33) Thrombocytopenia: -0.0900 (1.33) Summary AE disutility: -0.0012	Beta SE assumption (10% of mean)	NICE TA1055 ²⁸	3.5.4

L1.1 Assumptions

Table 170 provides a summary of the key assumptions used in the economic model.

Table 170. Summary of key assumptions used in the economic model

#	Assumption	Justification
1	The economic model assumes a partitioned survival structure with health states aimed at capturing the key elements of the disease and care pathway of 1L aOC patients, their health outcomes and costs.	Our <i>de novo</i> 3-health state partitioned survival model is enabled to capture the key outcomes from the pivotal trial (PRIMA ^{12,16}), and the main features of the clinical pathway and patient experience within the NHS, while adhering to the principles of model parsimony and transparency. This model structure was selected primarily due to the lack of availability of relevant PFS2 data. While PFS2 is available in PRIMA, relevant high-risk population PFS2 data is not available for the comparators outside of the PRIMA trial, limiting the possibility of adequately parametrising the relative effectiveness for niraparib vs. active comparators. Furthermore, a 3-state PSM is considered

Company evidence submission for niraparib for first-line maintenance treatment of advanced ovarian cancer

#	Assumption	Justification
		sufficient to capture the difference in costs and outcomes between arm given the common treatment pathway regardless of 1L PARPi after the first progression event. (Section 3.3.2)
3	Comparator rucaparib PFS and OS approaches assuming HR = 1 (i.e. equivalence)	An HR = 1 was assumed supported by evidence from a Bucher ITC for PFS-IRC of PRIME (niraparib) vs ATHENA-MONO (rucaparib). ^{14,16} and clinical feedback that there are no clinically meaningful differences between the HRs observed in PRIMA and ATHENA-MONO Bucher ITCs for this comparison and across different subgroups and ITT indicated that OS and PFS benefits were likely to be similar between niraparib and rucaparib, regardless of the biomarker subgroup. Equivalence between treatment was consistently observed across all populations. (Section 3.4.6)
4	Comparator olaparib PFS and OS approaches assuming HR = 1 (i.e. equivalence)	An HR = 1 was assumed supported by evidence from a Bucher ITC for PFS of PRIMA (niraparib) vs SOLO-1 (olaparib). ^{16,17} OS equivalence is supported by SACT data. (Section 3.4.6)
5	Capping OS by PFS data	Niraparib arm OS KM curve from PRIMA trial data ¹⁶ was capped from below by PFS and assumed that long-term OS is driven by the group of patients who remain progression-free long-term. That is, given the cure element being evident (potential plateauing of PFS KM) and the further maturity of PFS relative to OS, the proportion of progression-free / cured individuals drive OS long-term extrapolations (Section 3.4.5)
7	Cure assumption and 10-year cure landmark timepoint	Clinical experts from previous NICE appraisals (TA962 and TA946) ^{27,70} have highlighted the possibility of cure or long-term survival for a small but significant proportion of patients who remain progression-free. UK clinical experts contacted by GSK agreed that a cure is plausible in a PRIMA-like population and across all biomarker subgroups based on BRCA or HR status. All clinical experts concurred that first progression events are highly uncommon after 7-10 years, and uncommon after 5 years. A clinical expert indicated that patients remaining progression-free for around 10 years can be assumed to be cured as it is very unlikely that their disease will come back. (Section 3.4.2)
8	Added risk of death vs general population	For the BRCAm population, general population mortality applied after the cure point was adjusted with evidence from Mai 2009 ²⁰⁷ , in line with NICE TA946 ⁷⁰ and TA962 ²⁷ . For the BRCAwt no evidence was identified relating to the excess mortality in this subpopulation. Following NICE TA1055 ²⁸ , no additional mortality risk versus general population was considered. (Section 3.4.2)
9	TTDD: 90% of patients remaining on treatment were assumed to discontinue niraparib after 36 months, and 90% of olaparib and rucaparib patients after 24 months	Clinical experts feedback that a small proportion of patients would be expected to continue receiving niraparib after 36 months in UK clinical practice, likely limited to patients with visible disease which is extremely rare among those progression-free and responding to treatment after 3 years, with between 5% and 10% continuation expected.

#	Assumption	Justification
		Clinical experts indicated a similar proportion of patients would continue treatment after 2 years with olaparib and rucaparib, with continued use of olaparib after 2 years also observed in SOLO-1 and SACT (Section 3.4.7)
10	Approach to niraparib dosing	The modelling of niraparib dosing considered the proportion of patients starting on 200 mg versus 300 mg and incorporate the relative dose intensity for patients starting on each dose. The distribution provided by the SACT data was seen as the most accurate reflection of UK clinical practice. PRIMA data ¹⁶ and RWE from MONITOR-UK ²⁵ were explored in scenario analysis (Section 3.6.1)
11	RDI parameters for olaparib and rucaparib	RDI estimates were not included in the base case analysis for olaparib and rucaparib, given that lower dosing of these treatments was not anticipated to impact costs given the flat pricing structure for these comparators. A scenario analysis was conducted exploring the impact of using RDI parameters from TA1055 ²⁸ (Section 3.6.1)
12	TTDD for external comparators assumed exchangeable to PFS combined with AE-related discontinuation	TTDD curve was derived using PFS combined with AE-related discontinuation probabilities from the clinical trials (SOLO-1 ¹⁷ for olaparib, ATHENA-MONO ¹⁴ for rucaparib) as this was believed to be more reflective of the comparator treatment discontinuation, given median time on treatment data was only available for rucaparib for the overall ATHENA-MONO population. (Section 3.4.7)
13	AE distributions	AE probabilities for niraparib were informed by data from the MONITOR-UK study. ²⁵ AE data from MONITOR-UK were used given that the starting dose distribution in the MONITOR-UK study was anticipated to be reflective of the use of niraparib in clinical practice, and more similar to that observed in the SACT data used to model niraparib dose distributions for both populations. This approach was validated by two UK clinical experts, who confirmed that the AE frequencies were appropriate, and that MONITOR-UK was reflective of niraparib use in UK clinical practice. For comparators olaparib and rucaparib these were obtained from their respective pivotal trials (SOLO-1 ¹⁷ and ATHENA-MONO ¹⁴ , respectively). (Section 3.4.10)
14	AEs not differentiated by population	Not differentiating AEs by subgroup followed previous TAs (TA946 ⁷⁰ , TA962 ²⁷ , TA1055 ²⁸), where it was accepted by EAGs after companies presented summary evidence confirming similar safety profile across subgroups and/or by clinical advice received from clinical experts to the EAG. (Section 3.4.10)
15	Utility values are independent of treatment and population	Single utility values were applied to the health states regardless of the treatment (i.e., utility values are assumed to remain unchanged regardless of treatment arms), with the same utility values used for both populations of interest. This assumption is in line with clinical advice to the EAG in TA1055 ²⁸ , which highlighted that HRQoL is not likely to differ by subgroups. (Section 3.5.5)
16	Subsequent treatment distributions	Subsequent treatment distributions used for 2L+ and 3L+ were based on PRIMA data ¹⁶ and feedback from UK clinical experts. The proportion of patients receiving subsequent treatment in the niraparib arm of PRIMA were re-weighted to exclude subsequent PARPi use (if used in 1L

#	Assumption	Justification
		maintenance), with clinical experts confirming that the distributions were broadly representative of UK clinical practice (excluding bevacizumab usage). (Section 3.6.4)
17	7-year stopping rule	A 7-year stopping rule for monitoring costs applied to all comparators based on NICE TA962 ²⁷ and NICE TA946 ⁷⁰ . (Section 3.6.2)
18	Exclusion of genetic testing costs	Genetic testing costs were excluded from the analysis as it was assumed that testing is part of routine NHS care and that there would be no differences between PARPi comparators. (Section 3.6.5)

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the National Health Service (NHS) for use in England. It's a plain English summary of their submission written for patients participating in the evaluation. It's not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it's sent to you.

The Summary of Information for Patients template has been adapted for use at NICE from the [Health Technology Assessment International – Patient & Citizens Involvement Group](#) (HTAi PCIG). Information about the development is available in an open-access [IJTAHC journal article](#).

Section 1: submission summary

1a) Name of the medicine

Both generic and brand name.

Generic (brand) name: niraparib (Zejula)

1b) Population this treatment will be used by

Please outline the main patient population that is being appraised by NICE:

Niraparib will be used by adults with advanced (stages III and IV according to the Federation of Gynaecology and Obstetrics), high-grade (fast-growing and aggressive) ovarian, fallopian tube, or primary peritoneal cancer who have responded well (completely or partially) after completing first-line platinum-based chemotherapy.

For simplicity, this group will be referred to as "advanced ovarian cancer" in the following sections.

1c) Authorisation

Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

Niraparib (Zejula), 100 mg film-coated tablets was authorised by the Medicines and Healthcare products Regulatory Agency on 6 December 2022 ([link to the Summary of Product Characteristics](#)).

1d) Disclosures

Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

In 2024, GSK engaged with Ovacom to co-create a non-promotional disease awareness campaign ('Give Us Time Disease Awareness Campaign') and to participate in two patient advisory board meetings. In 2024 and April 2025 Ovacom shared their insights on the needs of the ovarian community at three internal GSK events. Ovacom were paid for their time contributing to this work according to fair market value.

Section 2: current landscape

2a) The condition – clinical presentation and impact

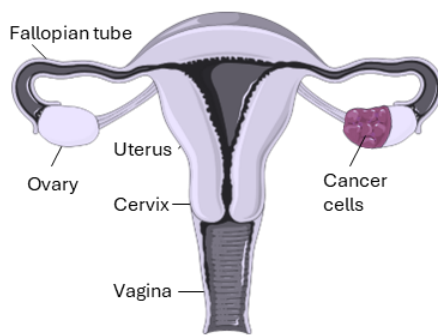
Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

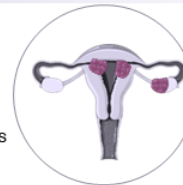
Ovarian cancer overview and its causes:

Ovarian cancer is a term used to describe different types of cancer¹ that affect female reproductive organs, including the ovaries, fallopian tubes, and the peritoneum.² It is classified into four stages (I–IV) defined by the International Federation of Gynaecology and Obstetrics (FIGO), which describe how far the cancer has spread.³ Stages III and IV are considered advanced disease because the cancer has spread beyond the pelvis to other parts of the body.⁴ Ovarian cancer is the sixth most common cancer among women in the United Kingdom.^{5,6} In 2022, there were 7,078 new cases of ovarian cancer, with approximately 60% of these being advanced cases.⁵ Additionally, 19,325 patients were living with ovarian cancer, having been diagnosed within the last five years.⁶

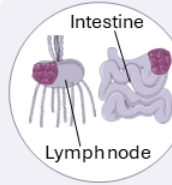
Ovarian cancer overview



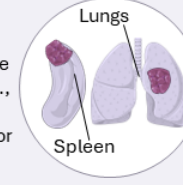
Stage I
Tumour found only in the ovaries or fallopian tubes



Stage II
Tumour has spread to other parts of the pelvis, e.g., uterus



Stage III
Tumour has spread outside the pelvis, e.g., to the nearby lymph nodes or intestines



Stage IV
Tumour has spread beyond the abdomen to distant organs, e.g., lungs or spleen

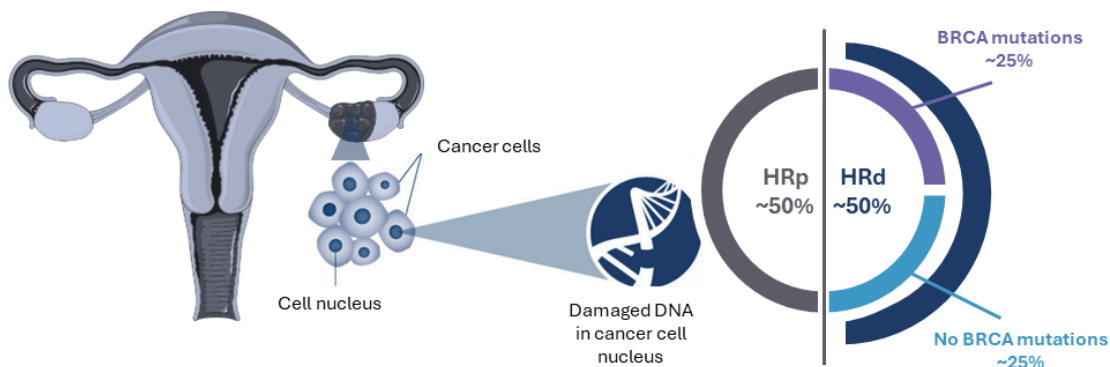
Advanced ovarian cancer



In 2022, there were **7,078** new cases of ovarian cancer, with **61%** of these being advanced cases

The exact causes of ovarian cancer are unknown, however it is estimated that approximately 50% of ovarian cancer cases are the result of abnormalities in how normal cells function.⁷ These abnormal cells are referred to as 'homologous repair deficient', or HRd for short, as they lack certain functions that help them stay healthy.⁷ Patients who do not have HRd are referred to as homologous repair proficient, or HRp for short. The most common reason for a cell being HRd is due to an abnormal BRCA gene, commonly referred to as a BRCA mutation.³⁸ It is estimated that people with harmful BRCA mutations have a 16% to 65% higher risk of getting ovarian cancer, especially the fast-growing type.^{1,9}

Risk factors of ovarian cancer



Mutations in the BRCA genes and homologous recombination deficiency (HRD) increase the risk of developing ovarian cancer. Up to 50% of fast-growing ovarian cancers are homologous recombination deficient, and up to 25% have mutations in the BRCA genes.

Impact of ovarian cancer on patients and their families:

Before the spread of disease, the symptoms of ovarian cancer are usually vague and can resemble those of less serious conditions, which can delay diagnosis.¹⁰⁻¹² The most common symptoms include abdominal or pelvic pain, increased abdominal size or bloating, and changes in bowel habits.¹³

In advanced stages, ovarian cancer significantly affects patients' lives beyond just their physical health.¹⁴ It impacts their emotional, social, and psychological well-being.¹⁴ A survey of UK ovarian cancer patients found that many patients with

advanced disease experience fear and uncertainty, leading to anxiety and depression.¹⁴

Mortality and morbidity of ovarian cancer

Ovarian cancer is a serious and life-threatening disease. In 2022, it caused 4,159 deaths in the United Kingdom, making it the fifth most common cause of cancer-related deaths among women.⁶ How long a patient may live with ovarian cancer depends on many factors, including the stage of the disease, genetic mutations, and whether the tumour can be removed entirely by surgery.¹⁵

Advanced ovarian cancer is rarely curable with current treatments, which include surgery and platinum-based chemotherapy.¹⁶⁻¹⁹ After initial treatment, about 80% of patients experience cancer recurrence which is typically treated with additional chemotherapy.^{3,20} Unfortunately, as the disease comes back treatment with chemotherapy isn't as effective and the benefits do not last as long. It is not uncommon for some people to experience the cancer reoccurring multiple times and having to receive chemotherapy again. The repeated re-occurrence of cancer and repeated treatment with chemotherapy have a large impact on how patients feel and their overall quality of life.

Maintenance treatments, such as niraparib, are used after first-line chemotherapy and their intent is to keep ovarian cancer from returning or worsening. By stopping or delaying the disease, women can live longer without symptoms of their cancer returning or the having to deal with the effects of repeated chemotherapy. Evidence shows that the longer a person lives without disease relapse, the lower the likelihood the cancer will return at all.

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

Ovarian cancer diagnosis

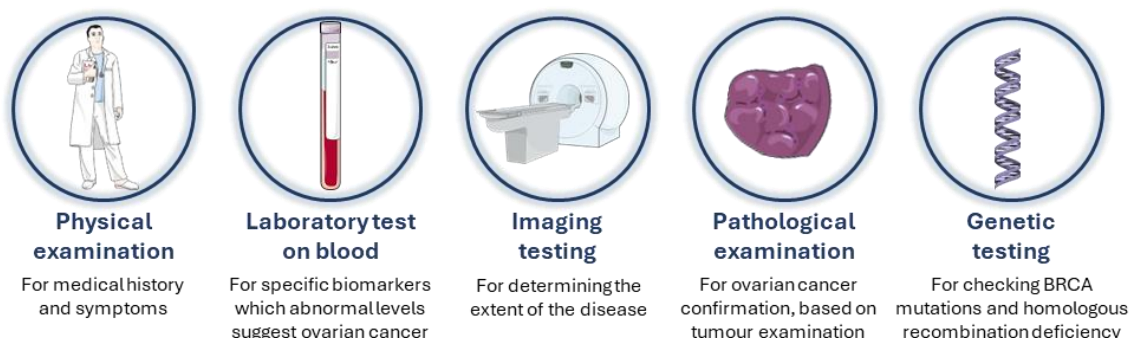
Diagnosing ovarian cancer involves following steps and tests:¹

- **Physical examination and medical history:** The process begins with a thorough physical examination, and the doctor asks detailed questions about the patient's medical history and symptoms that suggest ovarian cancer.
- **Laboratory tests:** Blood tests are conducted to measure specific substances (biomarkers) that can be abnormal in ovarian cancer, including CA-125, CEA, and CA-19-9 (proteins in the blood that help to diagnose and monitor certain cancers).
- **Imaging testing:** Ultrasound and computed tomography (CT) scans are used to get detailed images of the ovaries and other areas. Ultrasounds help detect abnormalities in the ovaries, while CT scans of the chest, abdomen, and pelvis help determine the extent of the disease (staging) and assist in planning surgery.

- **Pathological examination:** To confirm the diagnosis, a sample of the tumour is needed. Pathologists examine a sample of cells under a microscope to confirm if it is ovarian cancer.
- **Genetic testing:** For all patients with fast-growing ovarian cancer, it is recommended to test for genetic mutations in the BRCA genes (BRCAm) and for homologous repair deficiency (HRD). These tests can help in understanding the genetic factors involved and in planning appropriate treatments.

Niraparib treatment does not require any additional diagnostic tests beyond those already performed for diagnosing and staging the cancer.²¹

Ovarian cancer diagnosis



2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
 - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
 - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

Treatment of newly diagnosed patients:

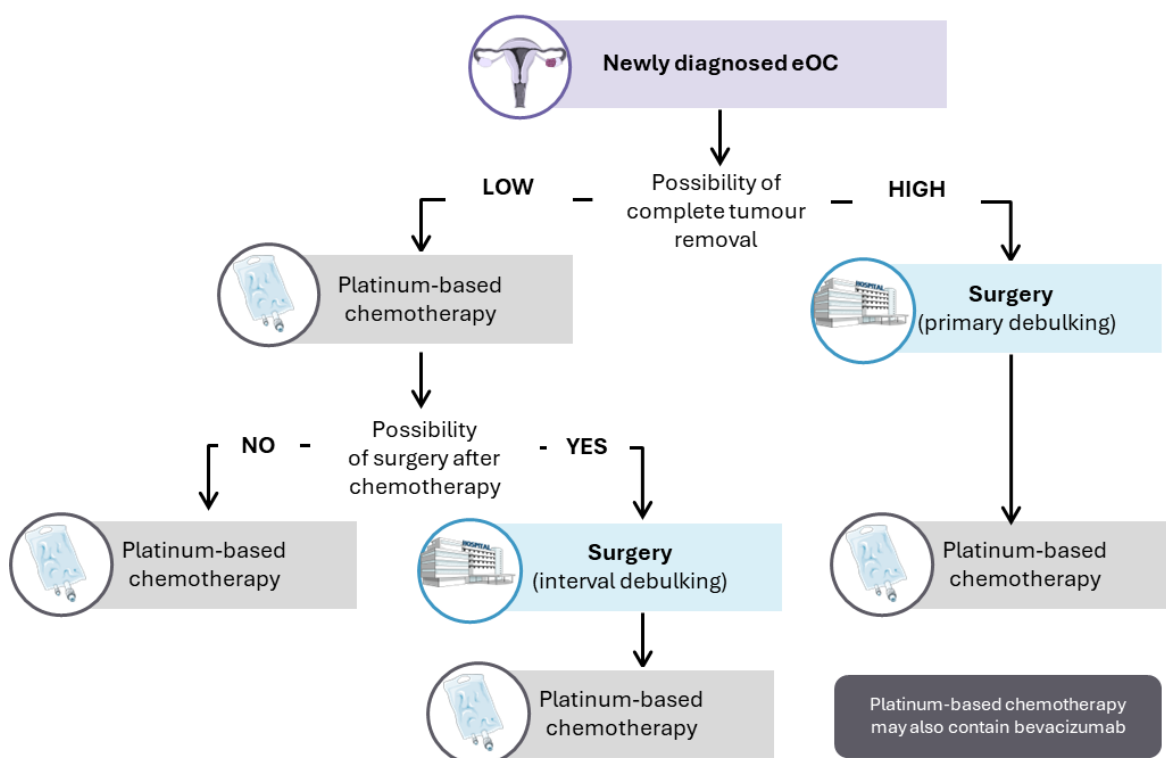
Managing advanced, newly diagnosed ovarian cancer involves a team approach with surgery and platinum-based chemotherapy.^{1,3,22,23} Treatment is tailored based on patient factors such as age, overall health, and the ability to achieve complete tumour removal, and includes:^{1,3}

- **Primary debulking surgery followed by chemotherapy:** This is when patients undergo surgery to completely remove, or remove as much as possible, any visible cancer. Following surgery, patients are then treated with chemotherapy to further damage any cancer cells remaining after the surgery. One course of chemotherapy typically comprises of 6 doses, spaced 3 weeks apart. This is often referred to as '6 cycles' of chemotherapy.
- **Neoadjuvant (given before surgery) chemotherapy followed by interval debulking surgery and chemotherapy:** For patients who may not be good candidates for immediate surgery, some initial chemotherapy can reduce tumour size before surgery, with the goal of making the tumour suitable for surgical removal. After surgery, additional chemotherapy is given to further damage any cancer cells remaining after the surgery.
- **Chemotherapy alone:** For patients who cannot undergo surgery due to advanced disease or other health issues.

The goal of surgical treatment, whether primary or interval, is to remove as much of the tumour as possible. Less disease remaining after surgery is associated with lower risk of relapse and longer life expectancy.^{1,3,22,23}

The standard chemotherapy approach involves the use of a platinum agent (carboplatin or cisplatin) in combination with a taxane (paclitaxel or docetaxel).^{1,3,22,23} Additionally, bevacizumab, which targets blood vessel growth in tumours,¹ can be added to chemotherapy with the aim to improve treatment outcomes in some patients.²⁴

Treatment of newly diagnosed patients with advanced ovarian cancer



Maintenance treatment after first-line therapy:

Maintenance therapy using poly-(ADP)-ribose polymerase inhibitors (PARPi) is now considered the standard care for ovarian cancer.^{1,3,22,23} This type of treatment helps prevent the cancer from coming back after initial chemotherapy.^{1,3,22,23}

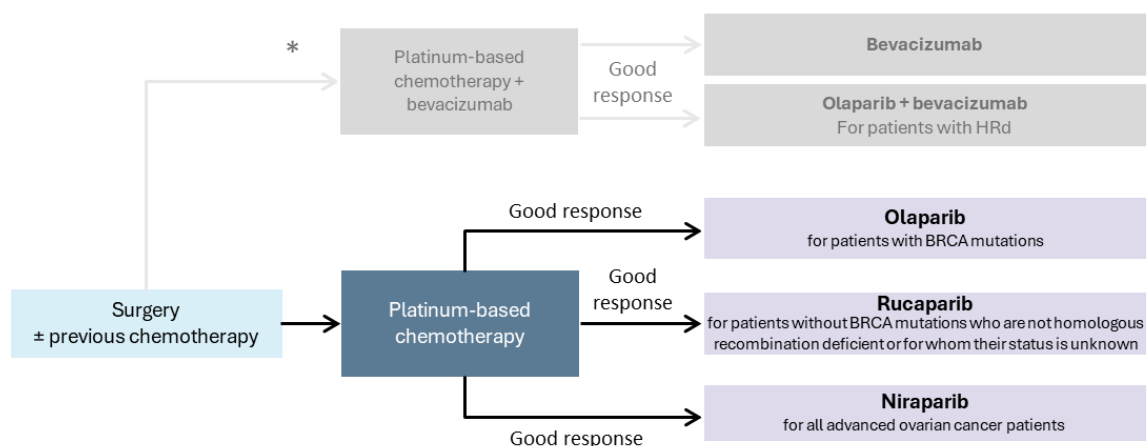
Currently, in England, there are three different PARPis approved as maintenance therapy for advanced ovarian cancer in patients who responded to first-line platinum-based chemotherapy. These drugs are suitable for different patient groups:

- **Olaparib:** recommended only for patients with BRCA mutations²⁵
- **Rucaparib:** recommended for patients without BRCA mutations who are HRd or are HRp or have unknown HRD status, especially if bevacizumab is not an option for them,²⁶
- **Niraparib:** currently available through the Cancer Drugs Fund for maintenance treatment without restrictions related to genetic mutations.²⁷

Some patients who received bevacizumab as part of their initial chemotherapy treatment can also continue to use bevacizumab on its own if they are HRp, or in combination with olaparib as a maintenance treatment if they are HRd.^{24,28,29}

This application is for the continued availability of niraparib as a maintenance treatment for all patients with advanced ovarian cancer under standard reimbursement policies.

Maintenance therapy in advanced ovarian cancer



*Patients who receive bevacizumab as part of their initial chemotherapy can continue to receive bevacizumab or olaparib + bevacizumab as maintenance therapy. Since PARPi monotherapy as maintenance therapy is recommended only for patients who did not receive or could not tolerate bevacizumab during their initial chemotherapy, the bevacizumab treatment pathway is greyed out.

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any

such evidence included in the SIP should be formally referenced wherever possible and references included.

Patient-based evidence:

A survey of 142 UK ovarian cancer patients revealed that they face significant emotional, social, and psychological challenges.¹⁴ The study reported that:

- 58% of patients felt their emotional well-being was severely affected,
- 66% felt it severely impacted their ability to plan for the future,
- 49% reported a severe impact on their personal identity,
- 45% experienced severe impacts on their relationships with a spouse or partner,
- 40% saw significant effects on their family and social life,
- 51% reported severe impacts on sleep.¹⁴

Additionally, more than 70% of patients experienced moderate to severe anxiety and nervousness, 64% felt frightened or angry, 57% felt helpless, and 56% felt numb or empty.¹⁴

Patients' emotional well-being is a major concern after completing first-line treatment for advanced ovarian cancer.³⁰⁻³² The uncertainty about their future health, due to the lack of ongoing treatment, causes significant anxiety and fear for up to 80% of women who worry about the high risk of cancer returning.³⁰⁻³² As a result, many patients prefer receiving maintenance therapy, which is ongoing treatment to help keep the cancer from returning, rather than active surveillance, which involves regular monitoring without any treatment.^{33,34} Maintenance therapy can help limit the psychological impact of disease on patients, with fewer patients who receive maintenance therapy reporting anger and resentment (49% vs 83%), anxiety and nervousness (63% vs 81%), and fear (55% vs 77%) compared with those being actively monitored.¹⁴

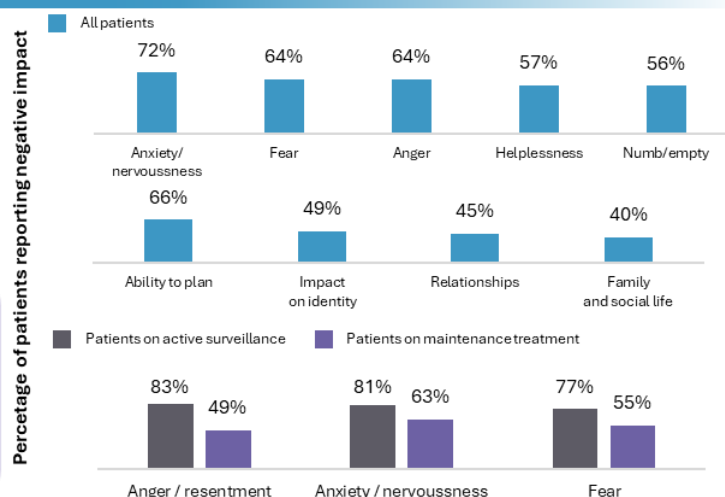
Impact of ovarian cancer on patients



72% of patients with ovarian cancer experience anxiety, **64%** feel fear or anger, **57%** feel helpless, and over **40%** believe that the disease affects their relationships with others.



Patients feel more comfortable when they receive **maintenance therapy** compared to active surveillance, as evidenced by a lower percentage of patients experiencing negative emotional impacts.



Section 3: the treatment

3a) How does the new treatment work? What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

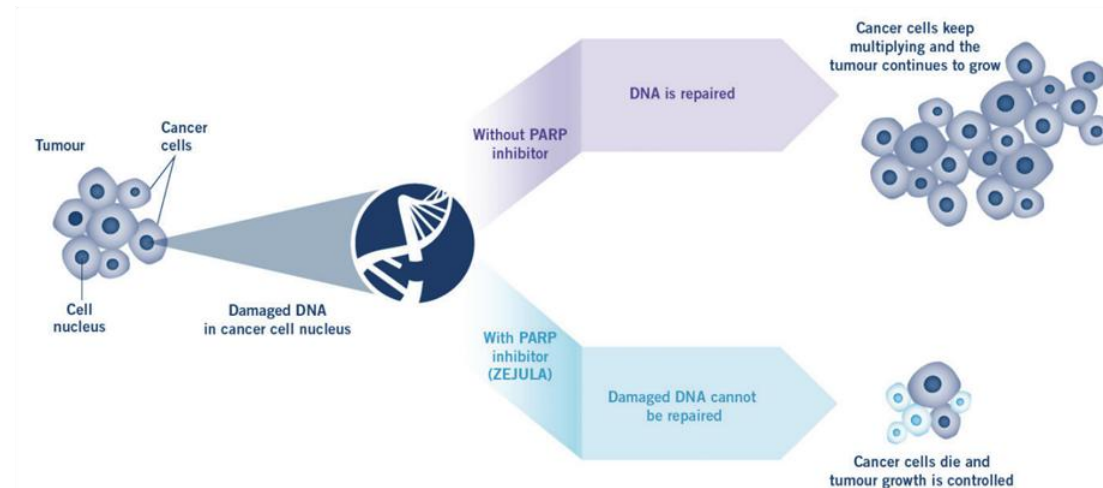
Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

How niraparib works

Niraparib is a type of anti-cancer medicine called a PARP inhibitor. PARP inhibitors block an enzyme called poly [adenosine diphosphate-ribose] polymerase (PARP), which helps cells repair damaged DNA. By blocking PARP, niraparib prevents cancer cells from repairing their DNA, leading to cell death and helping to stop the cancer spreading.²¹ Studies have shown niraparib is effective in causing damage to cancer cells (which can in turn kill them), regardless of whether they have mutations in the BRCA genes or not, and whether they have HRd or not.²¹

Niraparib's mechanism of action



3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

☐ Yes

☒ No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

Not applicable.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

Niraparib administration and dosing:

The starting dose of niraparib depends on the patient's body weight and platelet count in the blood:²¹

- For patients weighing <77 kg or with a baseline platelet count <150,000/ μ L: **200 mg** (two 100-mg tablets) taken orally once daily.
- For patients weighing $\geq$ 77 kg with a baseline platelet count $\geq$ 150,000/ μ L: **300 mg** (three 100-mg tablets) taken orally once daily.

Patients should take their dose at the same time each day, preferably at bedtime, to help manage nausea. If a dose is missed, patients should take the next dose at the usual scheduled time.²¹

Treatment should continue until the disease worsens or returns or side effects become unmanageable. Some PARPis are recommended for a maximum of 2 years, reflecting how they were used in the clinical trials. Niraparib is typically used for up to 3 years, provided that patients do not experience serious side effects or worsening of the cancer.

Side effects can occur as part of treatment but are generally managed with dose adjustments or with interruptions to treatment as necessary; serious side effects may require treatment to be stopped completely.²¹ Some side effects are usually experienced during the initial phase of treatment so it is recommended to monitor for these by testing blood pressure and blood counts over this time.²¹ The general approach to managing side effects involves initially stopping the treatment for up to 28 days to allow recovery, then restarting at the same dose.²¹ If the side effects return, treatment should be stopped again and restarted at a lower dose (as shown below).²¹ If the side effects continue beyond the 28-day break or cannot be managed with these breaks and dose reductions, niraparib needs to be stopped completely.²¹ There are some instances when treatment with niraparib should be discontinued immediately, such as when a person develops blood disorders such as myelodysplastic syndrome/acute myeloid leukaemia (MDS/AML).²¹

The administration method and dosing of niraparib are designed to be straightforward and should not have a negative impact on patients or caregivers.

One advantage of niraparib compared to other PARP inhibitors is its packaging. Niraparib comes in a form that allows easy dose adjustments without the need for different packaging with various doses. This flexibility can simplify treatment management and reduce the treatment burden.

Niraparib dosing

Starting dosing



Body weight
<77 kg

OR



Platelet count
<150,000/ μ L



200 mg
(2x 100-mg tablets)
orally once daily



Body weight
 $\geq$ 77 kg

AND



Platelet count
 $\geq$ 150,000/ μ L



300 mg
(3x 100-mg tablets)
orally once daily

Dose modifications

Starting dose	200 mg (2 tablets)	300 mg (3 tablets)
First dose reduction	100 mg (1 tablet)	200 mg (2 tablets)
Second dose reduction	Stop completely	100 mg (1 tablet)*

*If further dose reduction below 100 mg/day is required, stop completely.

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

Clinical trials for niraparib:

Two clinical trials, **PRIMA** and **PRIME**, were conducted to study niraparib as a maintenance therapy after first-line maintenance treatment for advanced ovarian cancer.

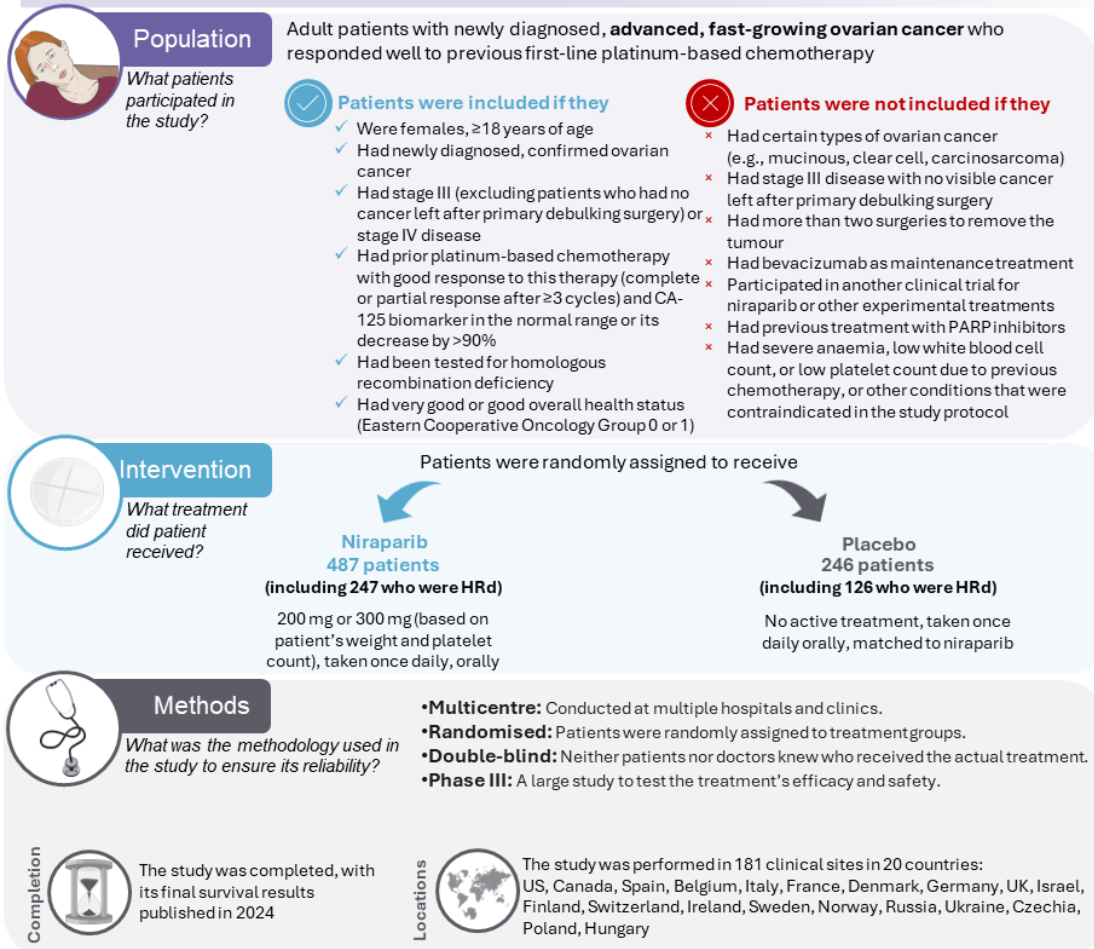
PRIMA was designed to evaluate the effectiveness and safety of niraparib as a maintenance therapy for advanced ovarian cancer.³⁵ The study was a multicentre, randomised, double-blind, placebo-controlled phase III trial.³⁵ This means that it took place at multiple hospitals and clinics, patients were randomly assigned to different treatment groups to avoid bias, and neither patients nor doctors knew which treatment each patient was receiving (niraparib or placebo – no active treatment) to avoid this knowledge influencing results.³⁵

The study included adult women with confirmed advanced (stage III or IV) ovarian cancer who had previously undergone a platinum-based chemotherapy and had responded well to it.³⁵ This trial disproportionately included patients who were at a higher risk of their cancer returning, and excluded some patients who had a lower risk of disease returning (e.g., those who had no signs of disease after surgery).³⁵ A total of 733 patients participated in the study. They were divided into two groups – one group received niraparib (487 patients) and the other group received a placebo (246 patients), which appeared identical to niraparib capsules.³⁵ Among

the participants, 246 patients in the niraparib group and 126 patients in the placebo group had HRd.³⁵

PRIME had very similar methodology to PRIMA and included patients with advanced ovarian cancer, however this trial didn't limit patients joining the trial based on how likely their cancer was to return.³⁶ This study was conducted in China, and 255 patients received niraparib, while 129 patients received a placebo.³⁶

PRIMA clinical trial



3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a.

- Are any of the outcomes more important to patients than others and why?
- Are there any limitations to the data which may affect how to interpret the results?

Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

PRIMA is the key clinical trial to provide evidence for the treatment effect of niraparib as a maintenance therapy for advanced ovarian cancer.³⁵ The main objective of the trial was to investigate how well treatment with niraparib could delay the cancer from returning or worsening (i.e., relapse) following treatment with chemotherapy. Results from the PRIMA study show:³⁵

- Niraparib treatment reduced the rate of disease progression (relapse) or death by 57% specifically in patients with HRd ovarian cancer and by 38% in the total trial population
- Secondary objectives of the trial included investigating if niraparib delayed the need for additional anticancer treatment, and whether patients lived longer overall. Consistent with the primary objective, patients treated with niraparib were able to delay their cancer from getting worse and postpone the need for more treatments compared to those who received placebo. However, the study could not show whether taking niraparib helped patients live longer. This might be because the trial couldn't control how patients were treated when the disease returned, and this can affect how long patients live overall.
- The PRIMA trial also showed that niraparib helped reduce disease progression, irrespective of the BRCA mutation or HRd status.³⁵

The **PRIME** study is very similar to the PRIMA study but includes a broader patient population, which included both higher-risk and lower-risk patients.³⁶ Results from the PRIME study show:³⁶

- Niraparib treatment reduced the rate of disease progression (relapse) or death by 55% in the overall population
- Secondary objectives of the trial included investigating if niraparib delayed the need for anticancer treatment, and whether patients lived longer overall.
- Consistent with the primary objective, treatment with niraparib was shown to delay the need for additional anticancer treatments such as additional chemotherapy.
- The PRIME trial has not yet been running long enough for it to show whether niraparib results in people living longer overall. However, a trend towards benefit with niraparib treatment was observed.

Safety results from the PRIMA and PRIME studies are presented in the response to question 3g.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as patient reported outcomes (PROs).

Please include any patient preference information (PPI) relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

Quality of life results:

In the PRIMA study, several commonly used questionnaires that measure quality of life were completed by patients, including:³⁷

- EORTC-QLQ-C30: assess overall health and quality of life and specific domains and symptoms, as physical functioning, pain or fatigue,
- EORTC-QLQ-OV20: specific for ovarian cancer symptoms, including abdominal/gastrointestinal symptoms, attitude towards disease and treatment, and chemotherapy side effects
- FOSI: measures symptoms and concerns related to ovarian cancer,
- EQ-5D-5L: measures general health status.

During the PRIMA study, the quality of life measured by FOSI did not change much over time in either the niraparib or placebo groups, and the results were similar between the two groups.³⁷ Health-related quality-of-life, as measured by EQ-5D-5L, slightly improved over time in both groups.³⁷ Similarly, there were no differences between the groups in terms of overall quality of life, physical functioning, pain, abdominal symptoms, attitude towards the disease and treatment, and chemotherapy side effects, as measured by the EORTC-QLQ-C30 and EORTC-QLQ-C28 questionnaires.³⁷ However, patients taking niraparib reported less fatigue over time compared to those taking a placebo.³⁷ Overall, data from the PRIMA trial showed that niraparib did not negatively impact patient quality of life.

In the PRIME study, the quality of life of patients was not assessed.³⁶

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could

potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

In the **PRIMA** study, side effects were reported in both groups of patients, as shown in the table below.³⁵ Some patients in either treatment group stopped taking the treatments because of the side effects they experienced.³⁵ The most common side effects experienced by patients receiving niraparib were low number of platelets (thrombocytopenia), low number of red blood cells (anaemia) and feeling sick (nausea).³⁵ The most common side effects in the placebo group were abdominal pain, fatigue and feeling sick (nausea).³⁵

PRIMA clinical trial		Percentage of patients showing side effect	
		Niraparib (n=484)	Placebo (n=244)
Any side effect		99.0%	93.9%
Serious side effect		40.9%	17.6%
Stopped taking the treatment because of side effect		16.3%	3.7%
Common side effects (more than 20% of patients in either treatment group)	Low number of platelets (thrombocytopenia)	67.4%	4.9%
	Low number of red blood cells (anaemia)	65.3%	19.7%
	Nausea	58.3%	29.9%
	Low number of neutrophils (neutropenia) ¹	43.4%	7.8%
	Constipation	41.7%	21.7%
	Fatigue	37.2%	31.3%
	Headache	28.1%	17.2%
	Insomnia	25.6%	15.2%
	Abdominal pain	25.0%	32.8%
	Vomiting	24.4%	13.1%
	Joint pain (arthralgia)	21.7%	25.8%
	Hypertension	20.7%	9.4%
	Difficulty or discomfort in breathing (dyspnoea)	20.2%	15.6%
	Diarrhoea	19.8%	25.0%

Similarly in the **PRIME** study, side effects were reported in both groups of patients, as shown in the table below.³⁶ Some patients in the niraparib and placebo arms stopped taking the treatments because of the side effects they experienced.³⁶ The most common side effects experienced by patients receiving niraparib and placebo were decreased number of neutrophils (neutropenia), decreased number of white blood cells and decreased number of red blood cells (anaemia).³⁶

PRIME clinical trial		Percentage of patients showing side effect	
		Niraparib (n=255)	Placebo (n=129)
Common side effects (more than 20% of patients in either treatment group)	Any side effect	99.2%	93.8%
	Serious side effect	18.8%	8.5%
	Stopped taking the treatment because of side effect	6.7%	5.4%
	Neutrophil count decreased	65.5%	39.5%
	White blood cell count decreased	65.1%	37.2%
	Low red blood cells (anaemia)	57.3%	26.4%
	Platelet count decreased	52.2%	10.1%
	Nausea	44.7%	18.6%
	Aspartate transaminase increased	38.0%	19.4%
	Alanine transaminase increased	36.1%	23.3%
	Insomnia	31.4%	10.9%
	γ-Glutamyl transferase increased	28.6%	17.1%
	Fatigue	27.8%	14.7%
	Constipation	21.2%	8.5%
	Vomiting	20.4%	9.3%

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

Niraparib has key benefits for patients as a maintenance therapy for advanced ovarian cancer. In particular:

Benefits of niraparib as a maintenance therapy



Maintenance treatment with niraparib **reduces the risk of the cancer worsening over time** compared to not receiving maintenance therapy



Maintenance treatment with niraparib **does not worsen the quality of life** for patients compared to not receiving maintenance therapy



Niraparib is **conveniently administered once daily**



Niraparib comes in a form that allows for **dose adjustments** to be made easily without having to dispense different packets with different doses which is unlike other medicines in the same class (PARP inhibitors)



Niraparib shows a treatment benefit across a range of patients with different mutations. This means niraparib can be prescribed to patients regardless of their HRD status. However, other maintenance treatment options are only available for patients with certain mutations, so they cannot be prescribed to everyone, like niraparib.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

It is important to highlight the key disadvantages and considerations regarding niraparib for the maintenance treatment of advanced ovarian cancer. These are listed below:

Disadvantages of niraparib as a maintenance therapy



Niraparib can lead to side effects, including a lowering number of platelets, low number of red blood cells and feeling sick. However, these can be managed with dose interruptions, reductions or discontinuations.

Considerations regarding niraparib as a maintenance therapy



Results from the key PRIMA trial for survival and time to next treatment need to be interpreted with caution because the data did not reach statistical significance. This means that there isn't strong enough evidence to say that the difference between niraparib and placebo is real. It doesn't prove that there is no effect; it just means we can't be confident that there is one based on the data we have.



It is difficult to directly compare niraparib with other maintenance therapy options for advanced ovarian cancer. This is because the PRIMA trial and other treatment trials included patients with different characteristics and the trials were conducted differently. These differences make it hard to determine the treatment effect of niraparib compared to other available treatments.

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes,

addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)

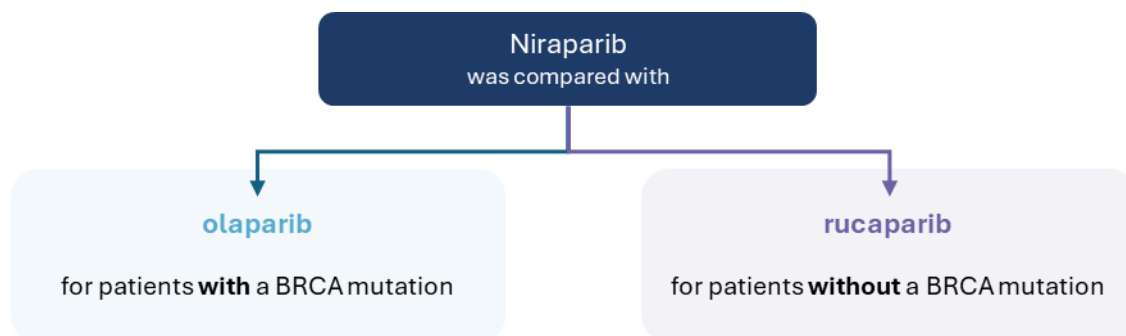
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

Health technology assessment includes economic evaluation to ensure that new treatments provide 'good value for money' compared to other available treatments. To do so, it evaluates how much it costs to treat each patient and how much the patients' health will improve. The company (GSK) provided NICE with the information they need to make this assessment in the form of a health economic model.

How the model reflects advanced ovarian cancer:

The goal of the economic model is to compare the costs and quality of life associated with niraparib to the costs and quality of life associated with other available treatment options. If niraparib maximises survival and quality of life for the amount of money it costs, niraparib is considered 'good value for money'.

To treat ovarian cancer, patients receive different treatments depending on their BRCA mutation. Because of this, the economic model conducted different analyses for patients with different mutations and who received different treatments.



To determine if a treatment is 'good value for money' different outcomes relating to survival, quality of life and side effects were taken from trials and inputted in the model. Data of treatment costs were also added. Different analyses were conducted on these outcomes to predict the treatments cost and impact.

Input and considerations of the economic model



Modelling how much the treatment extends life

Clinical trials collect information about a treatment over a limited time period. In the economic model, this data needed to be projected over a longer period of time to predict the effect of the treatment over the patient's lifetime. To do this:

The economic model used data on:

- How long patients stay alive without their disease worsening (progression-free survival)
- How long patients stay alive (overall survival)



The data was taken from:

- The key clinical trials for niraparib, olaparib and rucaparib



Modelling how much the treatment improves quality of life

In the economic model, quality of life was inputted to understand how treatments impact people's overall well-being and not just their health costs. This ensures that the benefits of the treatment are measured in terms of both improved health and better quality of life.

The economic model used data on:

- A patients' quality of life before, during and slightly after receiving treatment



The data was taken from:

- The key clinical trials for niraparib, olaparib and rucaparib



Modelling side effects of a treatment

Side effects can lead to additional healthcare costs and can influence whether a treatment is 'good value for money'. The economic model therefore accounted for side effects caused by the treatments.

The economic model used data on:

- Side effects experienced by patients when they received treatment



The data was taken from:

- The key clinical trials for niraparib, olaparib and rucaparib
- Data was also used from the MONITOR-UK study where patients received niraparib in a real-world setting



Modelling how cost of treatment differ

To provide an understanding of the total costs associated with treatments, different financial costs were considered. This helps in evaluating the cost-effectiveness and overall financial impact of treatments.

The economic model used data on:

- Drug acquisition and administration costs
- Side effect management costs

- Patient follow-up and monitoring
- Terminal care costs
- Subsequent treatment costs

Uncertainty

- When data from clinical trials are projected beyond the end of observed data (follow-up period), there is uncertainty in the predicted outcomes. This can be due to unpredictable events, changes in data, or random factors.
- To address this, various different analyses were conducted to test the impact of changing variables on results. However, the company determined that there are no specific uncertainties beyond those inherent to any evaluation in advanced ovarian cancer.

Economic analysis

All the above considerations affect whether niraparib represents good value for money and a good use of NHS resources. GSK's economic model predicted that:

The economic model shows

Quality-adjusted life years



Patients with a BRCA mutation (niraparib compared with olaparib)

Niraparib and olaparib had largely equivalent quality-adjusted life years suggesting both treatments provide the same overall value in terms of quality and length of life

Patients without a BRCA mutation (niraparib compared with rucaparib)

Niraparib and rucaparib had largely equivalent quality-adjusted life years suggesting both treatments provide the same overall value in terms of quality and length of life

Cost-effectiveness



Niraparib was associated with cost-savings compared to olaparib

Niraparib was associated with cost-savings compared to rucaparib

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations.

If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Not applicable.

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme

Find more general information about the Equality Act and equalities issues here

Not applicable.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc. Where possible, please provide open access materials or provide copies that patients can access.

Further information on niraparib and other targeted treatments for advanced ovarian cancer:

- Cancer research UK summary of niraparib, including how it works and key side effects: <https://www.cancerresearchuk.org/about-cancer/treatment/drugs/niraparib>
- Cancer research UK summary on targeted cancer drugs for ovarian cancer: <https://www.cancerresearchuk.org/about-cancer/ovarian-cancer/treatment/targeted-cancer-drugs-about>
- Cancer research UK summary on PARP inhibitors: <https://www.cancerresearchuk.org/about-cancer/treatment/targeted-cancer-drugs-immunotherapy/PARP-inhibitors>

Further information on NICE and the role of patients:

- [Public Involvement at NICE](#)
- [NICE's guides and templates for patient involvement in HTAs](#)
- [EFPIA – Working together with patient groups](#) (PDF)
- [National Health Council Value Initiative](#)

4b) Glossary of terms

Term	Definition
Acute Myeloid Leukemia (AML)	A cancer of the blood and bone marrow
BReast CAncer gene mutation (BRCAm)	BRCA refers to two genes, BRCA1 and BRCA2. Mutations in these genes can increase the risk of ovarian cancer.
Cancer antigen (CA)-125	A protein in the blood which can be used to measure and diagnosis certain types of cancer
Cancer antigen (CA)-19-9	A protein in the blood which can be used to measure and diagnosis certain types of cancer

Carcinoembryonic antigen (CEA)	A protein that can be found in the blood which can be used to measure and diagnoses certain types of cancer
Chemotherapy	Treatment for cancer that uses chemical drugs to stop the growth of cancer cells
Clinical trial/clinical study	A type of research study that tests how well new medical treatments work in people.
Eastern Cooperative Oncology Group (ECOG)	A scale used by doctors to assess a patient's level of functioning and ability to look after themselves
Efficacy	The ability of a drug to produce the desired beneficial effect on a disease or illness in a clinical trial.
EORTC-QLQ-C30	A measure used to assess the quality of life of patients with cancer. The questionnaire includes 30 questions that cover aspects such as physical functioning, emotional well-being and overall health
EORTC-QLQ-OV20	A measure used to assess the quality of life of patients with ovarian cancer. The questionnaire includes 20 questions that address symptoms and issues relevant to patients with ovarian cancer, such as, abdominal discomfort, gastrointestinal issues and sexual functioning
EQ-5D-5L	A measure of health-related quality of life. The questionnaire consists of five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), each with five levels of severity (no problems, slight problems, moderate problems, severe problems, and extreme problems)
Functional Ovarian Cancer Symptom Index (FOSI)	A measure designed to assess the symptoms and functional impact of ovarian cancer on patients. The questionnaire helps to measure the severity and frequency of symptoms related to ovarian cancer, such as abdominal pain, bloating, and gastrointestinal issues, and their effects on daily activities and overall quality of life
International Federation of Gynaecology and Obstetrics (FIGO)	A worldwide organisation of professional societies of obstetricians and gynaecologists. FIGO also develops staging systems for gynaecological cancers, such as ovarian cancer, to help determine the extent of cancer spread and guide treatment decisions.
Homologous recombination deficiency (HRD)	A condition where the cell's ability to repair DNA damage through the homologous recombination repair pathway is impaired. This can lead to genomic instability and an increased risk of developing ovarian cancer.

Homologous recombination deficient (HRd)	Positive for HRD
Homologous recombination repair (HRR)	A cellular process that repairs double-strand breaks in DNA. This repair mechanism is essential for preventing mutations that could lead to cancer
Homologous recombination proficient (HRp)	Negative for HRD
Maintenance therapy	A type of treatment that helps prevent the cancer from coming back after initial chemotherapy
Myelodysplastic Syndrome (MDS)	A blood disorder where the bone marrow doesn't make enough healthy blood cells
Overall survival	A measure used in clinical trials to determine the effectiveness of the treatment in prolonging life
Poly(ADP-ribose) polymerase (PARP) inhibitors	PARPs are a family of enzymes involved in DNA repair, which detect breaks in DNA to facilitate the repair process. PARP inhibitors are used in cancer treatment to prevent cancer cells from repairing their DNA and so promoting cell death
Placebo	A substance designed to have no therapeutic value
Platelet	Fragments of large bone marrow cells that help with blood clotting by clumping together.
Platelet count	The calculated number of platelets in a volume of blood. Normal platelet counts are 50 - 450 x 10 ⁹ per litre)
Progression-free survival	A measure used in clinical trials to determine the effectiveness of a treatment in delaying disease progression
Quality of life	The overall enjoyment of life. Many clinical trials assess the effects of cancer and its treatment on the quality of life. These studies measure aspects of an individual's sense of well-being and their ability to carry out activities of daily living.
Side effect (also called adverse event)	An unexpected medical problem that arises during treatment with a medication or other therapy. Side effects may be mild, moderate, or severe.

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

1. González-Martín A, Harter P, Leary A, et al. Newly diagnosed and relapsed epithelial ovarian cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol* 2023;34(10):833-848. (In eng). DOI: 10.1016/j.annonc.2023.07.011.
2. Cancer Research UK. What is ovarian cancer? 25 November 2024 (<https://www.cancerresearchuk.org/about-cancer/ovarian-cancer/what-is-ovarian-cancer>).
3. Berek JS, Renz M, Kehoe S, Kumar L, Friedlander M. Cancer of the ovary, fallopian tube, and peritoneum: 2021 update. *Int J Gynaecol Obstet* 2021;155 Suppl 1(Suppl 1):61-85. (In eng). DOI: 10.1002/ijgo.13878.
4. Cancer Research UK. Stages and grades of ovarian cancer. 5 December 2024 (<https://www.cancerresearchuk.org/about-cancer/ovarian-cancer/stages-grades>).
5. National Disease Registration Service. Cancer incidence and mortality. (https://nhsd-ndrs.shinyapps.io/incidence_and_mortality/).
6. International Agency for Research on Cancer. Global Cancer Observatory: Cancer Today. (<https://gco.iarc.fr/today/en>).
7. Pennington KP, Walsh T, Harrell MI, et al. Germline and somatic mutations in homologous recombination genes predict platinum response and survival in ovarian, fallopian tube, and peritoneal carcinomas. *Clin Cancer Res* 2014;20(3):764-75. (In eng). DOI: 10.1158/1078-0432.Ccr-13-2287.
8. Frey MK, Pothuri B. Homologous recombination deficiency (HRD) testing in ovarian cancer clinical practice: a review of the literature. *Gynecol Oncol Res Pract* 2017;4:4. (In eng). DOI: 10.1186/s40661-017-0039-8.
9. Cancer Genome Atlas Research Network. Integrated genomic analyses of ovarian carcinoma. *Nature* 2011;474(7353):609-15. (In eng). DOI: 10.1038/nature10166.
10. Cancer Research UK. Symptoms of ovarian cancer. 25 November 2024 (<https://www.cancerresearchuk.org/about-cancer/ovarian-cancer/symptoms>).
11. Zakkak N, Barclay ME, Swann R, et al. The presenting symptom signatures of incident cancer: evidence from the English 2018 National Cancer Diagnosis Audit. *Br J Cancer* 2024;130(2):297-307. (In eng). DOI: 10.1038/s41416-023-02507-4.
12. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer. Version 1.2025 — March 5, 2025. 2025 2025.
13. Dilley J, Burnell M, Gentry-Maharaj A, et al. Ovarian cancer symptoms, routes to diagnosis and survival - Population cohort study in the 'no screen' arm of the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS). *Gynecol Oncol* 2020;158(2):316-322. (In eng). DOI: 10.1016/j.ygyno.2020.05.002.
14. Tookman L, Green C, Leonard K, et al. Diagnosis, treatment and burden in advanced ovarian cancer: a UK real-world survey of healthcare professionals and patients. *Future Oncol* 2024;20(23):1657-1673. (In eng). DOI: 10.1080/14796694.2024.2358742.
15. Chase D, Perhanidis J, Gupta D, Kalilani L, Golembesky A, González-Martín A. Association of Multiple High-Risk Factors on Observed Outcomes

- in Real-World Patients With Advanced Ovarian Cancer Treated With First-Line Therapy. *JCO Clin Cancer Inform* 2023;7:e2200189. (In eng). DOI: 10.1200/cci.22.00189.
16. Boubberhan S, Pujade-Lauraine E, Cannistra SA. Advances in the Management of Platinum-Sensitive Relapsed Ovarian Cancer. *Journal of Clinical Oncology* 2019;37(27):2424-2436. DOI: 10.1200/jco.19.00314.
 17. Pitiyarachchi O, Friedlander M, Java JJ, et al. What proportion of patients with stage 3 ovarian cancer are potentially cured following intraperitoneal chemotherapy? Analysis of the long term (≥ 10 years) survivors in NRG/GOG randomized clinical trials of intraperitoneal and intravenous chemotherapy in stage III ovarian cancer. *Gynecol Oncol* 2022;166(3):410-416. (In eng). DOI: 10.1016/j.ygyno.2022.07.004.
 18. Lambert HE, Gregory WM, Nelstrop AE, Rustin GJ. Long-term survival in 463 women treated with platinum analogs for advanced epithelial carcinoma of the ovary: life expectancy compared to women of an age-matched normal population. *Int J Gynecol Cancer* 2004;14(5):772-8. (In eng). DOI: 10.1111/j.1048-891X.2004.014507.x.
 19. GlaxoSmithKline. Meeting report. GSK UK PRIMA CDF Exit Health Technology Assessment Advisory Board. 22 May 2025 2025.
 20. National Cancer Institute. Ovarian Epithelial, Fallopian Tube, and Primary Peritoneal Cancer Treatment (PDQ®)—Health Professional Version. 12 February 2025.
 21. GlaxoSmithKline UK Limited. Zejula 100 mg film-coated tablets. Summary of Product Characteristics (SPC). 4 June 2024 2024.
 22. National Institute for Health and Care Excellence. Ovarian cancer: recognition and initial management. Clinical guideline [CPG122].
 23. National Institute for Health and Care Excellence. Maximal cytoreductive surgery for advanced ovarian cancer. Interventional procedures guidance [IPG757].
 24. NHS England. National Cancer Drugs Fund List. 2025.
 25. National Institute for Health and Care Excellence. Olaparib for maintenance treatment of BRCA mutation-positive advanced ovarian, fallopian tube or peritoneal cancer after response to first-line platinum-based chemotherapy. Technology appraisal guidance [TA962]. 28 March 2024 2024.
 26. 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. Technology appraisal guidance [TA1055]. 9 April 2025 2025.
 27. National Institute for Health and Care Excellence. Niraparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy. Technology appraisal guidance [TA673]. 17 February 2021 2021.
 28. Roche Products Limited. Avastin 25 mg/ml concentrate for solution for infusion. Summary of Product Characteristics (SPC). 4 July 2023 2023.
 29. National Institute for Health and Care Excellence. Olaparib with bevacizumab for maintenance treatment of advanced high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer. Technology appraisal guidance [TA962]. 17 January 2024 2024.
 30. Cesario SK, Nelson LS, Broxson A, Cesario AL. Sword of Damocles cutting through the life stages of women with ovarian cancer. *Oncol Nurs Forum* 2010;37(5):609-17. (In eng). DOI: 10.1188/10.Onf.609-617.

31. Matulonis UA, Kornblith A, Lee H, et al. Long-term adjustment of early-stage ovarian cancer survivors. *Int J Gynecol Cancer* 2008;18(6):1183-93. (In eng). DOI: 10.1111/j.1525-1438.2007.01167.x.
32. Mirabeau-Beale KL, Kornblith AB, Penson RT, et al. Comparison of the quality of life of early and advanced stage ovarian cancer survivors. *Gynecol Oncol* 2009;114(2):353-9. (In eng). DOI: 10.1016/j.ygyno.2009.05.009.
33. Chase DM, Wenzel L. Health-related quality of life in ovarian cancer patients and its impact on clinical management. *Expert Rev Pharmacoecon Outcomes Res* 2011;11(4):421-31. (In eng). DOI: 10.1586/erp.11.41.
34. Reb AM. Transforming the death sentence: elements of hope in women with advanced ovarian cancer. *Oncol Nurs Forum* 2007;34(6):E70-81. (In eng). DOI: 10.1188/07.Onf.E70-e81.
35. González-Martín A, Pothuri B, Vergote I, et al. Niraparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. *N Engl J Med* 2019;381(25):2391-2402. (In eng). DOI: 10.1056/NEJMoa1910962.
36. Li N, Zhu J, Yin R, et al. Treatment With Niraparib Maintenance Therapy in Patients With Newly Diagnosed Advanced Ovarian Cancer: A Phase 3 Randomized Clinical Trial. *JAMA Oncol* 2023;9(9):1230-1237. (In eng). DOI: 10.1001/jamaoncol.2023.2283.
37. Pothuri B, Han S, Chase DM, et al. Health-related quality of life in patients with newly diagnosed advanced ovarian cancer treated with niraparib vs placebo: Results from the phase 3 randomized PRIMA/ENGOT-OV26/GOG-3012 trial. *Gynecol Oncol* 2024;184:168-177. (In eng). DOI: 10.1016/j.ygyno.2024.01.021.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Niraparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy (review of TA673) [ID6403]

Clarification questions

August 2025

File name	Version	Contains confidential information	Date
ID6403 Niraparib EAG clarification questions [CON]	1	Yes	18/08/2025

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

Comparators - bevacizumab

A1. Priority Question. The external assessment group (EAG) notes that no comparisons of niraparib versus olaparib + bevacizumab or niraparib versus bevacizumab are reported in the company submission (CS).

a) Please clarify if the company is seeking a NICE recommendation for niraparib in a similar population to that which rucaparib received in TA1055:

- **BRCA mutation-negative and homologous recombination deficiency (HRD)-positive patients; and**
- **Those with BRCA mutation-negative, and HRD status is negative or unknown, and bevacizumab is not a treatment option.**

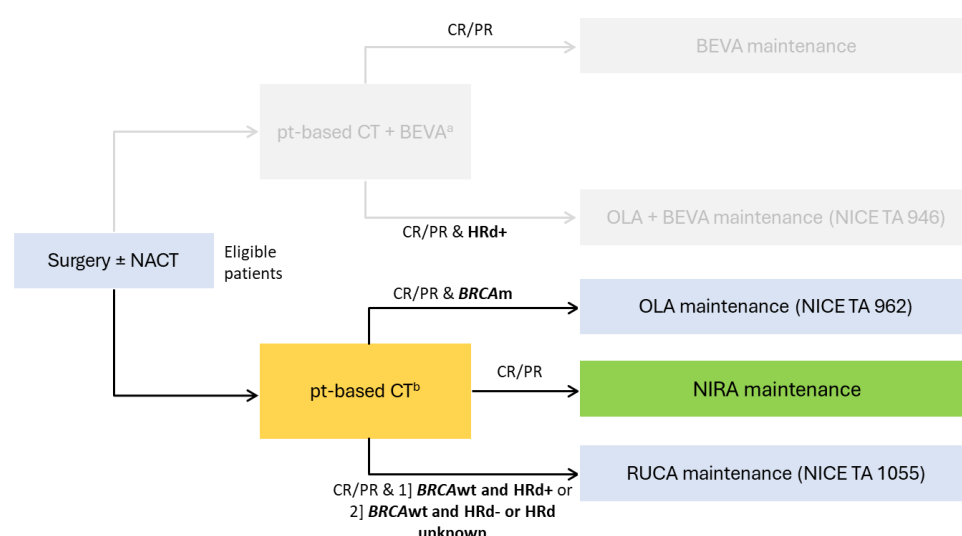
The company is seeking a NICE recommendation for niraparib in line with its licensed indication for maintenance treatment in adults with advanced epithelial (FIGO stages III and IV) high-grade ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response following first-line platinum-based chemotherapy.

This population includes patients regardless of BRCA mutation or HRD status, provided they meet the criteria for platinum response. Therefore, the population for niraparib is broader than that for rucaparib under TA1055, which does not include patients with BRCAm.

Furthermore, the restriction outlined in TA1055 for rucaparib, which limits its use to non-HRD-positive patients who are ineligible for bevacizumab maintenance, aligns with current clinical practice and the treatment pathway for PARPi monotherapies. Therefore, it does not introduce any additional access restrictions for rucaparib in the non-HRD-positive patient population and is reimbursed in the NHS for all BRCA mutation-negative ovarian cancer patients following a response to 1L PBC.¹

As outlined in the submission, PARPi monotherapy is considered for patients who did not receive or were unable to tolerate bevacizumab during induction chemotherapy (Figure 1).

Figure 1. Positioning of PARPi monotherapy in the treatment pathway



Abbreviations: BEVA = bevacizumab; BRCAm, breast cancer gene mutant; BRCAwt, breast cancer gene wildtype; CR/PR = complete response/partial response; CT = chemotherapy; HRd = homologous recombination deficient; NACT = neoadjuvant chemotherapy; NICE = National Institute for Health and Care Excellence; NIRA = Niraparib; OLA = olaparib; PARPi = poly(ADP-ribose) polymerase inhibitor; pt = platinum; RUCA = rucaparib; TA = Technology Appraisal

^a Patients who receive BEVA during induction chemotherapy can then receive BEVA or OLA + BEVA as maintenance therapy. Since PARPi monotherapy as maintenance therapy is recommended only for patients who did not receive or could not tolerate BEVA during induction chemotherapy, the bevacizumab treatment path is greyed out in the figure above.

^b PARPi monotherapy is usually given to patients who do not receive BEVA during induction.

This is further supported by SACT data for niraparib, which shows that the majority of patients had not been exposed to bevacizumab during induction treatment and received platinum-based chemotherapy alone (please see Table 30 in company submission [CS]; pg 108). Furthermore, BEV10 commissioning criteria for bevacizumab as maintenance therapy clearly specifies that bevacizumab monotherapy can only be used following completion of first-line induction chemotherapy in combination with bevacizumab.²

b) If the company is seeking a recommendation from NICE for niraparib use in patients who would currently receive olaparib + bevacizumab and/or bevacizumab maintenance therapy, please conduct analyses and provide results for all relevant outcomes for niraparib versus olaparib + bevacizumab, and niraparib versus bevacizumab in the relevant populations(based on NICE TA946 and the NHS England BEV3 and BEV10 commissioning approval criteria) using data for niraparib from the *PRIMA* trial.

NICE TA946 recommends olaparib in combination with bevacizumab, within its marketing authorisation, as maintenance treatment for adults with advanced (FIGO stages III and IV) high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer that is HRD-positive and has completely or partially responded to *first-line platinum-based chemotherapy with bevacizumab*.³

Similarly, BEV10 commissioning criteria for bevacizumab as maintenance therapy clearly specifies that bevacizumab monotherapy can only be used following completion of first-line induction chemotherapy in combination with bevacizumab.²

Given the distinct treatment pathway for bevacizumab-based maintenance therapies in advanced ovarian cancer (Figure 1), olaparib + bevacizumab and bevacizumab monotherapy are not relevant comparators for niraparib.

A2. If in response to question A1 the company is seeking a recommendation from NICE for niraparib use in patients who would currently receive olaparib + bevacizumab and/or bevacizumab maintenance therapy, please conduct analyses and provide results for all relevant outcomes for niraparib versus olaparib + bevacizumab, and niraparib versus bevacizumab in the relevant populations (based

on NICE TA946 and the NHS England BEV3 and BEV10 commissioning approval criteria) using data for niraparib from the *PRIME* trial.

[Please see response to A1](#)

Comparators - rucaparib

A3. Priority question. In TA1055, analyses were presented in the HRD-positive (homologous recombination deficient [HRd]), and HRD status negative (homologous recombination proficient [HRp]) or HRD unknown subgroups. The EAG appreciates the company's position about the lack of comparability of PRIMA and ATHENA-MONO; however, the EAG requests that the company conduct the following analyses and include its interpretation of the results in light of these concerns.

Please conduct indirect treatment comparisons (ITCs) for niraparib versus rucaparib using data for niraparib from the PRIMA trial and ATHENA-MONO for rucaparib, for the following subgroups (irrespective of BRCA mutation status):

- a) Patients who are HRd. (The EAG notes that there is an imbalance between the 2 trials as far as BRCA status is concerned. The EAG therefore recommends that the company rebalances the PRIMA population for this analysis, for example, using Method of Moments. Alternatively the EAG considers that the company could break randomisation in PRIMA and perform a subgroup analysis using the BRCAwild-type/HRd subgroup from both trials. The EAG's preference would be to avoid breaking randomisation); and
- b) Patients who are HRp or have unknown HRD status. (The EAG notes that there may not be outcomes data available to include the unknown HRD status subgroup from ATHENA-MONO, in which case, please use only the HRp subgroup data from both trials).

Please provide baseline characteristics for patients in the analyses and the results for overall survival (OS), investigator-assessed progression-free survival (PFS), blinded independent central review (BICR) PFS, progression-free survival to second progression (PFS2) and time to first subsequent

therapy (TFST), including the sample sizes, hazard ratio (HR), 95% confidence intervals (95% CIs) and p-value.

As described in the CS, an ITC comparing PRIMA and ATHENA-MONO was not feasible due to the absence of high-risk subgroup data for ATHENA-MONO. The PRIMA trial was designed to include patients with high-risk characteristics, such as a greater proportion of individuals with known prognostic factors for relapse (e.g., stage IV disease and NACT), while specifically excluding patients with stage III disease without VRD following primary debulking surgery—low-risk patients who generally have the best prognosis. In contrast, ATHENA-MONO included these low-risk patients, with a substantially higher proportion of patients having no visible residual disease compared to PRIMA (75% vs. 46%, respectively in the ITT population).^{4,5} Given that clinical risk is a key treatment effect modifier, restricting ITCs based on PRIMA to a high-risk population is essential for valid statistical inference.^{6,7}

A naïve comparison of PFS HRs between PRIMA and ATHENA-MONO indicates no clinically meaningful differences, with any observed variations likely attributable to the exclusion of stage III NVRD patients in the PRIMA trial and the shorter duration of follow-up in ATHENA-MONO. Furthermore, it must be noted that both trials were designed with PFS as the primary endpoint, making it the most reliable outcome for any comparisons. Differences in post-progression treatments and potential unblinding after progression may have introduced bias in secondary outcomes such as PFS2 and OS.

Table 1. Summary of results – PRIMA and ATHENA-MONO

Endpoint	Subgroup	PRIMA ⁸	ATHENA-MONO ^{1,9}
		Niraparib vs placebo (mFU: 73.9 months)	Rucaparib vs. placebo (mFU: 26.1 months/~38 months*)
PFS IA, HR (95% CI)	ITT	0.66 (0.55, 0.78)	0.52 (0.40, 0.68)
	BRCAm	0.43 (0.31, 0.59)	0.40 (0.21, 0.75)
	HRd/BRCAwT	0.67 (0.45, 1.00)	0.58 (0.33, 1.01)
	HRd	0.51 (0.40, 0.66)	0.47 (0.31, 0.72)
	HRp	0.67 (0.50, 0.89)	0.65 (0.45, 0.95)
PFS2, HR (95% CI)	ITT	0.96 (0.79, 1.17)	0.84 (0.63, 1.13)*
	BRCAm	0.90 (0.61, 1.32)	-
	HRd/BRCAwT	0.88 (0.57, 1.36)	0.83 (0.43, 1.60)*

Endpoint	Subgroup	PRIMA ⁸	ATHENA-MONO ^{1,9}
		Niraparib vs placebo (mFU: 73.9 months)	Rucaparib vs. placebo (mFU: 26.1 months/~38 months*)
	HRd	0.87 (0.66, 1.17)	0.75 (0.46, 1.24)*
	HRp	0.90 (0.66, 1.23)	0.77 (0.52, 1.14)*
OS, HR (95% CI)	ITT	1.01 (0.84, 1.23)	0.83 (0.58, 1.17)*
	BRCAm	0.94 (0.63, 1.41)	-
	HRd/BRCAwT	0.97 (0.62, 1.53)	0.61 (0.29, 1.30)*
	HRd	0.95 (0.71, 1.29)	0.84 (0.44, 1.58)*
	HRp	0.93 (0.69, 1.26)	0.75 (0.48, 1.17)*

Abbreviations: BRCAm = breast cancer gene mutation; BRCAwT = breast cancer gene wild type; CI = confidence interval; HR = hazard ratio; HRd = homologous recombination deficient; HRp = homologous recombination proficient; IA = investigator assessed; ITT = intent-to-treat; mFU = median follow-up; OS = overall survival; PFS = progression free survival; PFS2 = progression free survival 2

The PRIME study included both high and low-risk patient groups, allowing comparisons between niraparib and rucaparib in a mixed population. However, the proportions of low- and high-risk patients in both ATHENA- MONO and PRIME are unknown, and individual patient data are unavailable for either study. Consequently, Bucher ITCs, which are unadjusted for population differences, was the only feasible approach.

As noted in Section 2.7.1 of the company submission, there are substantial differences in key prognostic factors/effect modifiers (e.g., ECOG, primary tumour location, histology, BRCAm, response to 1L chemotherapy, CA-125) between PRIME and ATHENA-MONO. These differences generally favoured ATHENA-MONO, except for a higher proportion of BRCAm patients in PRIME. Given the number of limitations, ITCs were conducted across all biomarker subgroups (please see Section 2.7.1 of the company submission and response to A4).

A4. Please conduct ITCs for niraparib versus rucaparib using data for niraparib from the PRIME trial and ATHENA-MONO for rucaparib, for the following subgroups:

- a) Patients who are HRd; and
- b) Patients who are HRp or have unknown HRD status.(The EAG notes that there may not be data available to include the unknown HRD status subgroup

from ATHENA-MONO, in which case, please use only the HRp subgroup data from both trials).

Please provide baseline characteristics for patients in the analyses and results for OS, investigator-assessed PFS, BICR PFS, PFS2 and TFST, including the sample sizes, hazard ratio (HR), 95% confidence intervals (95% CIs) and p-value.

As PRIME is not a GSK sponsored trial it is not possible to access the individual patient-level data (IPD), and therefore we are limited in the ITCs we can conduct. Furthermore, due to the lack of IPD from PRIME, we are unable to provide baseline characteristics by subgroup, as this information is not available in the published data.

Based on the data available in published sources (Li et al., 2023)¹⁰, we have presented Bucher ITCs for the reported subgroups and outcomes in Section 2.7.1 of the company submission (Table 2).

Table 2. Summary of ITCs

Comparisons	Data Source	ITT	HRd	HRd/BRCAwt	BRCAm	HRp
Niraparib vs Rucaparib	ATHENA-MONO [rucaparib] and PRIME [niraparib])	Bucher ITC for PFS-IRC, OS	Bucher ITC for PFS-IRC, OS	Bucher ITC for PFS-IRC ^a	Bucher ITC for PFS-IRC ^a	Bucher ITC for PFS-IRC

Abbreviations: BRCAm = breast cancer mutation; BRCAwt = breast cancer wild type; HRd = homologous recombination deficiency; HRp = homologous recombination proficiency; ITC = indirect treatment comparison; ITT = intent-to-treat; OS = overall survival; PFS-INV = progression-free survival investigator-assessed; PFS-IRC = Progression-free survival indirect review committee-assessed

In addition to these analyses, as requested, the results for Bucher ITCs based on published HRs for niraparib from PRIME and rucaparib from ATHENA-MONO for TFST and investigator-assessed PFS (PFS-INV) are presented below (Table 3). As these additional outcomes are only reported for the ITT population, the analyses have been conducted only for the overall population.

Table 3. Results for Bucher ITC based on PRIME and ATHENA-MONO for PFS-INV and TFST

Outcome	Study	Comparison	HR	95% CI LB	95% CI UB	P-value
PFS-INV	PRIME: ITT	NIRA vs RS	<u>0.47</u>	<u>0.36</u>	<u>0.62</u>	

Outcome	Study	Comparison	HR	95% CI LB	95% CI UB	P-value
	ATHENA-MONO: ITT	RUCA vs RS	0.52	0.40	0.68	
	BUCHER ITC					
TFST	PRIME: ITT	NIRA vs RS	0.45	0.34	0.59	
	ATHENA-MONO: ITT	RUCA vs RS	0.52	0.40	0.67	
	BUCHER ITC					

Abbreviations: BRCaM = breast cancer gene mutation; CI = confidence interval; HR = hazard ratio; ITC = indirect treatment comparison; INV = investigator assessed; ITT = intent-to-treat; LB = lower boundary; NIRA = niraparib; PFS = progression-free survival; RS = routine surveillance; RUCA = rucaparib; UB = upper boundary

Comparators - olaparib

A5. Priority question. The EAG notes that a naïve comparison of the hazard ratio (HR) for investigator-assessed PFS in the ITT population and the high-risk subgroup of SOLO-1 suggests they have similar HRs (0.34 and 0.33, respectively). Please conduct Bucher ITCs for niraparib versus olaparib in the BRCaM population using the ITT population from SOLO-1 and the BRCaM subgroup from PRIMA.

Please provide baseline characteristics for patients in the analyses and the results for OS, investigator-assessed PFS, BICR PFS, PFS2 and TFST, including the sample sizes, hazard ratio (HR), 95% confidence intervals (95% CIs) and p-value.

Given the substantial differences in patient populations, trial designs, baseline characteristics, and endpoints, conducting a Bucher ITC for niraparib versus olaparib using the ITT population from SOLO-1 and the BRCaM subgroup from PRIMA is not methodologically appropriate.

SOLO-1 primarily included a low-risk population, with a substantially higher proportion of patients having no visible residual disease post-surgery compared to PRIMA (75% vs. [REDACTED], respectively in the BRCaM population). Additionally, SOLO-1 had a notably high proportion of patients with favourable ECOG scores (77% had ECOG 0) and disease stage (85% were Stage III).¹¹

It is also important to note that the risk of relapse increases cumulatively with the presence of multiple high-risk factors (e.g., residual disease, Stage IV disease).¹² The

importance of the presence of multiple risk factors is further demonstrated in PAOLA-1 which included a lower proportion of patients with favourable disease characteristics compared to SOLO-1 (e.g., 60% had no visible residual disease and 70% had Stage III disease in the ITT population) and reported outcomes separately for high- and low-risk groups. High-risk BRCAm patients in PAOLA-1 had higher hazard ratios compared to the low-risk patients within the trial, highlighting the impact of cumulative risk factors on treatment outcomes.^{7,8}

A6. Please conduct Bucher ITCs for niraparib versus olaparib in the BRCAm population using the ITT population from SOLO-1 and the BRCAm subgroup from PRIME.

Please provide baseline characteristics for patients in the analyses and the results for OS, investigator-assessed PFS, BICR PFS, PFS2 and TFST, including the sample sizes, hazard ratio (HR), 95% confidence intervals (95% CIs) and p-value.

Unfortunately, IPD from PRIME are not available to facilitate a comparison of baseline characteristics or any outcome other than (BICR) PFS in the BRCAm subgroup. A Bucher ITC of (BICR) PFS between niraparib (using data from the BRCAm subgroup from PRIME) and olaparib (using data from the ITT population from SOLO-1) is the only comparison that is feasible based on the available data. The results are shown in the table below.

However, we would like to emphasise that this comparison may be subject to substantial bias due to potential imbalances in baseline characteristics (which cannot be verified). A further limitation is that the assumption of proportional hazards may not hold both within the BRCAm subgroup of PRIME and the ITT population of SOLO-1 (based on log cumulative hazard plot, Schoenfeld residuals and HR and time interaction, see response to Question B11 and the [Appendix](#)). For these reasons, this comparison should be interpreted with caution.

Table 4. Bucher ITC of PFS-BICR between niraparib (PRIME BRCAm) and olaparib (SOLO-1 ITT population)

Outcome	Study	Comparison	HR	95% CI LB	95% CI UB	p-value
(BICR) PFS	PRIME: BRCAm	NIRA vs RS	0.40	0.23	0.68	

	SOLO-1: ITT	OLA vs RS	0.28	0.20	0.39	
	BUCHER ITC	NIRA vs OLA	■■■■	■■■■	■■■■	■■■■■■

Abbreviations: BICR = Blinded Independent Central Review; BRCaM = breast cancer gene mutation; CI = confidence interval; HR = hazard ratio; ITC = indirect treatment comparison; ITT = intent-to-treat; LB = lower boundary; NIRA = niraparib; PFS = progression-free survival; RS = routine surveillance; UB = upper boundary

PRIMA and PRIME trials

A7. Priority question. Please provide baseline characteristics for the following subgroups in PRIMA:

- Patients who are HRd;
- Patients who are HRp;
- Patients who have unknown HRD status;
- Patients who are HRp or who have unknown HRD status;
- Patients who are BRCA mutation-positive.

Pooled analyses of the HRp population and HRunknown patients are not appropriate, as HRunknowns do not represent a biologically relevant subgroup and are therefore distinct from HRp patients.

Baseline characteristics for the other requested subgroups (i.e., HRd, HRp, HRunknown and BRCaM) are presented in Table 5-Table 8.

Table 5: Baseline characteristics of the HRd population (PRIMA)

Variable/Category	Niraparib	Placebo
	■■■■■■■■■■	■■■■■■■■■■
Age group, n (%)		
<65 years	■■■■■■	■■■■■■
≥65 years	■■■■■■	■■■■■■
BMI (kg/m ²), n (%)		
BMI <18.5	■■■■	■■■■
18.5≤BMI<25	■■■■■■	■■■■■■
25≤BMI<30	■■■■■■	■■■■■■
BMI≥30	■■■■■■	■■■■■■
Race, n (%)		
White	■■■■■■	■■■■■■
Non-white	■■■■	■■■■
Missing	■■■■	■■■■

Variable/Category	Niraparib	Placebo
Geographic region , n (%)		
North America		
RoW		
ECOG PS, n (%)		
0		
1		
FIGO stage, n (%)		
III		
IV		
Primary tumour location, n (%)		
Fallopian tube		
Ovarian		
Primary peritoneum		
Target lesions		
0		
1+		
Non-target lesions		
0		
1		
2+		
BRCA status		
BRCAmut		
BRCAwt/nd		
Debulking Surgery Type		
IDS		
PDS		
No surgery		
Residual disease status		
Visible residual disease		
No visible residual disease		
Missing/No Surgery		
Clinical response after chemo		
Complete response		
Partial response		
Prior chemotherapy cycles		
6		
7-9		
Missing		
EORTC QLQ-C30: GHS/QoL		

Variable/Category	Niraparib	Placebo
<50		
50 - <75		
≥75		
Missing		
Neoadjuvant chemotherapy		
No		
Yes		
Starting dose cohort		
Fixed		
Individualised		
Duration (wk) from end of chemo to randomization		
Duration		
Number of Treatment Cycles		
<12		
≥12		
≥24		
≥36		

Abbreviations: BMI = body mass index; BRCA = breast cancer gene; ECOG PS = Eastern Cooperative Oncology Group performance status; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30; FIGO = International Federation of Gynecology and Obstetrics; HRd = homologous recombination deficient; IDS = interval debulking surgery; PDS = primary debulking surgery; RoW = rest of world

Source: GSK Data on File¹³

Table 6: Baseline characteristics of the HRp population (PRIMA)

Variable/Category	Niraparib	Placebo
Age group, n (%)		
<65 years		
≥65 years		
Body mass index (kg/m2), n (%)		
BMI<18.5		
18.5 ≤ BMI <25		
25 ≤ BMI <30		
BMI ≥ 30		
Race, n (%)		
White		
Non-white		
Missing		
Geographic region , n (%)		

Variable/Category	Niraparib	Placebo
North America		
RoW		
ECOG PS, n (%)		
0		
1		
FIGO stage, n (%)		
III		
IV		
Primary tumor location, n (%)		
Fallopian tube		
Ovarian		
Primary peritoneum		
Target lesions		
0		
1+		
Non-target lesions		
0		
1		
2+		
BRCA status		
BRCAwt/nd		
Debulking Surgery Type		
IDS		
PDS		
No surgery		
Residual disease status		
Visible residual disease		
No visible residual disease		
Missing/No Surgery		
Clinical response after chemo		
Complete response		
Partial response		
Prior chemotherapy cycles		
6		
7-9		
EORTC QLQ-C30: GHS/QoL		
<50		
50 - <75		
≥75		

Variable/Category	Niraparib	Placebo
Missing		
Neoadjuvant chemotherapy		
No		
Yes		
Starting dose cohort		
Fixed		
Individualised		
Duration (wk) from end of chemo to randomization		
Duration		
Number of Treatment Cycles		
<12		
≥12		
≥24		
≥36		

Abbreviations: BMI = body mass index; BRCA = breast cancer gene; ECOG PS = Eastern Cooperative Oncology Group performance status; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30; FIGO = International Federation of Gynecology and Obstetrics; HRp= homologous recombination proficient; IDS = interval debulking surgery; PDS = primary debulking surgery; RoW = rest of world

Source: GSK Data on File¹³

Table 7: Baseline characteristics of the HRDnd (PRIMA)

Variable/Category	Niraparib	Placebo
Age group, n (%)		
<65 years		
≥65 years		
BMI (kg/m2), n (%)		
BMI <18.5		
18.5≤BMI<25		
25≤BMI<30		
BMI≥30		
Race, n (%)		
White		
Non-white		
Missing		
Geographic region , n (%)		
North America		
RoW		
ECOG PS, n (%)		
0		

Variable/Category	Niraparib	Placebo
1		
FIGO stage, n (%)		
III		
IV		
Primary tumour location, n (%)		
Fallopian tube		
Ovarian		
Primary peritoneum		
Target lesions		
0		
1+		
Non-target lesions		
0		
1		
2+		
BRCA status		
BRCAmut		
BRCAwt/nd		
Debulking Surgery Type		
IDS		
PDS		
No surgery		
Residual disease status		
Visible residual disease		
No visible residual disease		
Missing/No Surgery		
Clinical response after chemo		
Complete response		
Partial response		
Prior chemotherapy cycles		
6		
7-9		
EORTC QLQ-C30: GHS/QoL		
<50		
50 - <75		
≥75		
Missing		
Neoadjuvant chemotherapy		
No		

Variable/Category	Niraparib	Placebo
Yes		
Starting dose cohort		
Fixed		
Individualised		
Duration (wk) from end of chemo to randomization		
Duration		
Number of Treatment Cycles		
<12		
≥12		
≥24		
≥36		

Abbreviations: BMI = body mass index; BRCA = breast cancer gene; ECOG PS = Eastern Cooperative Oncology Group performance status; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30; FIGO = International Federation of Gynecology and Obstetrics; HRd = homologous recombination deficient; IDS = interval debulking surgery; PDS = primary debulking surgery; RoW = rest of world

Source: GSK Data on File¹³

Table 8: Baseline characteristics of the BRCAm (PRIMA)

Variable/Category	Niraparib	Placebo
Age group, n (%)		
<65 years		
≥65 years		
BMI (kg/m ²), n (%)		
BMI <18.5		
18.5≤BMI<25		
25≤BMI<30		
BMI≥30		
Race, n (%)		
White		
Non-white		
Missing		
Geographic region , n (%)		
North America		
RoW		
ECOG PS, n (%)		
0		
1		
FIGO stage, n (%)		
III		

Variable/Category	Niraparib	Placebo
IV		
Primary tumour location, n (%)		
Fallopian tube		
Ovarian		
Primary peritoneum		
Target lesions		
0		
1+		
Non-target lesions		
0		
1		
2+		
BRCA status		
BRCAmut		
BRCAwt/nd		
Debulking Surgery Type		
IDS		
PDS		
No surgery		
Residual disease status		
Visible residual disease		
No visible residual disease		
Missing/No Surgery		
Clinical response after chemo		
Complete response		
Partial response		
Prior chemotherapy cycles		
6		
7-9		
Missing		
EORTC QLQ-C30: GHS/QoL		
<50		
50 - <75		
≥75		
Missing		
Neoadjuvant chemotherapy		
No		
Yes		

Variable/Category	Niraparib	Placebo
Starting dose cohort		
Fixed		
Individualised		
Duration (wk) from end of chemo to randomization		
Duration		
Number of Treatment Cycles		
<12		
≥12		
≥24		
≥36		

Abbreviations: BMI = body mass index; BRCA = breast cancer gene; ECOG PS = Eastern Cooperative Oncology Group performance status; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30; FIGO = International Federation of Gynecology and Obstetrics; HRd = homologous recombination deficient; IDS = interval debulking surgery; PDS = primary debulking surgery; RoW = rest of world

Source: GSK Data on File¹³

A8. Please provide baseline characteristics for the following subgroups in PRIME:

- a) Patients who are HRd;
- b) Patients who are HRp;
- c) Patients who have unknown HRD status;
- d) Patients who are HRp or have unknown HRd status;
- e) Patients who are BRCA mutation-positive.

As PRIME is not a GSK sponsored trial it is not possible to access the IPD, and we are unable to provide baseline characteristics by subgroup.

A9. Priority question. Please provide the results including Kaplan-Meier plots for OS, investigator-assessed PFS, BICR PFS, PFS2, time to treatment discontinuation (TTD) and TFST in PRIMA for the following subgroups:

- a) Patients who are HRd;
- b) Patients who are HRp;
- c) Patients who have unknown HRD status;
- d) Patients who are HRp or have unknown HRD status;
- e) Patients who are BRCA mutation-positive.

The Kaplan-Meier plots for OS, INV-PFS, BICR PFS, PFS2, TTD and TFST for HRd, HRp, BRCAm and HRunknown populations are presented in the Appendix (Kaplan-Meier Curves for Subgroups2024 CSG).

As explained in our response for clarification question A7, it is inappropriate to pool HRp and HRunknown patients, as HRunknowns do not represent a biologically relevant subgroup.

A10. Priority question. Please provide the results including Kaplan-Meier plots for OS, investigator-assessed PFS, BICR PFS, PFS2, TTD and TFST in PRIME for the following subgroups:

- a) Patients who are HRd;**
- b) Patients who are HRp;**
- c) Patients who have unknown HRD status;**
- d) Patients who are HRp or have unknown HRD status;**
- e) Patients who are BRCA mutation-positive.**

Kaplan-Meier plots from PRIME are only available for BICR PFS in patients who are HRd (XXXXXX X), HRp (**Error! Reference source not found.**), BRCAm (**Error! Reference source not found.**) and HRD indeterminate (**Error! Reference source not found.**).

[Redacted]

[Redacted]

Abbreviations: BICR = blinded independent central review; CI = confidence interval; HRd = homologous recombination deficient; NE = not estimable; NR = not reached
Source: Li 2023¹⁰

[Redacted]

[Redacted]

Abbreviations: BICR = blinded independent central review; CI = confidence interval; HRp = homologous recombination proficient; NE = not estimable; NR = not reached
Source: Li 2023¹⁰

[Redacted]

[Redacted]

Abbreviations: BICR = blinded independent central review; BRCAm = breast cancer gene mutation; CI = confidence interval; NE = not estimable; NR = not reached
Source: Li 2023¹⁰

Abbreviations: BICR = blinded independent central review; CI = confidence interval; NE = not estimable; NR = not reached
Source: Li 2023¹⁰

A11. Please provide the results including Kaplan-Meier plots for OS, investigator-assessed PFS, BICR PFS, PFS2, TTD and TFST for the subgroup of patients with BRCA mutation-negative HRD-negative or HRD-unknown advanced ovarian cancer who would not be eligible for treatment with bevacizumab because they do not meet the commissioning approval criteria.

- a) PRIMA;
- b) PRIME.

It is not feasible to conduct these analyses using data from the PRIMA trial, as the relevant patient group (those not meeting the commissioning approval criteria for bevacizumab) was not included in the study.

According to commissioning criteria BEV3, patients are not eligible for bevacizumab as an add-on to first-line platinum-based chemotherapy if they have stage 3 disease with no visible residual disease following primary debulking surgery. This group of low-risk patients aligns with those excluded from the PRIMA trial.

Furthermore, as per commissioning criteria BEV10, patients are not eligible for bevacizumab as a maintenance treatment unless they received bevacizumab during induction alongside chemotherapy. In the PRIMA trial, only a negligible number of patients had prior exposure to bevacizumab, and discontinued treatment following enrolment to the study (N=7/733).

Similarly, the PRIME study does not provide individual patient data, which prevents us from performing subgroup analyses.

Subgroups

A12. Priority question. Please provide results for PRIME for OS, investigator-assessed PFS and BICR PFS for the following subgroups:

- a) Federation of Gynaecology and Obstetrics (FIGO) Stage III;**
- b) FIGO Stage IV;**
- c) Patients with FIGO Stage III not eligible for inclusion in PRIMA;**
- d) Patients eligible for inclusion in PRIMA.**

OS and PFS outcomes for the requested subgroups in PRIME cannot be provided as it is not a GSK-sponsored trial and IPD are not accessible for this study. It is also important to note the OS data was immature at the time of data cut off on 30th September 2021.

A13. Priority question. [REDACTED]

[REDACTED]

[REDACTED]

The hazard ratio of [REDACTED] observed in patients with FIGO Stage IV disease should be interpreted with caution. The PRIMA trial was not stratified by stage of disease, and the study was not designed to evaluate treatment effects specifically in this subgroup. Small sample sizes and retrospective nature of the analysis further limit the reliability of these findings, as no formal testing was performed. Additionally, it is challenging to isolate the effects of individual factors.

While this observation may be explained in part by small imbalances (<10% difference) in some of the baseline characteristics between the Stage IV niraparib and placebo

arms (examples include: ECOG PS, Region), it is unlikely that a singular or subset of molecular, clinical or demographic characteristics is causative of the trend observed for OS.

Stage IV disease at diagnosis is independently prognostic of poor long-term outcomes and is also known to be associated with other risk factors for disease progression and death, including use of neoadjuvant chemotherapy and postoperative residual disease.¹⁴⁻¹⁶ In the PRIMA trial, variations were observed in the number and location of new lesions in patients with stage III and IV disease at diagnosis who experienced disease progression. These variations may have contributed to differences in the overall prognoses of these patient subgroups.

Assumptions of equivalence

A14. Priority question. Within the CS, the company makes multiple references to the equivalence between treatments. Please can the company:

- a) Clarify if formal equivalence testing was performed to reach such conclusions.**

We would like to clarify that no formal testing of equivalence was previously performed.

- b) Perform formal equivalence testing, if not previously performed, to provide evidence to support, or otherwise, the company's claims of equivalence between treatments.**

The ideal setting for testing equivalence between niraparib and comparator treatments would have been a non-inferiority trial. No manufacturer has undertaken a head-to-head non-inferiority trial of PARPi monotherapies in ovarian cancer. Therefore, it is not possible to undertake robust formal non-inferiority testing of these treatments.

To address the above request, we ran post-hoc analyses (described in Kaul and Diamond 2007), referred to as "fixed margin analysis".¹⁷ However, we emphasise that these post-hoc analyses typically suffer from lack of statistical power and can only be interpreted as exploratory.

Fixed margin analyses seek to determine whether the new treatment (i.e. niraparib) is inferior to the standard treatment (e.g. olaparib or rucaparib) by no more than some predefined margin. They are applicable when the comparator study has demonstrated that the standard treatment (e.g. rucaparib or olaparib) is superior to placebo. According to the “mixed margin analysis”, the maximum noninferiority margin, d_{max} , is derived as the 95% lower confidence limit (LCL) of the HR for placebo versus the standard treatment. Non-inferiority of the new treatment versus the standard treatment is declared when the 2-sided 95% CI of the Bucher ITC comparing the new treatment vs the standard treatment is entirely below this margin.

For example, when investigating non-inferiority of niraparib vs rucaparib in the ITT population, the reported HR and 95%CI for rucaparib vs placebo in ATHENA-MONO ($HR_{RUC\ vs\ PBO}=0.47$ [95% CI: 0.36 – 0.63]) are inverted to obtain a HR and 95% CI for placebo vs rucaparib ($HR_{PBO\ vs\ RUC\ } = 2.128$ [95% CI: 1.587 – 2.778]). In this example, $d_{max} = 1.587$ and because the 95% CI for the effect of niraparib vs rucaparib from the Bucher ITC $HR_{NIRA\ vs\ RUC\ }HR_{NIRA\ vs\ RUC\ }=$ [REDACTED] is entirely below d_{max} [0.03], non-inferiority is established.

Furthermore, we used Monte-Carlo simulation to estimate the probability that the HR for niraparib vs placebo, $HR_{NIRA\ vs\ PBO}$, is lower than the HR for the comparator vs placebo, $HR_{COMP\ vs\ PBO}$. This simulation was conducted by drawing 1,000,000 values from two independent normal distributions, parameterized to match the reported hazard ratios (HRs) and their corresponding 95% confidence intervals.

- A probability of $HR_{NIRA\ vs\ PBO} < HR_{COMP\ vs\ PBO}$ that is close to 50%, supports the hypothesis of non-inferiority as it reflects that the distributions of the reported HRs are indistinguishable.
- A probability of $HR_{NIRA\ vs\ PBO} < HR_{COMP\ vs\ PBO}$ that is higher than 50% may indicate that the assumption of non-inferiority is conservative.
- The probability of $HR_{NIRA\ vs\ PBO} < HR_{COMP\ vs\ PBO}$ will typically be lower than 50% when the reported HR in PRIMA/PRIME is higher than the reported HR in the comparator study. However, niraparib could still be non-inferior to the

comparator treatment if both treatments are highly efficacious compared to placebo and the fixed margin analysis supports non-inferiority.

The table below shows the results and conclusions from the fixed margin analyses and the probability calculations conducted to investigate the non-inferiority of niraparib vs rucaparib and olaparib across all the Bucher ITC comparisons in our submission.

Table 9. Results and conclusions from fixed margin analyses and probability calculations conducted to investigate the non-inferiority of niraparib vs rucaparib and olaparib

[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED] [REDACTED]	[REDACTED]	[REDACTED]	[REDACTED] [REDACTED] [REDACTED]	
[REDACTED]	[REDACTED] [REDACTED]	[REDACTED] [REDACTED] [REDACTED]	[REDACTED] [REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED]
[REDACTED]	[REDACTED]	[REDACTED] [REDACTED] [REDACTED]	[REDACTED] [REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED]
[REDACTED]	[REDACTED] [REDACTED]	[REDACTED] [REDACTED] [REDACTED]	[REDACTED] [REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED]

[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED] [REDACTED]	[REDACTED]	[REDACTED]	[REDACTED] [REDACTED] [REDACTED]	[REDACTED]
		[REDACTED] [REDACTED]	[REDACTED] [REDACTED]	[REDACTED]			[REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED]
[REDACTED]	[REDACTED]	[REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED]	[REDACTED] [REDACTED] [REDACTED] [REDACTED]	[REDACTED] [REDACTED]	[REDACTED]	[REDACTED]	[REDACTED] [REDACTED] [REDACTED]
[REDACTED]	[REDACTED] [REDACTED]	[REDACTED] [REDACTED] [REDACTED]	[REDACTED] [REDACTED] [REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED]

Abbreviations: BICR = blind independent central review; BRCAm = breast cancer gene mutation; BRCAwt = breast cancer gene wild type; CI = confidence interval; HR = hazard ratio; HRd = homologous recombination deficient; HRp = homologous recombination proficient; INV = investigator assessed; ITC = indirect treatment comparison; ITT = intent-to-treat; NIRA = niraparib; OLA = olaparib; OS = overall survival; PBO = placebo; PFS = progression-free survival; RUCA = rucaparib

Section B: Clarification on cost-effectiveness data

If as a result of the responses to the cost-effectiveness clarification questions the company base case analyses are revised, please indicate what assumptions are considered for the revised base case and provide updated results, probabilistic sensitivity analyses, deterministic sensitivity analyses and scenario analyses in the response document.

Please provide all ERG-requested scenario analyses as drop-down menu options in the economic model to be run in combination with different scenarios

Comparators

B1. Priority question: As requested in CQ A1, unless the company is seeking a recommendation for niraparib in patients who are ineligible for bevacizumab, please include olaparib + bevacizumab and bevacizumab monotherapy in the economic model as comparators.

[Please see response to clarification question A1.](#)

Model structure

B2. Priority question: As noted in Section A, in TA1055, analyses were presented in the HRp and HRd. As such, please update the model structure to include the following populations:

- BRCAm (comparison with olaparib);
- HRp (comparison with rucaparib);
- HRd (comparison with rucaparib).

If in response to CQ A1b, the company is also seeking a recommendation for patients who are eligible to receive olaparib + bevacizumab and bevacizumab monotherapy, please ensure these comparators are also included in the model in the relevant populations, as noted above.

A comparison with olaparib for the BRCAm population was included in the submitted economic model and in the original submission dossier.

As rucaparib is reimbursed for the HRd BRCAwt population alone and not for the entire HRd population, the BRCAwt subgroup is the most appropriate population for comparison with rucaparib, as it captures all relevant populations currently reimbursed for rucaparib (i.e., HRd BRCAwt and non-HRD-positive). As outlined in our response to clarification question A1, the additional restriction for non-HRD-positive patients (i.e., ineligible for bevacizumab maintenance) aligns with current clinical practice for PARPi monotherapies.

Furthermore, results from the Bucher ITCs, clinical opinion, and the mechanism of action indicate comparable effectiveness between niraparib and rucaparib, regardless of biomarker status.

B3. Priority question: Based on the available trial data, the EAG considers PFS2 to be a key outcome that should be included in the economic model. The EAG notes that the model structure is already set up to include a PFS2 health state. Therefore, please incorporate data based on the EAG requested analyses from Section A to include PFS2 as a health state in the economic model. Through excluding this health state, the EAG does not consider the model structure to appropriately capture the key outcomes and impact of PARPis. Please also ensure that any updates to health state utility values and health care resource used in the PFS2 health state are described.

As stated in Section 3.3.2 of the CS, a 3-state model was utilised due to the lack of relevant PFS2 data in high-risk patients to conduct appropriate ITC analyses versus olaparib for the BRCAm population or rucaparib for the BRCAwt population. The inclusion of PFS2 was not expected to have a substantial impact on the model results as the treatment pathway following disease progression with PARPi monotherapy remains consistent irrespective of the first-line PARPi utilised. However, we have updated the economic model to include PFS2 data for niraparib from the PRIMA trial and have performed two additional scenario analyses utilising the 4-state model approach, with generalised gamma and 1-knot hazard spline models selected to extrapolate PFS2 for both populations (see

Additional Survival Analysis Inputs for more details on PFS2 parametric fit selection). Given the lack of statistically significant differences in PFS, OS and TFST observed from the Bucher ITC analyses presented in Section 2.7 of the CS and in response to clarification questions A4 and A6, as well as available real-world evidence comparing PFS and TFST between niraparib and olaparib, equivalence in PFS2 between niraparib and each comparator was assumed for these scenarios, in the absence of comparable PFS2 data.¹⁸

Health state utility values for the 4-state model, derived from PRIMA, are presented below in Table 10.

Table 10. Base-case utilities (PRIMA)

Health States	Mean	SE	Utility Sample Reference Age (Years)	Source
Progression Free	██████	██████	██████	PRIMA
First Progression	██████	██████		
Second Progression	██████	██████		

Abbreviations: SE = Standard error.

Resource use frequencies used for progressed patients in the 3-state model (see Section 3.6.2 of CS) were applied to both first and second progression patients in the 4-state model, in line with NICE TA1055 and NICE TA946.

For the 4-state model, 3L+ subsequent treatment costs are applied at the point of second progression based on PFS2 data, and therefore the proportion of first progression patients experiencing second progression used in the 3-state model (Table 55 of the CS) is no longer applied for this approach.

Given the equivalence assumption also adopted for PFS and OS in the base case, these scenarios did not show a change in incremental results compared to the base case analysis (see Table 20), although lower total subsequent treatment costs were generated (due to the changes in how 3L+ subsequent treatment costs are applied) along with slightly lower total QALYs (due to application of different health state utility values for first and second progression).

Treatment effectiveness

Niraparib versus olaparib:

B4. Priority question. The EAG does not consider there to have been robust evidence provided to underpin the company's assumption of equivalence between the included comparators. As the PRIMA trial showed no difference in overall survival compared to placebo and a statistically significant difference in OS was observed in the SOLO-1 trial, please include the following scenarios that:

- a. Implement the PFS, PFS2, OS HRs derived from the requested analysis of the SOLO-1 ITT data versus PRIMA, as noted in CQ A5**

Please note that the EAG's statement that a statistically significant difference in OS was observed in SOLO-1 is not strictly correct. As indicated in DiSilvestro 2023,¹⁹ the 7-year follow-up results from SOLO-1 showed a clinically meaningful difference rather than a statistically significant difference in OS, as the pre-specified criteria to declare statistical significance was not met. Regarding the requested analyses, please see our response to clarification question A5.

- b. Varies the comparative effectiveness of niraparib versus olaparib OS, for example, using results of a Bucher ITC for OS as was done PFS.**

Please note that the Bucher ITC was conducted for PFS, as relevant high-risk population data were available for SOLO-1, as described in Section 2.7 of CS. No OS data are available for SOLO-1 in the high-risk population, and comparing the SOLO-1 ITT population vs. the PRIMA population is inappropriate, as described in our response to clarification question A5. Nevertheless, we have performed the following two scenario analyses (see Table 20) for the BRCAm population comparison versus olaparib, assuming that the PH assumption is reasonable (see response to clarification question B11):

- Using an OS HR [95% CI] of [REDACTED] for niraparib versus olaparib derived from a naïve comparison of SACT OS data, along with a PFS HR [95% CI] of [REDACTED] based on the Bucher ITC results presented in Section

2.7.3 of the original CS, rather than assume PFS and OS equivalence as per the base case analysis.

- Use of the same HRs, but with the OS HR applied alongside a lognormal OS curve for niraparib fitted to the SACT OS data (rather than PRIMA), and use of SACT TTDD KM curves for both treatment arms (see response to clarification response B6 for further details).

However, we believe that both scenarios represent a highly conservative estimation of niraparib's relative efficacy compared to olaparib, particularly due to the assumption that the HRs remain constant over the lifetime horizon of the economic analysis, and that the numerical advantage for olaparib in the SACT OS HR was a result of differences in the tail of the KM curves, where there were low numbers of patients at risk for niraparib. In fact, SACT OS data for niraparib vs. olaparib are practically identical until 27 months, after which patients at risk for niraparib are limited. Furthermore, it is important to note that applying a PFS benefit for olaparib vs. niraparib, in addition to an OS benefit, results in an extended long-term OS advantage for olaparib vs. niraparib. This is due to the combined effect of the 10-year cure assumption and capping of OS by PFS, in addition to the OS benefit already captured through the use of an OS HR of [REDACTED] for niraparib vs olaparib.

B5. Priority question. In figure 33 of the CS, the company provide a comparison of OS data from SACT for both niraparib and olaparib. Please also provide a version of this diagram which includes the KM curve from the PRIMA trial for the BRCAm subgroup and SOLO-1 trial, with the equivalent OS milestones added to the equivalent of Table 39.

As explained in Section 2.7 of the CS and in the answer to clarification question A5, naïve comparison of PRIMA and SOLO-1 is not appropriate. Furthermore, as described in Section 2.11 of the CS and in our response to question A3, OS was a secondary endpoint across PARPi trials and is confounded by post-progression treatment management.

B6. Please include a scenario in the model based on a full SACT analysis for both niraparib and olaparib, in which:

- OS is informed by the SACT OS KM curves with fitted parametric curves
- Time to treatment discontinuation (TTD) is informed by SACT TTD curves with fitted parametric curves
- PFS is derived from a HR for TTD:PFS derived from PRIMA for niraparib and SOLO-1 for olaparib
- Starting dose informed from SACT data

Thank you for the request. It is not appropriate to derive the PFS extrapolation using an HR applied to TTDD, particularly given the stopping rules applied to both treatment arms in the model and the observed TTDD data from the PRIMA and SOLO-1 trials. While a drop in the TTDD curve was not observed for niraparib in PRIMA after 3 years, a sharp drop was observed for olaparib after 2 years in SOLO-1 resulting in a noticeable increase in the difference between PFS and TTDD curves thereafter. Furthermore, use of a TTDD:PFS HR oversimplifies the relationship between PFS and TTDD. In fact, while before the stopping rule, progression and AEs are expected to be the primary reason of discontinuation, PARPis are typically discontinued as per stopping rules as physicians would like to avoid long-term exposure. Therefore, beyond the stopping rule, progression does not relate to TTDD, and PFS cannot be extrapolated appropriately using a TTDD:PFS HR.

However, we have run an additional scenario analysis (see Table 20) using the following approach:

- OS for niraparib is based on the SACT KM curve, modelled using a lognormal distribution (see SACT OS (BRCAm) for more details on SACT OS parametric fit selection). For olaparib, the HR of [REDACTED] derived from a naïve comparison of SACT OS data between niraparib vs olaparib, is used to generate the OS extrapolation for olaparib.
 - i. Naïve comparisons of the SACT OS data for niraparib and olaparib (see Figure 33 of original CS) showed that the KM curves overlapped for the first 27 months, before a drop in the tail was observed for niraparib between approximately 27 and 33 months followed by a flat section at

the tail, where relatively few patients at risk were available to inform the niraparib KM curve.

- ii. Niraparib OS extrapolations appeared to be influenced by the drop in the KM curve between 27 and 33 months (see SACT OS (BRCAm) for more details on niraparib SACT OS parametric fits), which is likely driven by the relatively low number of patients at risk and thus limits the reliability of the OS KM curve in the tail. Therefore, the use of independent parametric models fitted to the SACT OS KM data for olaparib was not considered as it is likely to overestimate the differences in the long-term OS for olaparib
- Despite the available RWE and UK clinical expert feedback supporting a class effect for PARPi's, as the proportional hazards assumption appeared reasonable when conducting a naïve comparison of the niraparib and olaparib SACT OS KM curves (see response to clarification question B11), the OS HR [95% CI] of [REDACTED] for niraparib vs olaparib derived from a naïve comparison of the SACT OS data was conservatively applied which generated a more favourable OS extrapolation for olaparib compared to niraparib. Note that the OS HR in favour of olaparib is applied throughout the time horizon in the model, thus presenting a very conservative scenario, especially given that most patients will discontinue olaparib at 2 years
 - TTDD informed by SACT TTDD data, based on TTDD scenario 2 explored in the original CS (SACT TTDD until 42 months and 38 months for niraparib and olaparib, respectively, then assume all patients discontinue), to reflect the observed drop from 33% on treatment at 2 years to 13% at 3 years for olaparib noted in EAG clarification question B20
 - Rather than derive PFS from TTDD:PFS HRs from PRIMA for niraparib and SOLO-1 for olaparib, the original base case PFS extrapolation based on PRIMA was used (generalised gamma) for niraparib, with a conservative HR of [REDACTED] for niraparib vs olaparib based on the Bucher ITC results presented in Section 2.7.3 of the CS.

- i. As noted in response to clarification question B4, applying a PFS benefit for olaparib vs. niraparib in conjunction with an OS benefit presents an extremely conservative scenario for niraparib due to the capping of OS from below by PFS.
 - ii. Although the SACT OS extrapolations for niraparib appeared to be generally more conservative than OS extrapolations from PRIMA, the SACT OS extrapolations appeared plausible when applied in combination with PRIMA PFS extrapolations.
- Niraparib starting dose distribution informed from SACT data (as per the company base case analysis)

Niraparib versus rucaparib:

B7. Priority question. Based on the comparison of the PRIME trial to ATHENA-MONO for rucaparib for the BRCAwt analysis, the company assumed equivalence between the two treatments for both PFS and OS, which the EAG notes does not appear to have been based on any formal testing of equivalence:

- a. **Please clarify if any further real-world evidence, such as SACT data for rucaparib, could have been used to explore scenario analyses in which equivalence is not assumed? As such, please implement scenario analyses in the model in which the HRs for PFS and OS in the BRCAwt subgroup is not equal to 1.**

As olaparib and niraparib were both initially recommended via the CDF following their initial appraisals as first line maintenance treatments for advanced ovarian cancer (TA598 and TA673, respectively), SACT data were collected and available for the re-appraisals of both treatments, with olaparib SACT data published as part of the NICE TA962 committee papers. However, rucaparib was only recently recommended after its first appraisal for first line maintenance treatment (TA1055) and as such, at this current time, has not been available for use in the UK for a sufficiently long duration over which SACT data could be collected. No other appropriate real-world evidence was identified for conducting an ITC. However, we have run the following two additional scenario analyses for the BRCAwt population (see Table 21), using data

from the Bucher ITC analyses of PRIME vs ATHENA-MONO (see Section 2.7.1 of the CS) for the populations where both PFS and OS data were available:

- Applying a PFS HR of [REDACTED] and OS HR of [REDACTED] for niraparib versus rucaparib, based on Bucher ITC analyses for the ITT population
- Using a PFS HR of [REDACTED] and OS HR of [REDACTED] for niraparib versus rucaparib, based on Bucher ITC analyses for the HRd population

b. Based on the analyses requested in CQ A3 for niraparib (PRIMA trial) versus rucaparib, split by HRp and HRd, please implement the results of this in a scenario analysis in the economic model, using the requested 4-state model as noted in B3.

Please see our response to clarification question A3.

B8. As suggested in the company's advisory board, please implement a scenario analysis in the model that includes a comparison of niraparib against routine surveillance.

Clinical experts at the advisory board stated that the standard of care is to offer maintenance therapy to patients who respond to platinum-based chemotherapy, with only a small proportion of patients not receiving any treatment. Given the availability of olaparib as 1L maintenance therapy for BRCAm patients and rucaparib as 1L maintenance therapy for BRCAwt patients, it is not appropriate to include routine surveillance as a comparator in the economic model, as described in Section 1.2 of the CS.

B9. If SACT data are available for rucaparib, please include a scenario in the model based on a SACT analysis for both niraparib and rucaparib, in which:

- a. OS is informed by the SACT OS KM curves with fitted parametric curves
- b. Time to treatment discontinuation (TTD) is informed by SACT TTD curves with fitted parametric curves
- c. PFS is derived from a HR for TTD:PFS derived from PRIMA for niraparib and ATHENA-MONO for rucaparib
- d. Starting dose informed from SACT data

As indicated in response to clarification question B7, SACT data is not currently available for rucaparib to conduct these analyses.

B10. Please implement a scenario in the economic model for the comparison against rucaparib in which survival analysis is based on naive treatment comparisons of KM data from PRIMA and ATHENA-MONO.

Please see our response to clarification question A3.

Survival modelling

B11. Priority question. Based on the implementation of any of the EAG's previously requested analyses in the economic model using hazard ratios derived from an ITC, please ensure that the application of the HR is only applied to extrapolated survival curves that support the proportional hazards assumption.

As described in our submission, all Bucher ITCs were exploratory, despite the significant limitations identified in the FA. Specifically, they were conducted as a means to provide an unadjusted and approximate relative effect of niraparib vs olaparib and rucaparib, despite the challenges in adjusting for baseline differences and the lack of availability of data on key effect modifiers. Apart from these limitations, we also acknowledge the limitation that the estimated relative effects estimated from Bucher ITCs may not be appropriate when the assumption of PH is violated.

For all the studies included in the ITC analyses, the assumption of proportional hazards was assessed using three methods:

- **Log-cumulative hazard plots:** Under proportional hazards, the $\log(-\log(S(t)))$ vs. $\log(\text{time})$ curves for the treatment arms are parallel. Curves that cross or appear to converge or diverge over time may be indicative of violation of the PH assumption. The interpretation should weigh in the number of patients remaining, events or length of periods where the patterns are not parallel. For example, curves that cross very early but remain otherwise parallel may still support a PH assumption as the early crossing could be due to an insufficient number of events at that point. Similarly, crossing near the end of follow-up may be due to depletion of patients at risk and low event counts.
- **Schoenfeld Residuals:** The PH assumption can also be assessed based on the Schoenfeld residuals derived from fitting a PH model. When the effect is constant over time, the residuals should be independent of time. This can be assessed based on the spline function (with 3 df) fitted to the residuals; a relatively flat pattern at 0 would provide support for proportional hazards.
- **HR and Time Interaction:** The PH assumption can be assessed by checking for an interaction between the effect of treatment and time in a Cox regression model. A statistically significant interaction (with time or with log-time) indicates a change in the log-HR per unit of time which suggests that the PH assumption may not hold.

The table below (Table 11) presents the conclusions from this investigation. The log cumulative hazard plots, Schoenfeld residual plots and the results from the Cox models with interaction between time and treatment are available in the Appendix (Proportional Hazards Assumption Testing).

Table 11. Proportional Hazard Assumption Testing

Population	Study	Outcome	PH Assumption
ITT		OS	

Population	Study	Outcome	PH Assumption
	PRIME (NIRA vs PBO)	PFS-BICR	████████████████████ ████████████████████ ████████████████
	ATHENA-MONO (RUCA vs PBO)	PFS-BICR	████████████████████ ████████████████████ ██████████████
HRd	PRIME (NIRA vs PBO)	PFS-BICR	████████████████
	ATHENA-MONO (RUCA vs PBO)	PFS-BICR	████████████████
HRd/BRCAwt	PRIME (NIRA vs PBO)	PFS-BICR	████████████████
	ATHENA-MONO (RUCA vs PBO)	PFS-BICR	████████████████
BRCAm	SACT (NIRA vs OLA)	OS	████████████████
	PRIME (NIRA vs PBO)	PFS-BICR	████████████████████ ████████████████████ ████████████████████ ████████████████
	PRIMA (NIRA vs PBO)	PFS-BICR	████████████████
	ATHENA-MONO (RUCA vs PBO)	PFS-BICR	████████████████
	SOLO-1 (OLA vs PBO)	PFS-BICR	████████████████████ ████████████████████ ████████████████ ████████████████
BRCAm & high-risk	SOLO-1 (OLA vs PBO)	PFS-INV	████████████████████ ████████████████████ ████████████████

Population	Study	Outcome	PH Assumption
HRp	PRIME (NIRA vs PBO)	PFS-BICR	████████████████████ ██████████
	ATHENA-MONO (RUCA vs PBO)	PFS-BICR	████████████████████ ██████████

Abbreviations: BRCA = breast cancer gene mutation; BRCAwt = breast cancer gene wild type; BICR = blinded independent central review; HR = hazard ratio; HRd = homologous recombination deficient; HRp = homologous recombination proficient; ITT = intent-to-treat; NIRA = niraparib; OLA = olaparib; OS = overall survival; PBO = placebo; PFS = progression-free survival; RUCA = rucaparib

B12. Priority question. In the company's model, once patients have reached 10 years progression-free, it is assumed that 100% of patients are in long-term remission. Please clarify why it was assumed to apply to 100% of patients and explore the impact in a scenario analysis in which a lower proportion is implemented.

As highlighted in Sections 3.2 and 3.4.2 of the CS, the approach of assuming that all patients alive and progression-free at the cure time point are considered cured (i.e., follow general population mortality elevated by biomarker-specific excess mortality) is aligned with recent NICE appraisals (TA962 and TA946). Furthermore, as highlighted in Section 3.4.2 of the CS, the potential for long-term remission and functional cure is supported by both clinical experts from previous NICE appraisal (TA962, TA946), literature and UK clinical experts' feedback received during the development of the CS. In addition, in the recent NICE appraisal for olaparib (TA962) and olaparib + bevacizumab (TA946), a cure time point of 5-7 years was deemed plausible, with UK clinical experts at the advisory board also highlighting that the probability of relapse after 7-10 years is highly uncommon (and fairly uncommon after 5 years). Nevertheless, a more conservative cure point of 10 years was adopted in the current CS, with a 100% cure proportion adopted given the use of the upper bound of cure points provided by clinical experts, and approach to cure assumptions considered in prior PARPi appraisals.

An exploratory scenario analysis was conducted for both the BRCAm and BRCAwt populations, assuming that 95% (instead of 100%) of patients who are alive and progression-free at 10 years are deemed cured. The impact of these exploratory

scenarios on niraparib INMB vs. olaparib (BRCAm) or rucaparib (BRCAwt) was minimal (see Table 20 for BRCAm and Table 21 for BRCAwt).

B13. Priority question. In the economic model, once patients are considered to achieve long-term remission at 10 years, they receive general population mortality estimates. An excess hazard of 1.26 sourced from Mai 2009 was applied to the general population mortality in the BRCAm analysis only. Please clarify why an increased risk of death beyond the 'cure' point was assumed only to apply for the BRCAm group? Other than the precedent set in the previous NICE TAs, was this based on a systematic review of the evidence?

Although a formal systematic review was not performed, ad-hoc literature review was conducted to try and identify relevant sources to inform long-term excess mortality for patients without a BRCA mutation, with no appropriate evidence identified to use in the economic model for the BRCAwt population. A 1.26 HR was therefore applied only to the BRCAm population in line with prior appraisals for olaparib (TA962) and olaparib plus bevacizumab (TA946). However, an additional scenario analysis has been conducted applying the same excess mortality HR of 1.26 for the BRCAwt population, which had a limited impact on the results (see Table 21).

B14. Priority question. Please clarify if the position of the knots in the spline models were equally distributed across the range of available datapoints or if an alternative approach was used to set their position?

We can confirm that the knots were distributed equally across observed survival percentiles for all spline models.

B15. Priority question. Please provide the long-term parametric extrapolation curves (Figures 64, 65, 71 and 72 of Appendix J) without the 10 year cure point or cap for PFS applied.

Please see below the niraparib PFS long-term extrapolation curves without the 10-year cure point as well as without the 10-year cure point and general population mortality capping (XXXXXX and **Error! Reference source not found.** for standard parametric models and **Error! Reference source not found.** and **Error! Reference source not found.** for flexible parametric models, respectively). Also presented are the OS long-term extrapolation curves without the 10-year cure point and PFS capping

from below, as well as without the 10-year cure point, PFS capping from below and general population mortality capping (**Error! Reference source not found.** and **Error! Reference source not found.** for standard parametric models and **Error! Reference source not found.** and **Error! Reference source not found.** for flexible parametric models, respectively).

[REDACTED]

[REDACTED]

Abbreviations: KM = Kaplan-Meier; PFS = progression-free survival

[REDACTED]

[REDACTED]

Abbreviations: KM = Kaplan-Meier; PFS = progression-free survival

[REDACTED]

[REDACTED]

Abbreviations: KM = Kaplan-Meier; PFS = progression-free survival

[REDACTED]

[REDACTED]

Abbreviations: KM = Kaplan-Meier; PFS = progression-free survival

[REDACTED]

[REDACTED]

Abbreviations: KM = Kaplan-Meier; OS = overall survival

[REDACTED]

[REDACTED]

Abbreviations: KM = Kaplan-Meier; OS = overall survival

[REDACTED]

[REDACTED]

Abbreviations: KM = Kaplan-Meier; OS = overall survival

[REDACTED]

[REDACTED]

Abbreviations: KM = Kaplan-Meier; OS = overall survival

B16. Please provide scenarios in the model for each comparison whereby overall survival is not required to be capped by the chosen PFS curve and the choice of OS extrapolation curve is based on the best fitting model with PFS instead capped by OS rather than the other way.

Thank you for the request; however, we don't believe that application of capping from above with OS would be appropriate and may result in clinically implausible extrapolations for PFS.

As indicated in Section 3.4.2 of the original CS and in line with prior PARPi appraisals, PFS was used to model the cure point given that PFS has more mature data vs. OS, thus expected to more accurately reflect the long-term plateau associated with a long-term remission assumption (i.e. a plateau not yet clearly present in the PRIMA OS data).

All UK clinical experts interviewed indicated that cure was achievable in a PRIMA-like high-risk population, and that patients remaining progression-free after 7-10 years were highly unlikely to relapse, with a more conservative 10-year cure point adopted in the base case model (with 8 and 12-year cure points explored in scenario analysis). In addition, UK clinical experts also confirmed that only a small proportion of patients receiving PARPi maintenance in subsequent lines could achieve cure, which would not occur in clinical practice if patients previously received PARPi as 1L maintenance, implying that only patients remaining alive and progression free for a sufficient duration of time on 1L PARPi maintenance could be considered cured.

If it is assumed that the mechanic of capping from above with OS should take precedence over the cure mechanic, this would likely result in higher than general population mortality being applied to patients alive and progression free after the cure point, contradicting the cure assumption supported by clinical experts and accepted in prior NICE appraisals.

This is further validated by evidence from the PRIMA trial showing a negligible proportion of death events occur pre-progression; in the PRIMA trial in the overall population [REDACTED] of PFS events [REDACTED] were for the reason of 'death' with the remainder due to disease progression. It is therefore inappropriate to model death

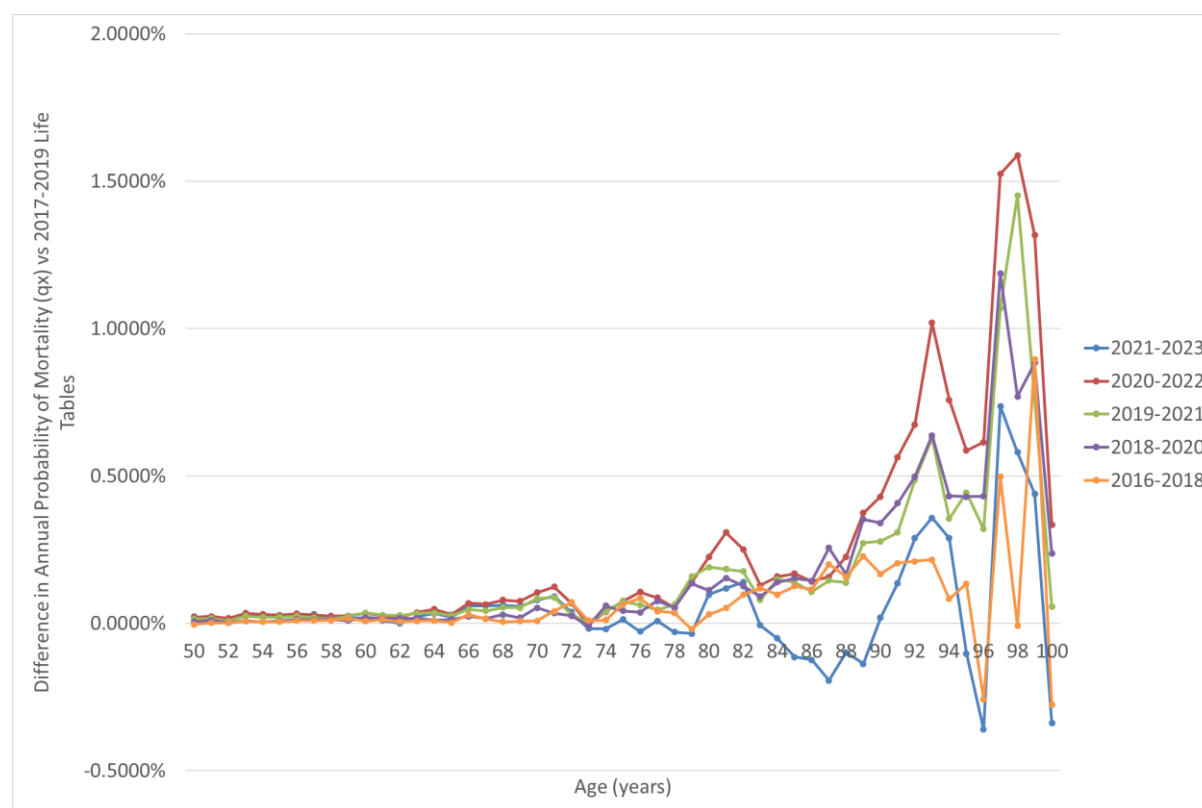
events occurring exclusively from the pre-progression state as would be implied by the PFS curve being capped by the OS extrapolation.

Furthermore, if it is assumed that the cure assumption mechanic should take precedence over capping from above with OS after the cure point (i.e. the OS capping from above mechanic only applies before the cure point), this would have no impact on the base case analysis (and either no impact or minimal impact on the scenario analyses) as the OS-PFS crossing points occur after the 10-year cure point.

B17. Guidance in NICE DSU TSD 23 recommends using the ONS life tables from 2017-2019 due to the uncertainty about the long-term impact of COVID-19 on data beyond 2020. As such, please update the model to use the 2017-2019 ONS life tables.

Although NICE DSU TSD23 guidance recommends use of 2017-2019 life table data, this was published in January 2024 likely prior to the availability of 2021-2023 life table data. Comparison of the differences in annual mortality probabilities (qx) by age for individuals 50 years and above (Figure 2) with 2017-2019 estimates shows that despite a consistent increase in mortality being observed in 2018-2020, 2019-2021 and 2020-2022 life tables across age groups (excluding age 73), this trend was not present in the latest 2021-2023 life tables where smaller overall differences were observed including lower mortality probabilities for several age groups, with comparable differences in mortality probabilities as seen for the 2016-2018 life tables. As such, the latest 2021-2023 life table estimates were used as a more recent source of life table estimates.

Figure 2. Comparison of Annual Mortality Probabilities between 2017-2019 Life Tables and Other Life Table Datasets



Nevertheless, we have included the option to use 2017-2019 life tables in the economic model and run an additional scenario analysis for both populations, where no differences in incremental outcomes were generated compared to the base case analysis (see Table 20 and Table 21), with only marginal changes in total LYs, QALYs and costs for all comparators.

Subsequent treatments

B18. Priority question. In regard to subsequent treatments (2L and 3L) listed in Tables 106 and 107 in Appendix C1.3, please clarify:

a. If these are all based on progression,

We can confirm that subsequent treatments listed in Tables 106 and 107 of Appendix C1.3 were based on progression. As per SAP Section 4.3.3.4 (if there are one or more progression dates) all the reported follow-up therapies were grouped into lines of therapies by comparing their reported start dates to the reported progression dates.

The follow-up therapies started prior to the first progression date following the start of any follow-up therapy are grouped as the first line of follow-up therapy. The follow-up therapies started after the first progression date and prior to the second progression date are grouped as the second line of follow-up therapy, and so on. As a result, patients may have more than one therapy within the same line.

- b. If patients in the placebo arm of PRIMA who received chemotherapy as 2L and then receive maintenance PARPi, is the PARPi classified as a 2L treatment or 3L treatment, i.e. are placebo patients receiving a PARPi listed as 2L receiving this as a maintenance therapy after chemotherapy at 2L or as a 2L treatment for their progressed disease?**

It is dependent on whether disease progression happened between the 2L chemotherapy treatment and the initiation of PARPi as 2L maintenance therapy. If patients experienced disease progression after 2L chemotherapy but prior to initiating PARPi, then PARPi was classified as 3L treatment. However, if PARPi was administered after chemotherapy and no progression occurred between the two therapies, it was still classified as 2L maintenance treatment.

Baseline characteristics

B19. Priority question. As noted by the company and explored in a scenario analysis, the average age of patients in PRIMA differed to that observed in SACT data. Please provide the median age of patients from PRIMA for the BRCAm and BRCAwt subgroups

The median age (IQR) of the BRCAm and BRCAwt populations of the PRIMA trial are presented in Table 12.

Table 12. Median age (range) and BRCAm and BRCAwt populations

	BRCAwt population (n=473)	BRCAm population (n=223)
Median age (IQR), years	████████	████████

Abbreviations: BRCAm = breast cancer gene mutation; BRCAwt = breast cancer gene wild type; IQR = interquartile range
Source: GSK Data on File

Time to treatment discontinuation

B20. In the comparison against olaparib, the company informs TTD by PFS and AE discontinuations, as was used for rucaparib, where it is assumed that at 2 years only 10% of patients remain on treatment, resulting in a sharp drop in the TTD curve used in the model at this time point. The EAG notes that SACT data for olaparib shows that at two years, 33% of patients remained on treatment and 13% at 3 years.

- a. Please clarify why 10% was assumed appropriate in the base case

As highlighted in Section 3.4.7 of the original CS, feedback from three UK clinical experts consulted by GSK at the advisory board for niraparib indicated an expectation that 5-10% of patients would continue after 36 months. Based on this feedback, an estimate of 10% was selected for the base case analysis for niraparib. Although clinical experts suggested that the proportion continuing treatment with olaparib and rucaparib may be higher due to the earlier stopping rule at 24 months and shorter overall treatment exposure, the 10% assumption was applied to both treatments as a conservative assumption, given that the potential concerns regarding cumulative toxicity and the associated risks of AML/MDS with prolonged use are present for all PARPi comparators.

An alternative TTDD scenario was previously included as part of the submitted economic analyses (Table 66 of the CS) using the full extent of available olaparib SACT TTDD KM data before assuming 100% discontinuation, which reflects the observed 33% at two years and 13% at 3 years remaining on treatment in the olaparib SACT TTDD noted by the EAG (see Figure 78, Appendix J of the CS).

- b. Please also provide a scenario in which the TTD curve from the SOLO-1 trial is used to inform TTD for olaparib

An additional TTDD scenario analysis was also included in the original CS derived based on fitting a simple exponential model through the median time on treatment estimate available from SOLO-1. Although not directly using the SOLO-1 TTDD curve for olaparib, estimates produced by this approach were reasonable similar, albeit slightly lower, to those from the observed SOLO-1 TTDD data (e.g. 71.3% versus ~74% at 1 year, 3.6% vs ~5% at 3 years) with only a small proportion of patients remaining on treatment after 24 months similar to the observed SOLO-1 TTDD curve.

As such, this scenario is anticipated to produce reasonably similar (albeit slightly more conservative) results compared to using the SOLO-1 TTDD curve directly, and so an additional scenario analysis directly using the SOLO-1 TTDD curve has not been conducted.

Costs

B21. Priority question. In light of the updated populations requested by the EAG (CQs A2 and B2) split by HRp and HRd, please provide the equivalent detailed individualised dosing details for niraparib for these populations, as provided in Appendix K of the CS and include this data in the economic model as an option.

Please see our response to clarification questions A1 and A2.

B22. Priority question. Please can the company provide the sources that have been used to inform the subsequent treatment costs. The EAG notes that the cost for doxorubicin (PLD) in the model is substantially higher than reported in the Drugs and Pharmaceutical Electronic Market Information Tool (eMIT) (£396 vs £283). For any treatment costs that are used in the model that have been sourced from BNF when a lower price is available in the eMIT, please update these prices to use eMIT costs only.

Thank you for highlighting this aspect. As indicated in Table 143, Appendix I of the CS, unit costs per package for 1L maintenance and subsequent treatments used eMIT data where available with BNF prices only used for PARPi therapies. It is our understanding that a new version of eMIT was released on 22nd July 2025 after submission with estimates obtained from the previous eMIT database (published 23rd October 2024) used to inform the submitted economic analyses (where a price of £396 per 50mg vial of doxorubicin (PLD) was provided compared to £283 in the updated version). We have updated the base case economic model using prices from the more recent version of eMIT where available, with updated price data presented below in Table 13.

Table 13. Updated subsequent treatment unit costs

Drugs	Unit size 1 (mg)	Pack size 1	List price per pack for size 1 (£)	Unit size 2 (mg)	Pack size 2	List price per pack for size 2 (£)	Source
Subsequent treatment							
Carboplatin	450.0 mg	1	£ 22.92	50.0 mg	1	£ 5.07	eMIT ¹²⁴
Cisplatin	50.0 mg	1	£ 24.33	10.0 mg	1	£ 3.68	eMIT ¹²⁴
Cyclophosphamide	50.0 mg	100	£ 73.95	---	---	---	eMIT ¹²⁴
Paclitaxel	100.0 mg	1	£ 9.48	30.0 mg	1	£ 4.31	eMIT ¹²⁴
Doxorubin (PLD)	50.0 mg	1	£ 9.89	20.0 mg	1	£ 6.94	eMIT ¹²⁴
Gemcitabine	1800.0 mg	1	£ 283.88	200.0 mg	1	£ 150.60	eMIT ¹²⁴

B23. The company used the dose of niraparib based on SACT data combined with the RDI taken from the PRIMA trial. However, the RDI from PRIMA is likely to be correlated with the dosing used. Please clarify why it was considered appropriate to combine these data sources to estimate treatment costs?

GSK agree with the EAG that RDI may be correlated with the starting dose. Therefore, within the submitted base-case, the RDI is indeed dependant on the starting dose received.

As the individualised dosing approach for niraparib is now the standard clinical practice, as supported by clinical opinion as well as RWE, the SACT data for patients starting on the 200mg and 300mg doses were considered more appropriate than PRIMA data, where most patients (n=359) received the higher starting dose of 300 mg (due to the amendment in trial protocol; please see section 2.4.1 of the CS) , and only 125 (approximately one third) received a starting dose of 200 mg.

The SACT data were then combined with the RDI for niraparib from PRIMA, as RDI data were not available from other RWE studies. To avoid or minimise potential bias associated with higher proportions of patients initiating niraparib treatment on the 300mg dose in the PRIMA trial, separate RDI inputs specific to the starting dose were derived from PRIMA, for patients starting on the 200mg and 300mg doses (see Table 47 of the CS) Consequently, higher RDI values were calculated and applied in the

CEM for individuals starting on a 200mg dose compared to a 300mg dose (72.9% vs 62.3% for BRCAm, 74.3% vs 59.9% for BRCAwt).

B24. The company stop applying any PFS health state costs beyond 7 years. However, the EAG notes that this was in line with the initial appraisal for niraparib, which assumed a 'cure point' at 7 years. As the point for long-term remission in the current model is based at 10 years, please clarify why this time point has not been used and provide a scenario analysis where this is applied?

Thank you for highlighting the stopping rule for follow-up and monitoring costs for patients who remain progression free. We agree that the progression free related costs stopping time point should coincide with the 'cure point', thus we have updated the economic model base case to consider a stopping rule for follow-up and monitoring costs applied to patients who remain progression free for at least 10 years. However, please note that the application of a 10-year stopping rule had a very limited impact on the results (see Table 16 and Table 17).

B26. End-of-life care costs for cancer are available from the latest PSSRU Unit Costs of Health and Social Care 2024 Manual (Table 7.2.2). Please explore the PSSRU cancer end of life care cost in a scenario.

An additional scenario analysis has been performed for both populations using the 2024 PSSRU estimate of £13,964 (subsequently inflated to 2024 prices) for general cancer patients (please see Table 20 and Table 21), which had a limited impact on the base case model analysis.

B25. During the previous appraisal for niraparib, it is noted in the final guidance that *"...At technical engagement, the company accepted the ERG's revised costs for heart rate and blood pressure monitoring"*. However, it does not appear that the costs associated with this have been implemented in the current model. Please include a scenario where this is included in line with the previous appraisal.

The niraparib SmPC states that blood pressure should be monitored weekly for the first two months, monthly for the remainder of the first year and periodically afterwards. Assuming that blood pressure measurements would be taken during the 1.33 consultant visits per month applied in the model for all progression-free patients on PARPi treatment, an additional scenario analysis was conducted for each population

including an additional 5.33 consultant outpatient visits as part of the initial one-off monitoring costs for niraparib to generate a total of 8 visits for the first two months of the model (please see Table 20 and Table 21).

However, inclusion of additional consultant-led visit costs for all patients was expected to be conservative for niraparib given that in-person heart rate and blood pressure monitoring were not anticipated to necessarily require a consultant-led outpatient visit, and as noted in TA673 and in the niraparib SmPC, that home-based blood pressure monitoring is expected to be appropriate for a proportion of patients receiving niraparib.

Health related quality of life

B27. The EAG notes that minimal detail is provided in the CS on the regression analysis performed to obtain utility values used in the economic model:

a) Was the regression analysis pre-specified?

Methods for all analyses were pre-planned and carefully reviewed prior to conducting the statistical analysis.

b) How was the model structure and final included variables decided upon?

Base-case utility values shown in Table 45 of the original CS were determined using the best multivariable linear model selected from 24 potential models. Each model considered different combinations of:

- the progression-free survival (PFS) status with either 2 states or 3 states as follows:
 - 2 states: “progression-free” vs “progressed”
 - 3 states: “progression-free” vs “first progression” (post PFS1- and pre-PFS2) vs “second progression” (post-PFS2)
- BRCA status: “BRCAm” vs “BRCAwt” vs “BRCAnd”
- HRD status: “HRd” vs “HRp” vs “HRnd”

- A composite variable for BRCA/HRD groups:
 - “BRCAmut” (i.e. “BRCAm & HRDd/HRnd”)
 - “BRCAwt/HRd” (i.e. “BRCAwt & HRd”)
 - “BRCAnd/HRd” (i.e. “BRCAnd & HRd”)
 - “HRp” (i.e. “BRCAwt & HRp”, or “BRCAnd & HRp”)
 - “HRnd” (i.e. “BRCAwt & HRnd”, or “BRCAnd & HRnd”)
- Treatment: Nira or Placebo.

In these models, the post-baseline utility score was the dependent variable, while the baseline (BL) utility score, PFS state, treatment (trt), and BRCA/HRD groups were candidate independent variables. The models varied by the inclusion of the independent variables and interactions between the PFS state and treatment; i.e., for each of the two PFS statuses (2 or 3 states), a total of 24 models were constructed as follows:

Table 14. Model Covariates

Models	Covariates							
	Baseline utility	2-state progression status	3-state progression status	Treatment	Treatment-by-progression state interaction term	BRCA status	HRD status	BRCA/HRD status ^a
1	x	x						
2	x	x				x		
3	x	x					x	
4	x	x						x
5	x	x		x				
6	x	x		x		x		
7	x	x		x			x	
8	x	x		x				x
9	x	x		x	x	x		
10	x	x		x	x		x	
11	x	x		x	x			x
12	x	x		x	x			
13	x		x					
14	x		x			x		
15	x		x				x	
16	x		x					x
17	x		x	x				
18	x		x	x		x		
19	x		x	x			x	
20	x		x	x				x
21	x		x	x	x	x		
22	x		x	x	x		x	
23	x		x	x	x			x
24	x		x	x	x			

^a For models including this covariate, exclude patients with BRCA/HRD status = "BRCAnd/HRd"

To address the positive correlation of utility scores across repeated patient visits, the Generalized Estimating Equation (GEE) method was utilized, employing either a compound symmetry (CS) or autoregressive (AR1) correlation structure to ensure model convergence. The model chosen as the final one had the lowest quasi-information criteria (QIC), a standard measure of model fit in the GEE approach. This final model included only PFS (i.e. with 2-states: progressed or not progressed) as a covariate for estimating base-case utility values. The resulting utility values from this model were uniformly applied to the health states, regardless of treatment arm.

- c) Details of the regression model outputs, including regression coefficients for the model fitted using data derived using UK tariffs, associated p values for each model coefficient, and evidence of goodness of fit (for example, R² values and residuals plots).

The output below presents the coefficient estimates used for the final economic model, with the QIC value displayed in the last column, which is [REDACTED]. For the 2-state progression status, a value of [REDACTED] indicates that the average utility score in the progressed state is expected to be [REDACTED] lower than in the progression-free state. This difference is statistically significant, with a p-value [REDACTED].

[REDACTED]

		[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]							[REDACTED]
[REDACTED]		[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	
[REDACTED]		[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	
	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]		

Abbreviations: CI = confidence interval; QIC = quasiliikelihood under the independence model criterion; SE = standard error

Source: GSK Data on File Table 7.1

The following output displays the Least Square Mean Estimates aligned with the health state utilities described in Table 45 of the CS. The expected mean value for the progressed state is calculated at [REDACTED], which is [REDACTED] lower than the value for the progression-free state, which is [REDACTED].

Abbreviations: CI = confidence interval; SE = standard error
Source: GSK Data on File Table 7.1

Section C: Textual clarification and additional points

Model implementation

C1. Priority question. The EAG notes that the company's base case probabilistic sensitivity analysis (PSA) takes around 40 minutes to run one analysis. Please provide a convergence plot for the probabilistic sensitivity analysis (PSA) to explore if a smaller number of iterations could be used in the PSA and ensure this is included in the economic model.

PSA convergence plots for incremental costs and QALYs for the BRCAm population are shown in [Error! Reference source not found.](#) and [Error! Reference source not found.](#), and for the BRCAwt population in [Error! Reference source not found.](#) and [Error! Reference source not found.](#), respectively. For the BRCAm population, the plots indicate that the mean incremental costs appear relatively stable after approximately 2,000 simulations, with incremental QALYs fairly stable after around 500 simulations. For the BRCAwt population, mean incremental costs and QALYs were both reasonably stable after approximately 2,000 simulations.

However, 5,000 simulations were conservatively explored in the original CS to ensure stability of the probabilistic INMB results given the small incremental differences in QALYs.

[REDACTED]

[REDACTED]

Abbreviations: OLA = olaparib

[REDACTED]

[REDACTED]

Abbreviations: OLA = olaparib

[REDACTED]

[REDACTED]

Abbreviations: RUCA = rucaparib

[REDACTED]

[REDACTED]

Abbreviations: QALY = quality adjusted life years; RUCA = rucaparib

C2. Priority question. The EAG notes that switching between the two model populations is quite slow. Please explore any methods that could be used to speed the model up. This may be related to having numerous rows/columns hidden between the two scenarios.

Changing the population dropdown triggers Visual Basic for Applications (VBA) code which updates the display of worksheets across the model for the given population, including rows and columns that hide or show model comparators relevant for the selected population. However, we have updated the VBA code to try and improve the speed when switching between populations.

References

C3. Priority question. Please provide the following references:

- a. the relevant papers for any data used in the indirect treatment comparisons reported in the company submission if not already supplied e.g. Banerjee 2021 for SOLO-1; and**

Table 15 outlines references which were included in the ITC for the ATHENA-MONO, SOLO-1, PRIMA and PRIME studies. For the reference pack, please see 'Question C3_References' folder.

Table 15. List of included clinical studies

Study	Citation
ATHENA–MONO	Monk, B. J., Parkinson, C., Lim, M. C., O'malley, D. M., Oaknin, A., Wilson, M. K., & Kristeleit, R. S. (2022). A randomized, phase III trial to evaluate rucaparib monotherapy as maintenance treatment in patients with newly diagnosed ovarian cancer (ATHENA–MONO/GOG-3020/ENGOT-ov45). <i>Journal of Clinical Oncology</i> , 40(34), 3952-3964.
ATHENA–MONO	Fujiwara, K., Kristeleit, R., Ghamande, S., Lim, M. C., Parkinson, C., Morgan, M., Wilson, M. K., Oaknin, A., Buscema, J., Bessette, P., Lorusso, D., Ueland, F., Safra, T., Barlin, J. N., Marme, F., Herzog, T. J., McNeish, I. A., Goble, S., Hume, S., Monk, B. J. Rucaparib maintenance treatment in patients (pts) with newly diagnosed ovarian cancer (OC): Defining benefit according to disease risk subgroups within the phase III ATHENA-MONO study. <i>Annals of Oncology</i> . 2022. 33:S1505-S1506
ATHENA–MONO	Monk, B. J., Parkinson, C., Lim, M. C., O'Malley, D. M., Oaknin, A., Wilson, M. K., Coleman, R. L., Lorusso, D., Oza, A. M., Ghamande, S. A., Christopoulou, A., Prendergast, E., Demirkiran, F., Littell, R. D., Chudecka-Glaz, A. M., Morgan, M. A., Goble, S. M., Hume, S., Fujiwara, K., Kristeleit, R.. ATHENA-MONO (GOG-3020/ENGOT-ov45): A randomized, double-blind, phase 3 trial evaluating rucaparib monotherapy versus placebo as maintenance treatment following response to first-line platinum-based chemotherapy in ovarian cancer. <i>Journal of Clinical Oncology</i> . 2022. 40:#pages#
ATHENA–MONO	Oaknin, A., Kristeleit, R. S., Mahdi, H. S., Lim, M. C., De Vivo, R., Salinas, E. A., Wilson, M. K., Lontos, M., Santin, A. D., Provencher, D. M., Demirkiran, F., Willmott, L. J., Chudecka-Glaz, A. M., Herzog, T. J., Beiner, M. E., Copeland, L. J., McNeish, I. A., Lin, K. K., Monk, B. J.. PATIENTS WITH NEWLY DIAGNOSED OVARIAN CANCER TREATED WITH MAINTENANCE RUCAPARIB: EXPLORATORY BIOMARKER ANALYSIS FROM THE PHASE 3 ATHENA-MONO STUDY (GOG-3020/ ENGOT-OV45; NCT03522246). <i>International Journal of Gynecological Cancer</i> . 2022. 32:A472
ATHENA–MONO	O'Malley, D., Christopoulou, A., Lim, M. C., Diaz, J., Demirkiran, F., Wilson, M., Jewell, A., Drochytsek, V., Bessette, P., Morris, R., Van Gorp, T., Van Le, L., Lindahl, G., Eskander, R., Collins, D., Goble, S., Hume, S., Fujiwara, K., Monk, B., Kristeleit, R.. EFFICACY ANALYSIS BY DISEASE RISK SUBGROUP FOR THE PHASE 3 ATHENA-MONO STUDY (GOG- 3020/ENGOT-OV45) EVALUATING RUCAPARIB MAINTENANCE TREATMENT IN PATIENTS WITH NEWLY DIAGNOSED OVARIAN CANCER. <i>International Journal of Gynecological Cancer</i> . 2022. 32:A16
ATHENA–MONO	Interim post-progression data and updated survival in patients with newly-diagnosed advanced ovarian cancer in ATHENA-MONO
ATHENA–MONO	O'Malley, D. M., Monk, B. J., Lim, M. C., Pradera, J. F., Buscema, J., Wilson, M. K., De Vivo, R., Herzog, T. J., Zagouri, F., Oza, A. M., Mikheeva, O. N., Diaz, J. P., Lisyanskaya, A. S., Morris, R., Bruchim, I., Craib, M., Connor, C., Shih, D., Fujiwara, K., Kristeleit, R.. Final safety results from ATHENA-MONO (GOG-3020/ENGOT-ov45), a randomized, placebo-controlled, double-blind, phase 3 trial evaluating rucaparib monotherapy as maintenance treatment in patients with newly diagnosed ovarian cancer. <i>J Clin Oncol</i> . 2024;42(16):#Pages#.
ATHENA–MONO	Kristeleit, R., O'Malley, D., Lim, M. C., McNeish, I., Herzog, T. J., Wilson, M., Fehm, T. N., Coleman, R. L., Van Gorp, T., Oza, A. M., Mikheeva, O., Buscema, J., Lisyanskaya, A. S., Lindahl, G., Gao, B., Lorusso, D., Morgan, M., Shih, D., Fujiwara, K., Monk, B. J.. 49MO Updated progression-free survival (PFS) in patients (pts) with newly diagnosed advanced ovarian cancer (OC) treated with rucaparib (RUC) in ATHENA-MONO. <i>ESMO open</i> . 2024;9():#Pages#.

Study	Citation
ATHENA-COMBO	Monk, B. J.,Oaknin, A.,O'Malley, D. M.,Wilson, M.,Lorusso, D.,Westin, S.,Oza, A. M.,Zagouri, F.,Herzog, T. J.,Mikheeva, O.,Parkinson, C.,Coleman, R. L.,Lim, M. C.,Chudecka-Glaz, A. M.,Eskander, R. N.,Bruchim, I.,Ghamande, S.,Despain, D.,Fujiwara, K.,Kristeleit, R.. LBA30 ATHENA-COMBO, a phase III, randomized trial comparing rucaparib (RUCA) + nivolumab (NIVO) combination therapy vs RUCA monotherapy as maintenance treatment in patients (pts) with newly diagnosed ovarian cancer (OC). Ann Oncol. 2024;35():S1223.
SOLO-1	A Phase III, Randomised, Double Blind, Placebo Controlled, Multicentre Study of Olaparib Maintenance Monotherapy in Patients With BRCA Mutated Advanced (FIGO Stage III-IV) Ovarian Cancer Following First Line Platinum Based Chemotherapy https://clinicaltrials.gov/ct2/show/NCT01844986
SOLO-1	DiSilvestro, P., Banerjee, S., Colombo, N., Scambia, G., Kim, B. G., Oaknin, A., Friedlander, M., Lisyanskaya, A., Floquet, A., Leary, A., Sonke, G. S., Gourley, C., Oza, A., Gonzalez-Martin, A., Aghajanian, C., Bradley, W., Mathews, C., Liu, J., McNamara, J., . . . Moore, K. N. (2022). Overall Survival With Maintenance Olaparib at a 7-Year Follow-Up in Patients With Newly Diagnosed Advanced Ovarian Cancer and a BRCA Mutation: The SOLO1/GOG 3004 Trial. Journal of clinical oncology, 41(3), 609-617.
SOLO-1	Banerjee, S., Moore, K. N., Colombo, N., Scambia, G., Kim, B. G., Oaknin, A., ... & DiSilvestro, P. (2021). Maintenance olaparib for patients with newly diagnosed advanced ovarian cancer and a BRCA mutation (SOLO1/GOG 3004): 5-year follow-up of a randomised, double-blind, placebo-controlled, phase 3 trial. The Lancet Oncology, 22(12), 1721-1731.
SOLO-1	Colombo, N., Moore, K., Scambia, G., Oaknin, A., Friedlander, M., Lisyanskaya, A., ... & DiSilvestro, P. (2021). Tolerability of maintenance olaparib in newly diagnosed patients with advanced ovarian cancer and a BRCA mutation in the randomized phase III SOLO1 trial. Gynecologic oncology, 163(1), 41-49.
SOLO-1	Friedlander, M., Moore, K. N., Colombo, N., Scambia, G., Kim, B. G., Oaknin, A., ... & DiSilvestro, P. (2021). Patient-centred outcomes and effect of disease progression on health status in patients with newly diagnosed advanced ovarian cancer and a BRCA mutation receiving maintenance olaparib or placebo (SOLO1): a randomised, phase 3 trial. The Lancet Oncology, 22(5), 632-642.
SOLO-1	Wu, L., Zhu, J., Yin, R., Wu, X., Lou, G., Wang, J., ... & Zhang, J. (2021). Olaparib maintenance therapy in patients with newly diagnosed advanced ovarian cancer and a BRCA1 and/or BRCA2 mutation: SOLO1 China cohort. Gynecologic Oncology, 160(1), 175-181.
SOLO-1	DiSilvestro, P., Colombo, N., Scambia, G., Kim, B. G., Oaknin, A., Friedlander, M., ... & Moore, K. N. (2020). Efficacy of maintenance olaparib for patients with newly diagnosed advanced ovarian cancer with a BRCA mutation: subgroup analysis findings from the SOLO1 trial. Journal of Clinical Oncology, 38(30), 3528-3537.
SOLO-1	Moore, K., Colombo, N., Scambia, G., Kim, B. G., Oaknin, A., Friedlander, M., ... & DiSilvestro, P. (2018). Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer. New England Journal of Medicine, 379(26), 2495-2505.
SOLO-1	Friedlander, M. L., Moore, K., Colombo, N., Scambia, G., Kim, B. G., Oaknin, A., ... & DiSilvestro, P. (2020). 234O Maintenance olaparib for patients (pts) with newly diagnosed, advanced ovarian cancer (OC) and a BRCA mutation (BRCAm): 5-year (y) follow-up (f/u) from SOLO1. Annals of Oncology, 31, S1334.
SOLO-1	Colombo, N., Bradley, W., Moore, K., González-Martín, A., Scambia, G., Oaknin, A., ... & Disilvestro, P. (2020). 392 Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer and a BRCA mutation: subgroup analysis by risk in the phase III SOLO1 study. International Journal of Gynecologic Cancer 2020, 30, A76-A77.

Study	Citation
SOLO-1	Bradley, W., Moore, K., Colombo, N., Scambia, G., Kim, B. G., Oaknin, A., ... & DiSilvestro, P. (2021). Maintenance olaparib for patients with newly diagnosed, advanced ovarian cancer and a BRCA mutation: 5-year follow-up from SOLO1. <i>Gynecologic Oncology</i> , 162, S25-S26.
PRIMA	Barretina-Ginesta, M. P., Monk, B. J., Han, S., Pothuri, B., Auranen, A., Chase, D., Lorusso, D., Anderson, C., Abadie-Lacourtoisie, S., Cloven, N., Braicu, E. I., Amit, A., Redondo, A., Shah, R., Kebede, N., Hawkes, C., Gupta, D., Woodward, T., O'Malley, D. M., Gonzalez Martin, A. J.. Quality-adjusted time without symptom or toxicity (QA-TWiST) and quality-adjusted progression-free survival (QA-PFS) of first-line (1L) maintenance niraparib in patients with advanced ovarian cancer (OC): Results from the PRIMA trial. <i>Annals of Oncology</i> . 2021. 32:S736-S737
PRIMA	Barretina-Ginesta, M. P., Monk, B. J., Han, S., Pothuri, B., Auranen, A., Chase, D. M., Lorusso, D., Anderson, C., Abadie-Lacourtoisie, S., Cloven, N., Braicu, E. I., Amit, A., Redondo, A., Shah, R., Kebede, N., Hawkes, C., Gupta, D., Woodward, T., O'Malley, D. M., Gonzalez-Martin, A.. Quality-adjusted time without symptoms of disease or toxicity and quality-adjusted progression-free survival with niraparib maintenance in first-line ovarian cancer in the PRIMA trial. <i>Therapeutic Advances in Medical Oncology</i> . 2022. 14:#pages#
PRIMA	Braicu, E. I., Pothuri, B., Perez-Fidalgo, J. A., O'Malley, D., Honhon, B., Graybill, W., Fabbro, M., Dahlstrand, H., Gupta, D., Monk, B. J.. Efficacy of niraparib therapy in patients with newly diagnosed advanced ovarian cancer by brcawt status: Prima/engot-OV26/GOG-3012 study. <i>International Journal of Gynecological Cancer</i> . 2020. 30:A70-A71
PRIMA	Chase, D. M., Romeo Marin, M., Backes, F., Han, S., Graybill, W., Lund, B., Pothuri, B., Mangili, G., O'Malley, D., Berton, D., Willmott, L., Baumann, K., Coleman, R., Safra, T., Heinzelmann-Schwarz, V., Lorusso, D., Karl, F., Woodward, T., Monk, B. J., Gonzalez-Martin, A.. Impact of disease progression on healthrelated quality of life of advanced ovarian cancer (AOC) patients-pooled analysis from the prima trial. <i>International Journal of Gynecological Cancer</i> . 2021. 31:A284
PRIMA	Chase, D. M., Marin, M. R., Backes, F., Han, S., Graybill, W., Mirza, M. R., Pothuri, B., Mangili, G., O'Malley, D. M., Berton, D., Willmott, L., Baumann, K., Coleman, R. L., Safra, T., Heinzelmann-Schwarz, V., Lorusso, D., Karl, F. M., Woodward, T., Monk, B. J., Gonzalez-Martin, A.. Impact of disease progression on health-related quality of life of advanced ovarian cancer patients - Pooled analysis from the PRIMA trial. <i>Gynecologic Oncology</i> . 2022. 166:494-502
PRIMA	Freyer, G., Pothuri, B., Han, S., Chase, D., Monk, B., Heitz, F., Burger, R., Gaba, L., Van Le, L., Guerra, E., Bender, D., Korach, J., Cloven, N., Chhruca, C., Follana, P., DiSilvestro, P., Baurain, J. F., Jardon, K., Pisano, C., Peen, U., Maenpaa, J., Hoskins, P., Bacque, E., Li, Y., Eliason, L., Gonzalez-Martin, A.. Safety and patient-reported outcomes in patients receiving niraparib in the prima/ENGOTOV26/ GOG-3012 trial. <i>International Journal of Gynecological Cancer</i> . 2020. 30:A12-A13
PRIMA	González-Martín A, Pothuri B, Vergote I, DePont Christensen R, Graybill W, Mirza MR, McCormick C, Lorusso D, Hoskins P, Freyer G, Baumann K, Jardon K, Redondo A, Moore RG, Vulsteke C, O'Cearbhaill RE, Lund B, Backes F, Barretina-Ginesta P, Haggerty AF, Rubio-Pérez MJ, Shahin MS, Mangili G, Bradley WH, Bruchim I, Sun K, Malinowska IA, Li Y, Gupta D, Monk BJ; PRIMA/ENGOT-OV26/GOG-3012 Investigators. Niraparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. <i>N Engl J Med</i> . 2019 Dec 19;381(25):2391-2402. doi: 10.1056/NEJMoa1910962. Epub 2019 Sep 28. PMID: 31562799.
PRIMA	Gonzalez Martin, A. J., Pothuri, B., Vergote, I. B., Graybill, W., Mirza, M. R., McCormick, C., Lorusso, D., Freyer, G., Backes, F., Baumann, K. H., Redondo Sanchez, A., Moore, R. G., Vulsteke, C., O'Cearbhaill, R. E., Malinowska, I., Shtessel, L., Compton, N., Monk, B. J.. PRIMA/ENGOT-OV26/GOG-3012 study: Updated long-term PFS and safety. <i>Annals of Oncology</i> . 2022. 33:S789

Study	Citation
PRIMA	González-Martín, A., Pothuri, B., Vergote, I., Graybill, W., Lorusso, D., McCormick, C. C., ... & Monk, B. J. (2023). Progression-free survival and safety at 3.5 years of follow-up: results from the randomised phase 3 PRIMA/ENGOT-OV26/GOG-3012 trial of niraparib maintenance treatment in patients with newly diagnosed ovarian cancer. <i>European Journal of Cancer</i> , 189, 112908.
PRIMA	Gonzalez-Martin, A., Pothuri, B., Barretina Ginesta, M. P., Graybill, W. S., Vergote, I. B., McCormick, C., Mirza, M. R., Moore, R. G., Lorusso, D., O'Cearbhaill, R. E., Freyer, G., O'Malley, D. M., Heitz, F., Shahin, M. S., Bruchim, I., Bradley, W. H., Compton, N., Malinowska, I., Redondo, A., Monk, B. J.. LBA29 Final overall survival (OS) in patients (pts) with newly diagnosed advanced ovarian cancer (aOC) treated with niraparib (nir) first-line (1L) maintenance: results from PRIMA/ENGOT-OV26/GOG-3012. <i>Ann Oncol.</i> 2024;35():S1222.
PRIMA	W. Graybill, M. Mirza, A. González-Martín, D. O'Malley, L. Gaba, O.W.S. Yap, E. Guerra, P.G. Rose, J. Baurain, S. Ghamande, H. Denys, E. Prendergast, C. Pisano, P. Follana, E.I. Braicu, P.M. Calvert, J. Korach, Y. Li, D. Gupta, B.J. Monk, 13 Efficacy on individualized starting dose (ISD) and fixed starting dose (FSD) of niraparib per investigator-assessment (IA) in newly diagnosed advanced ovarian cancer (OC), <i>International Journal of Gynecological Cancer</i> , Volume 30, Supplement 3, 2020, Page A10, ISSN 1048-891X, https://doi.org/10.1136/ijgc-2020-IGCS.13 . (https://www.sciencedirect.com/science/article/pii/S1048891X2409145X)
PRIMA	Graybill, W. S., Pardo Burdalo, B., O'Malley, D. M., Vergote, I., Monk, B. J., Auranen, A., Copeland, L. J., Sabbatini, R., Herzog, T. J., Follana, P., Pothuri, B., Braicu, E. I., McCormick, C., Yubero, A., Moore, R. G., Vuylsteke, P., Raaschou-Jensen, N., York, W., Hartman, J., Gonzalez-Martin, A.. Predictors of long-term progression-free survival in patients with ovarian cancer treated with niraparib in the PRIMA/ENGOT-OV26/GOG-3012 study. <i>Int J Gynecol Cancer.</i> 2024;34(7):1041 EP - 1050.
PRIMA	Han, S. N., Monk, B. J., Gonzalez-Martin, A.. Time to first subsequent therapy (TFST) and progression-free survival 2 (PFS2) from the phase 3 randomized, double-blind PRIMA/ENGOT-OV26/GOG-3012 study in patients with newly diagnosed ovarian cancer. <i>Gynecologic Oncology.</i> 2020. 159:18-19
PRIMA	Haslund, C. A., Willmott, L. J., Perez, M. J. R., Cloven, N., Van den Bulck, H. F. M., Moore, R. G., Pisano, C., O'Cearbhaill, R. E., Selle, F., Pothuri, B., Harter, P., Ghamande, S., Bruchim, I., Disilvestro, P., Ginesta, M. P. B., Koliadi, A., Malinowska, I., York, W., Gonzalez-Martin, A., Monk, B. J.. 51P Efficacy and safety by time to maintenance therapy treatment initiation in PRIMA/ENGOT-OV26/GOG-3012. <i>ESMO open.</i> 2024;9():#Pages#.
PRIMA	Herzog, Thomas et al.. EP224/#531 Optimization of assessment of disease progression between blinded central independent review and investigator assessment in the PRIMA/ENGOT-ov26/GOG-3012 trial. <i>International Journal of Gynecological Cancer</i> , Volume 32, A140 - A141
PRIMA	Herzog, T. J., Wahab, S. A., Mirza, M. R., Pothuri, B., Vergote, I., Graybill, W. S., ... & Monk, B. J. (2023). Optimizing disease progression assessment using blinded central independent review and comparing it with investigator assessment in the PRIMA/ENGOT-ov26/GOG-3012 trial: challenges and solutions. <i>International Journal of Gynecological Cancer</i> , 33(11).
PRIMA	Martin, A. G., Pothuri, B., Vergote, I. B., Graybill, W., Mirza, M. R., McCormick, C., ... & Monk, B. J. (2023). 33O PRIMA/ENGOT-OV26/GOG-3012 study: long-term conditional PFS. <i>ESMO Open</i> , 8(1).
PRIMA	Mirza, M. R., Martin, A. G., Graybill, W., O'Malley, D. M., Gaba, L., Yap, O. W. S., Guerra, E. M., Rose, P. G., Baurain, J. F., Ghamande, S. A., Denys, H., Prendergast, E., Pisano, C., Follana, P., Baumann, K., Calvert, P., Korach, J., Li, Y., Gupta, D., Monk, B. J.. Evaluation of an individualized starting-dose of niraparib in the PRIMA/ENGOT-OV26/GOG-3012 study. <i>Journal of Clinical Oncology.</i> 2020. 38:#pages#

Study	Citation
PRIMA	Mirza, M. R., González-Martín, A., Graybill, W. S., O'Malley, D. M., Gaba, L., Stephanie Yap, O. W., ... & Monk, B. J. (2023). Prospective evaluation of the tolerability and efficacy of niraparib dosing based on baseline body weight and platelet count: Results from the PRIMA/ENGOT-OV26/GOG-3012 trial. <i>Cancer</i> , 129(12), 1846-1855.
PRIMA	Monk, B. J., Martin, A. G.. Efficacy of niraparib therapy in patients with newly diagnosed advanced ovarian cancer by BRCA and homologous recombination status: PRIMA/ENGOT-OV26/GOG-3012 study. <i>Gynecologic Oncology</i> . 2020. 159:18
PRIMA	Monk, B. J., Barretina-Ginesta, M. P., Pothuri, B., Vergote, I., Graybill, W., Mirza, M. R., McCormick, C. C., Lorusso, D., Moore, R. G., Freyer, G., O'Cearbhaill, R. E., Heitz, F., O'Malley, D. M., Redondo, A., Shahin, M. S., Vulsteke, C., Bradley, W. H., Haslund, C. A., Chase, D. M., Pisano, C., Holman, L. L., eacute,, rez, M. J. R., DiSilvestro, P., Gaba, L., Herzog, T. J., Bruchim, I., Compton, N., Shtessel, L., Malinowska, I. A., Gonz,, aacute,, lez, Mart, iacute,, n, A.. Niraparib first-line maintenance therapy in patients with newly diagnosed advanced ovarian cancer: final overall survival results from the PRIMA/ENGOT-OV26/GOG-3012 trial. <i>Annals of oncology : official journal of the European Society for Medical Oncology</i> . 2024;35(11):981.
PRIMA	A Study of Niraparib Maintenance Treatment in Patients With Advanced Ovarian Cancer Following Response on Front-Line Platinum-Based Chemotherapy. A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study of Niraparib Maintenance Treatment in Patients With Advanced Ovarian Cancer Following Response on Front-Line Platinum-Based Chemotherapy. https://clinicaltrials.gov/ct2/show/NCT02655016
PRIMA	A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study of Niraparib Maintenance Treatment in Patients with Advanced Ovarian Cancer Following Response on Front-Line Platinum-Based Chemotherapy. https://www.clinicaltrialsregister.eu/ctr-search/trial/2015-000952-11/results
PRIMA	O'Cearbhaill, R., Perez-Fidalgo, J. A., Monk, B. J., Vulsteke, C., McCormick, C., Hietanen, S., Moore, R. G., Artioli, G., Shahin, M. S., Selle, F., Bradley, W. H., Baumann, K., O'Malley, D., Tusquets, I., Slomovitz, B. M., Levy, T., Joly, F., Malinowska, I., Gupta, D., Gonzalez-Martin, A.. Efficacy of niraparib by timing of surgery and residual disease: A post-hoc analysis of patients in the prima/engot-ov26/gog-3012 study. <i>International Journal of Gynecological Cancer</i> . 2021. 31:A203-A204
PRIMA	O'Cearbhaill, R. E., Perez-Fidalgo, J. A., Monk, B. J., Tusquets, I., McCormick, C., Fuentes, J., Moore, R. G., Vulsteke, C., Shahin, M. S., Forget, F., Bradley, W. H., Hietanen, S., O'Malley, D. M., Dorum, A., Slomovitz, B. M., Baumann, K., Selle, F., Calvert, P. M., Artioli, G., Levy, T., Kumar, A., Malinowska, I. A., Li, Y., Gupta, D., Gonzalez-Martin, A.. Efficacy of niraparib by time of surgery and postoperative residual disease status: A post hoc analysis of patients in the PRIMA/ENGOT-OV26/GOG-3012 study. <i>Gynecologic Oncology</i> . 2022. 166:36-43
PRIMA	Pothuri, B., Han, S., Chase, D., Heitz, F., Burger, R., Gaba, L., Van Le, L., Guerra, E., Bender, D., Korach, J., Cloven, N. G., Follana, P., Baurain, J. F., Pisano, C., Peen, U., Maenpaa, J., Bacque, E., Li, Y., Martin, A. G., Monk, B. J.. Patient-reported outcomes (PROs) in patients (pts) receiving niraparib in the PRIMA/ENGOT-OV26/GOG-3012 trial. <i>Annals of Oncology</i> . 2020. 31:S612-S613
PRIMA	Pothuri, B., Han, S., Chase, D. M., Heitz, F., Burger, R. A., Gaba, L., ... & González-Martín, A. (2024). Health-related quality of life in patients with newly diagnosed advanced ovarian cancer treated with niraparib vs placebo: Results from the phase 3 randomized PRIMA/ENGOT-OV26/GOG-3012 trial. <i>Gynecologic oncology</i> , 184, 168-177.
PRIMA	Valabrega, G., Pothuri, B., Oaknin, A., Graybill, W., Sánchez, A. B., McCormick, C., ... & Martín, A. G. (2020). 819P Efficacy and safety of niraparib in older patients (pts) with advanced ovarian cancer (OC): Results from the PRIMA/ENGOT-OV26/GOG-3012 trial. <i>Annals of Oncology</i> , 31, S619.

Study	Citation
PRIMA	Valabrega, G., et al. 2024. Examining health-related quality-of-life outcomes in older patients with advanced ovarian cancer treated with niraparib first-line maintenance therapy in context with efficacy and safety findings: results from the PRIMA/ENGOT-OV26/GOG-3012 Trial
PRIMA	Valabrega, G., Pothuri, B., Oaknin, A., Graybill, W. S., Sanchez, A. B., McCormick, C., Baurain, J. F., Tinker, A. V., Denys, H., O'Cearbhaill, R. E., Hietanen, S., Moore, R. G., Knudsen, A., Oslash, de La Motte Rouge, T., Heitz, F., Levy, T., York, W., Gupta, D., Monk, B. J., Gonzales, Martinez, A. Efficacy and safety of niraparib in patients aged 65 years and older with advanced ovarian cancer: results from the PRIMA/ENGOT-OV26/GOG-3012 trial. <i>Gynecol Oncol.</i> 2024;187():128.
PRIMA	Vulsteke, C. et al., 2024. Tolerability of the niraparib individualised starting dose in the PRIMA/ENGOT-OV26/GOG-3012 trial of niraparib first-line maintenance therapy
PRIMA	Vulsteke, C., Chambers, S. K., Perez, M. J. R., Chan, J. K., Raaschou-Jensen, N., Zhuo, Y., Lorusso, D., Herzog, T. J., de la Motte Rouge, T., Thomes Pepin, J. A., Braicu, E. I., Chen, L. M., Levy, T., Barter, J. F., Pilar Barretina-Ginesta, M., Joosens, E., York, W., Malinowska, I. A., Gonzales, Martinez, A., Monk, B. J.. Tolerability of the niraparib individualized starting dose in the PRIMA/ENGOT-OV26/GOG-3012 trial of niraparib first-line maintenance therapy. <i>European journal of cancer (Oxford, England: . 2024;208():114157.</i>
PRIME	Wang, J., Wu, L., Zhu, J., Yin, R., Pan, L., Kong, B., Zheng, H., Liu, J., Wu, X., Wang, L., Huang, Y., Wang, K., Zou, D., Zhao, H., Wang, C., Lu, W., Lin, A., Zhen, X., Hang, W., Hou, J.. IMPACT OF INITIATION TIMING OF NIRAPARIB MAINTENANCE TREATMENT IN NEWLY DIAGNOSED ADVANCED OVARIAN CANCER. <i>International journal of gynecological cancer.</i> 2022. 32:A174
PRIME	Li, N., Zhu, J., Yin, R., Wang, J., Pan, L., Kong, B., ... & Wu, L. (2023). Treatment with niraparib maintenance therapy in patients with newly diagnosed advanced ovarian cancer: a phase 3 randomized clinical trial. <i>JAMA oncology</i> , 9(9), 1230-1237.
PRIME	Li, N., Zhu, J., Yin, R., Wang, J., Pan, L., Kong, B., Zheng, H., Liu, J., Wu, X., Wang, L., Huang, Y., Wang, K., Zou, D., Zhao, H., Wang, C., Lu, W., Lin, A., Lou, G., Li, G., Qu, P., Yang, H., Zhen, X., Hang, W., Hou, J., Wu, L.. Efficacy and safety of niraparib as maintenance treatment in patients with newly diagnosed advanced ovarian cancer using an individualized starting dose (PRIME Study): A randomized, double-blind, placebo-controlled, phase 3 trial (LBA 5). <i>Gynecologic Oncology.</i> 2022. 166:S50-S51
PRIME	Zhu, J., Wu, L., Yin, R., Wang, J., Pan, L., Kong, B., ... & Hou, J. (2023). Impact of dose modifications due to treatment-emergent adverse events (TEAEs) on the efficacy of niraparib maintenance treatment with an individualized starting dose in patients (Pts) with newly diagnosed advanced ovarian cancer (aOC)(1266). <i>Gynecologic Oncology</i> , 176, S168-S169.
PRIME	Pan, L., Wu, L., Zhu, J., Yin, R., Wang, J., Kong, B., ... & Hou, J. (2023). 37MO Niraparib maintenance therapy in patients with newly diagnosed advanced ovarian cancer: A post hoc analysis on efficacy by surgical timing and residual disease status in the phase III PRIME trial. <i>ESMO Open</i> , 8(1).
PRIME	Yin, R., Li, N., Wu, L., Wang, J., Zhu, J., Pan, L., Kong, B., Zheng, H., Liu, J., Wu, X., Wang, L., Huang, Y., Wang, K., Zou, D., Zhao, H., Wang, C., Lu, W., Zhen, X., Hang, W., Hou, J.. Efficacy of niraparib maintenance therapy in patients with newly diagnosed advanced ovarian cancer in phase 3 PRIME study: A subgroup analysis by response to first-line platinum-based chemotherapy. <i>Journal of Clinical Oncology.</i> 2022. 40:#pages#

b. the clinical study report (CSR) for PRIME.

The CSR for PRIME is not available, as the study was not conducted by GSK.

Additional points

C4. Priority question. Within the CS, the company has highlighted the entirety of figures blue where these figures contain confidential information. In doing so, this renders figures difficult to interpret. Please can the company provide new versions of these figures where a blue border has been used to mark confidentiality instead of highlighting the entirety of the figures.

Please note, the following figure numbers are aligned to the company submission (as opposed to the clarification questions).



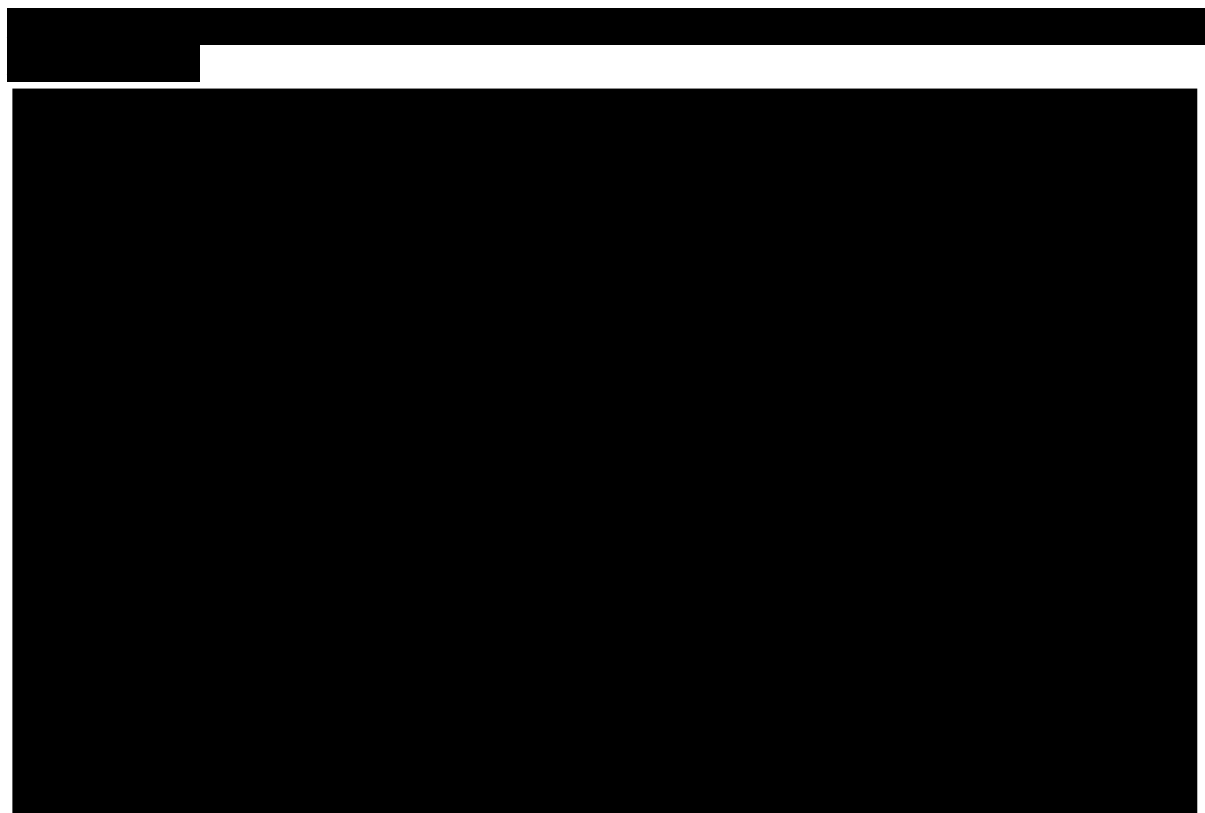
Abbreviations: CI = confidence interval; ITT = intention-to-treat; PFS = progression-free survival
Source: Monk 2024⁸



Abbreviations: CI = confidence interval; HRd = homologous deficient population; PFS = progression-free survival
Source: Monk 2024⁸



Abbreviations: CI = confidence interval; HR = hazard ratio; ITT = intention-to-treat; TFST = time to first subsequent therapy
Source: OS CSR 2024²¹



Abbreviations: CI = confidence interval; HR = hazard ratio; ITT = intention-to-treat; PFS2 = progression-free survival
2
Source: OS CSR 2024²¹



Abbreviations: CI = confidence interval; ITT = intention-to-treat; OS = overall survival
Source: Monk 2024⁸

Abbreviations: BRCA = breast cancer gene; CI = confidence interval; CR = complete response; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report form; HR = hazard ratio; HRDnd = homologous recombination deficiency not determined; HRDneg = homologous recombination deficiency negative; HRDpos = homologous recombination deficiency positive; PFS = progression-free survival; PR = partial response; tBRCA = tumour breast cancer gene; tBRCAmut = tumour breast cancer gene mutated; tBRCAwt = tumour breast cancer gene wild type
Source: CSR 2024²¹

[Redacted]

[Redacted]

Abbreviations: BICR = blinded independent central review; CI = confidence interval; ITT = intention-to-treat; NE = not estimable; PFS = progression-free survival
Source: Li 2023¹⁰

[Redacted]

[Redacted]

Abbreviations: CI = confidence interval; ITT = intention-to-treat; NE = not estimable; TFST = time to first subsequent anti-cancer therapy
Source: Li 2023¹⁰

[REDACTED]

[REDACTED]

Abbreviations: ITT = intention-to-treat; mo = months NE = not estimable; NR = not reached; OS = overall survival
Source: Li 2023¹⁰

[REDACTED]

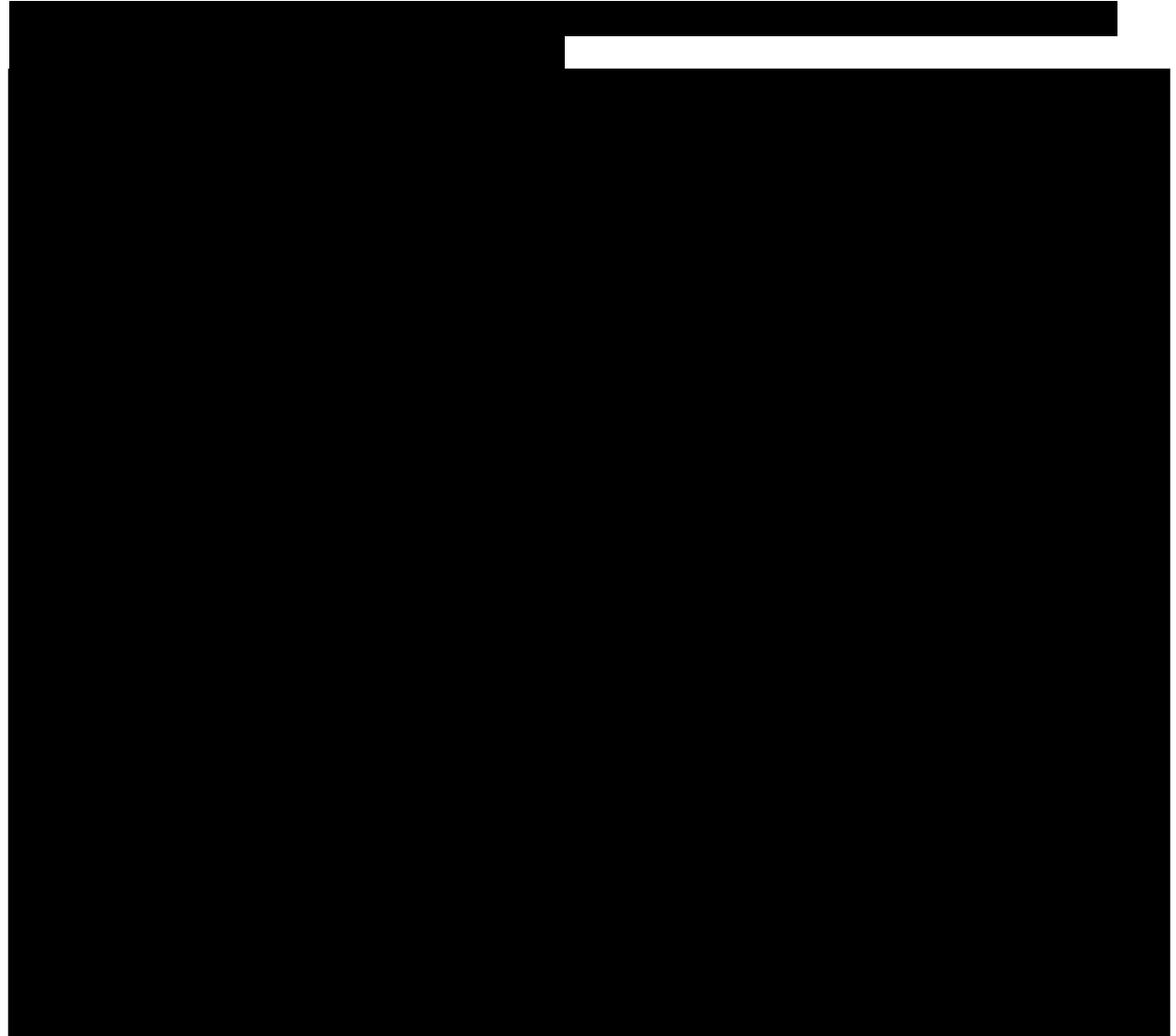
[REDACTED]

Abbreviations: BRCA = breast cancer gene; CI = confidence interval; ITT = intention to treat; PFS = progression-free survival

^a The germline BRCA variants include pathogenic and suspected pathogenic ones; the others were classified as non-germline BRCA variants

^b The homologous recombination status was deficient if a patient had germline BRCA variants and/or the tumour homologous recombination deficiency (HRD) status was positive on the HRD assay (BGI Genomics), proficient if a patient had no germline BRCA variants and the tumour HRD status was negative on the HRD assay, and indeterminate if a patient had no germline BRCA variants and the tumour HRD status was unknown on the HRD assay.

Source: Li 2023¹⁰



Abbreviations: BRCAm = breast cancer mutation; BRCAwt = breast cancer wild type; CI = confidence interval; HRd = homologous recombination deficiency; HRp = homologous recombination proficiency; ITC = indirect treatment comparison; ITT = intent-to-treat; PFS = progression-free survival.

[Redacted]

[Redacted]

Abbreviations: HR = hazard ratio; HRd = homologous recombination deficiency; ITC = indirect treatment comparison; ITT = intent-to-treat; OS = overall survival

[REDACTED]

[REDACTED]

Abbreviations: BRCAm = breast cancer mutation; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; ITT = intent-to-treat; PFS-INV = progression-free survival investigator-assessed.

[REDACTED]

[REDACTED]

Abbreviations: BRCAm = breast cancer mutation; CI = confidence interval; HR = hazard ratio; ITT = intent-to-treat; PFS-INV = progression-free survival investigator-assessed.

[REDACTED]

[REDACTED]

Abbreviations: PFS = progression-free survival



Abbreviations: KM = Kaplan-Meier; PFS = progression-free survival



Abbreviations: KM = Kaplan-Meier; OS = overall survival; PFS = progression-free survival

[REDACTED]

Abbreviations: KM = Kaplan-Meier; OS = overall survival; PFS = progression-free survival

[REDACTED]

Abbreviations: NIRA = niraparib; OLA = olaparib

[REDACTED]

[REDACTED]

Abbreviations: NIRA = niraparib; RUCA = rucaparib

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

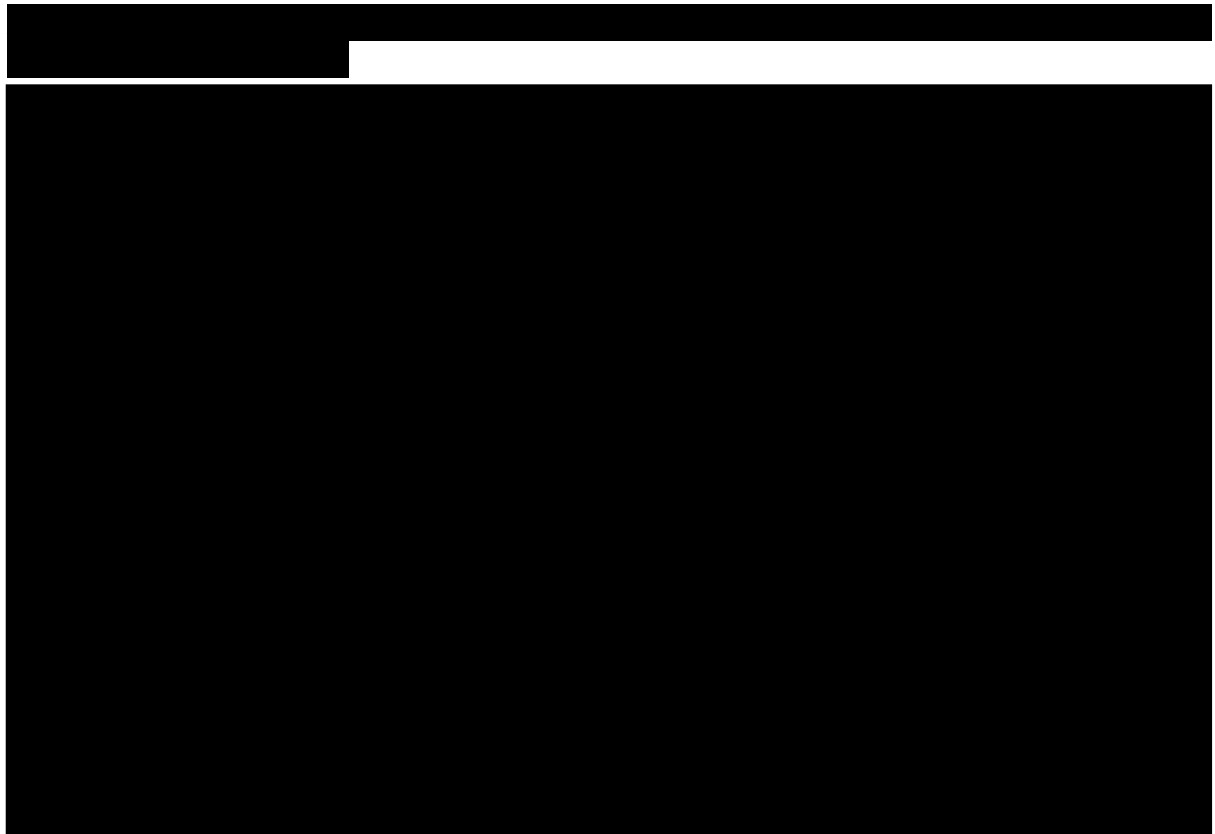
[REDACTED]



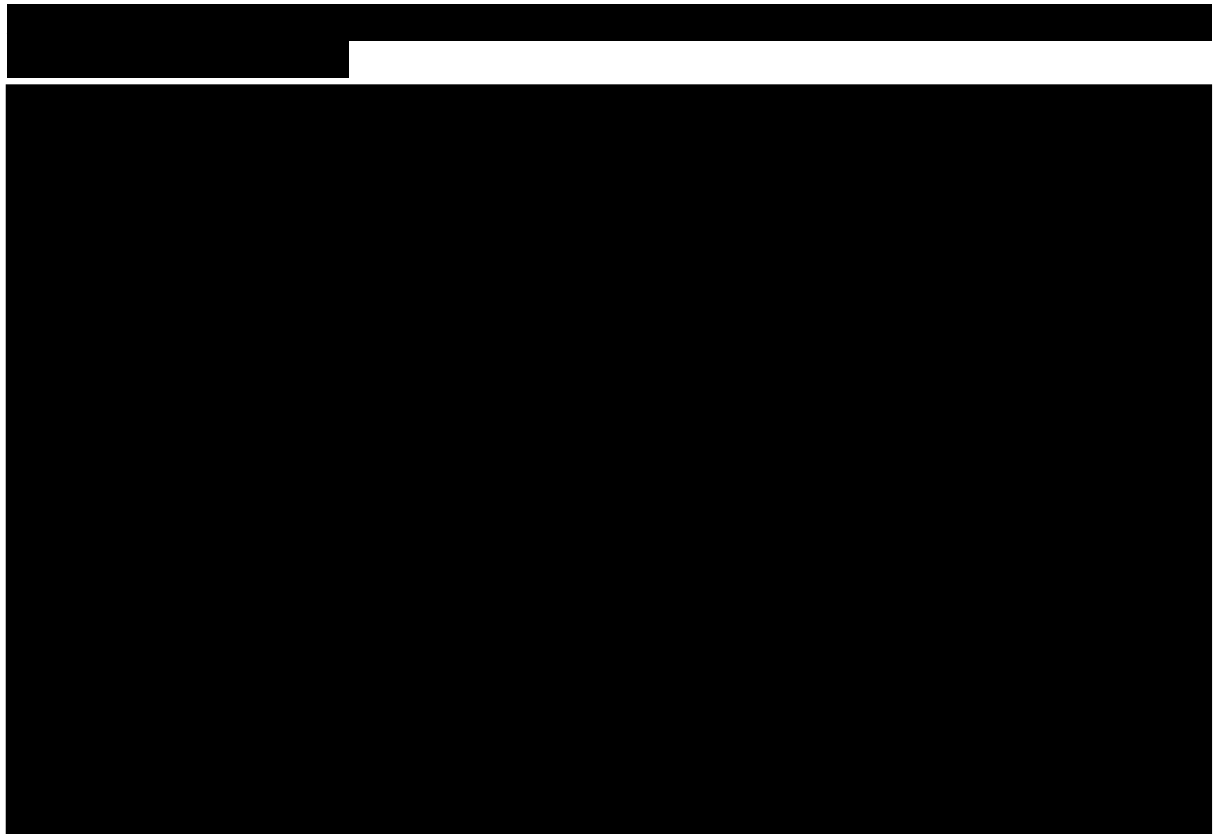
Abbreviations: AE = adverse event; HCRU = healthcare resource use; KM = Kaplan-Meier; NIRA = niraparib; OLA = olaparib; PFS = progression-free survival; RDI = relative dose intensity
Note: PFS parametric fit P1 and P2 are the first and second coefficients of the parametric survival model. TTDD KM random sample is the random number used to vary, with the SE, the TTDD Kaplan-Meier curve.



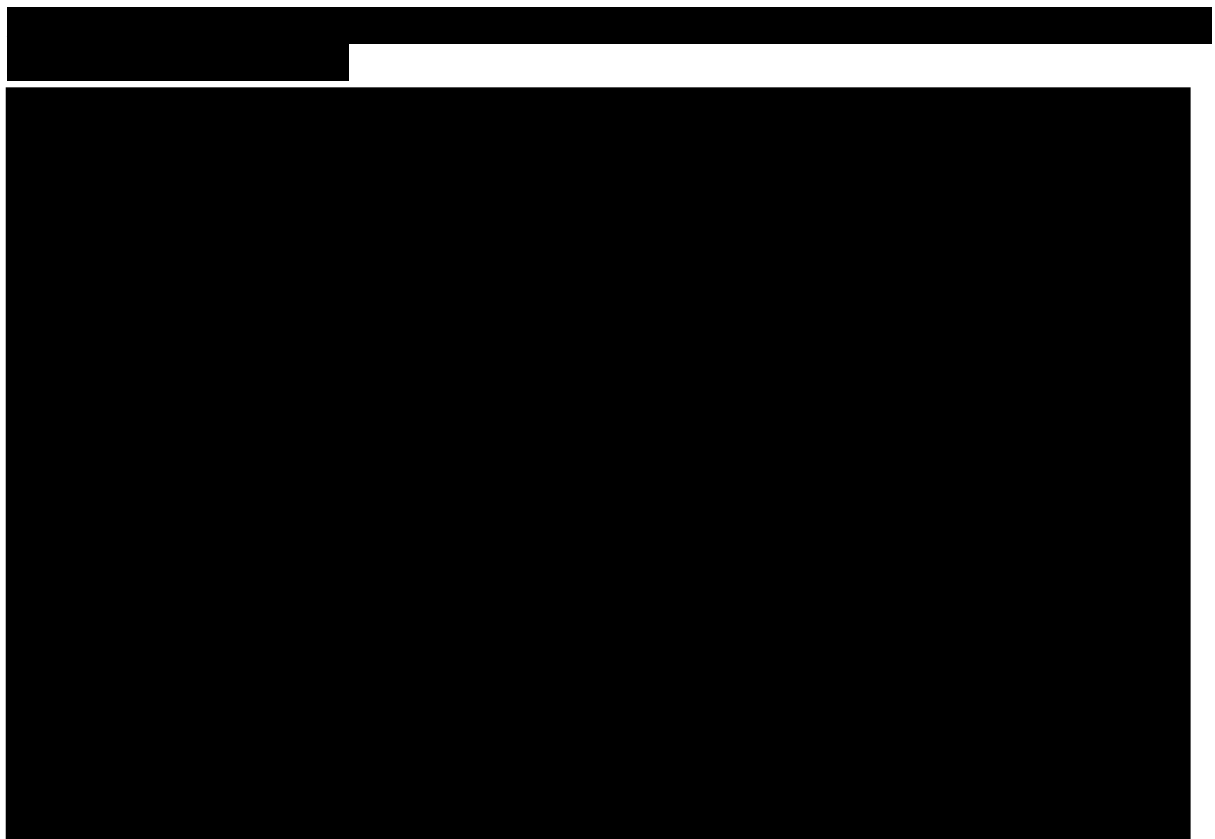
Abbreviations: AE = adverse event; HCRU = healthcare resource use; KM = Kaplan-Meier; NIRA = niraparib; PFS = progression-free survival; RDI = relative dose intensity; RUCA = rucaparib
Note: PFS parametric fit P1 and P2 are the first and second coefficients of the parametric survival model. TTDD KM random sample is the random number used to vary, with the SE, the TTDD Kaplan-Meier curve.



Abbreviations: BRCAm = BRCA mutation; CI = confidence interval; HRd = homologous recombination deficient;
PFS = progression-free survival
Source: Monk 2024⁸



Abbreviations: BRCAwt = BRCA wild type; CI = confidence interval; PFS = progression-free survival
Source: Monk 2024⁸



Abbreviations: CI = confidence interval; HRp = homologous recombination proficient; PFS = progression-free survival
Source: Monk 2024⁸



Abbreviations: BICR = blinded independent central review; CI = confidence interval; HR = homologous recombination deficient; NE = not estimable; NR = not reached; PFS = progression-free survival
Source: Li 2023

[Redacted]

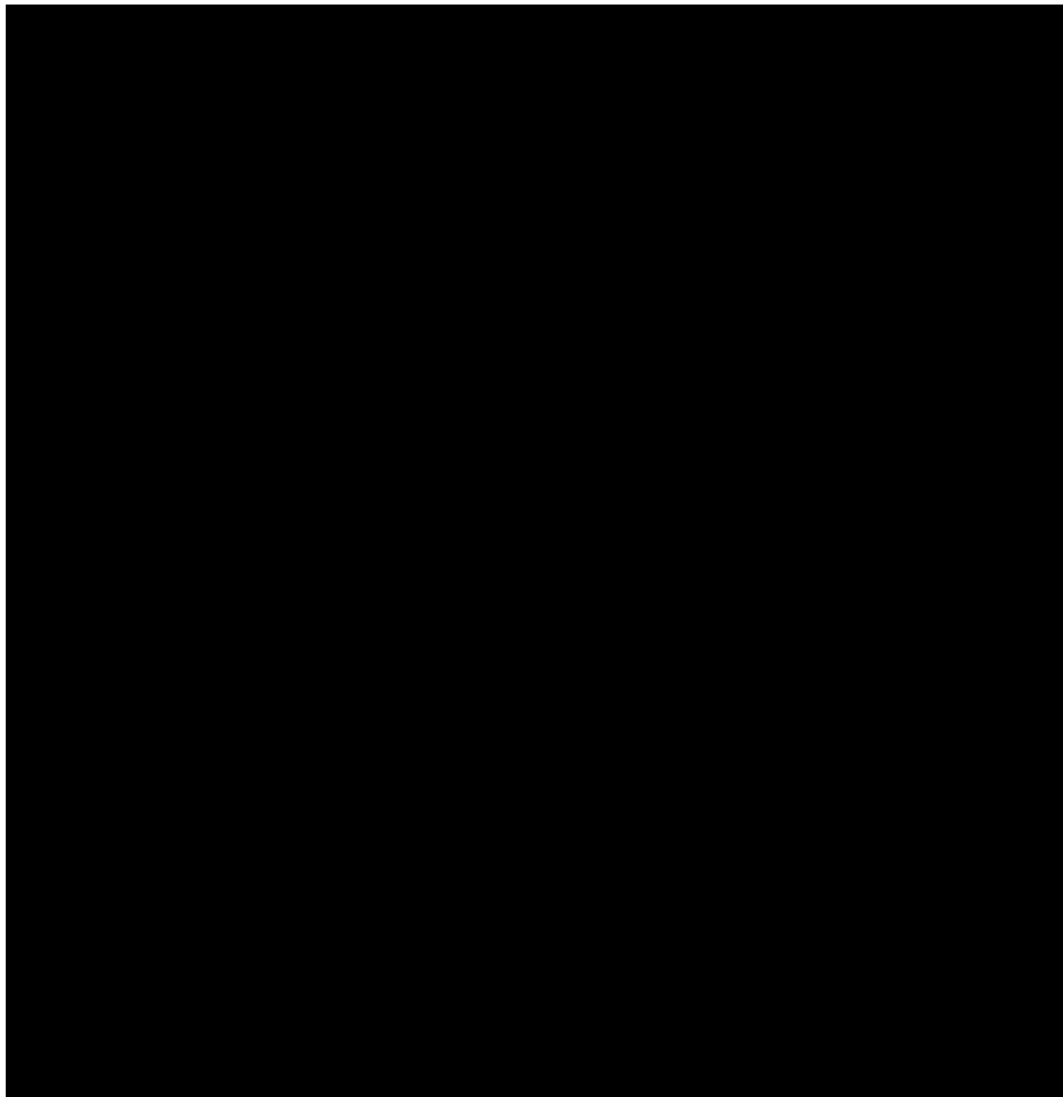
[Redacted]

Abbreviations: BICR = blinded independent central review; BRCAm = BRCA mutated; BRCAwt = BRCA wild type; CI = confidence interval; NE = not estimable; NR = not reached; PFS = progression-free survival
Source: Li 2023

[Redacted]

[Redacted]

Abbreviations: BICR = blinded independent central review; CI = confidence interval; HRD = homologous recombination deficiency; HRp = homologous recombination proficient; NE = not estimable; PFS = progression-free survival
Source: Li 2023



Abbreviations: BRCAm = breast cancer gene mutation; BRCAwt = breast cancer gene wild type; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; FIGO = International Federation of Gynaecology and Obstetrics; FSD = fixed starting dose; HRD = homologous recombination deficiency; HRd = homologous recombination deficient; HRnd = homologous recombination no data; HRp = homologous recombination proficient; ISD = individual starting dose; NACT = neoadjuvant chemotherapy; OS = overall survival; PBCT = platinum-based chemotherapy; PFS = progression-free survival; PS = performance status
Source: Monk 2024⁸

[Redacted]

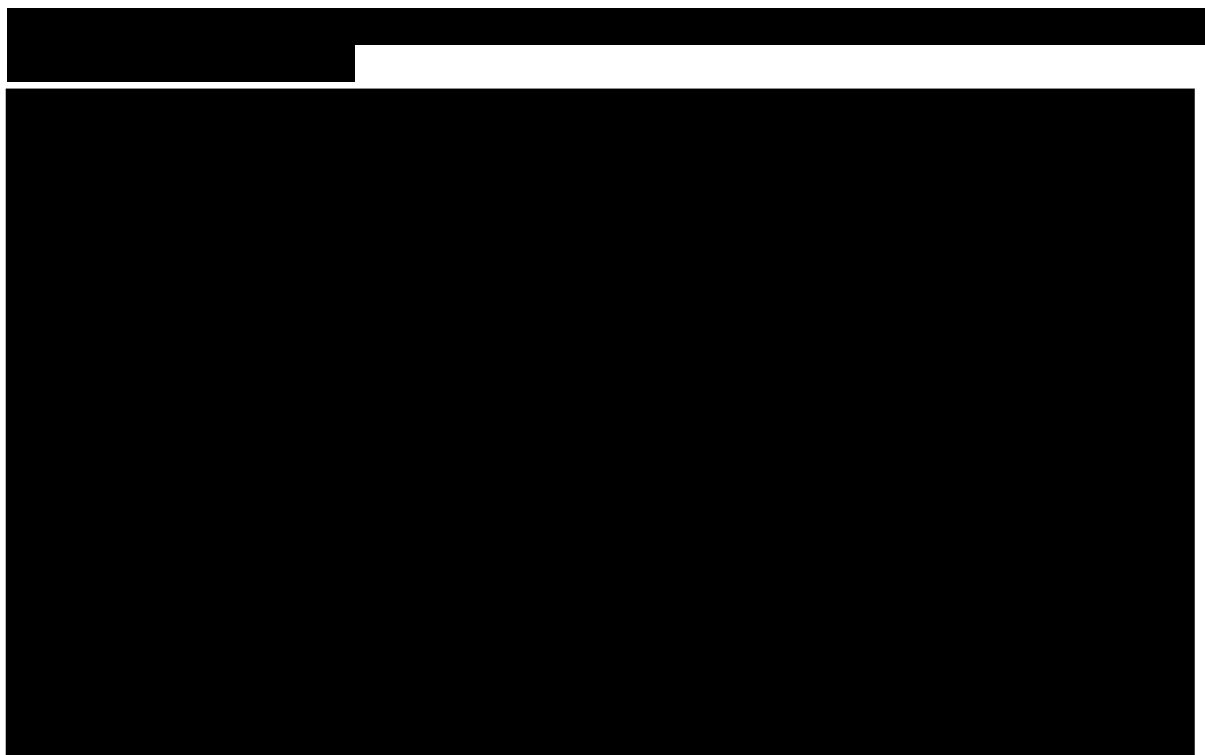
[Redacted]

Abbreviations: CI = confidence interval; HRd = homologous recombination deficient; OS = overall survival
Source: Monk 2024⁸

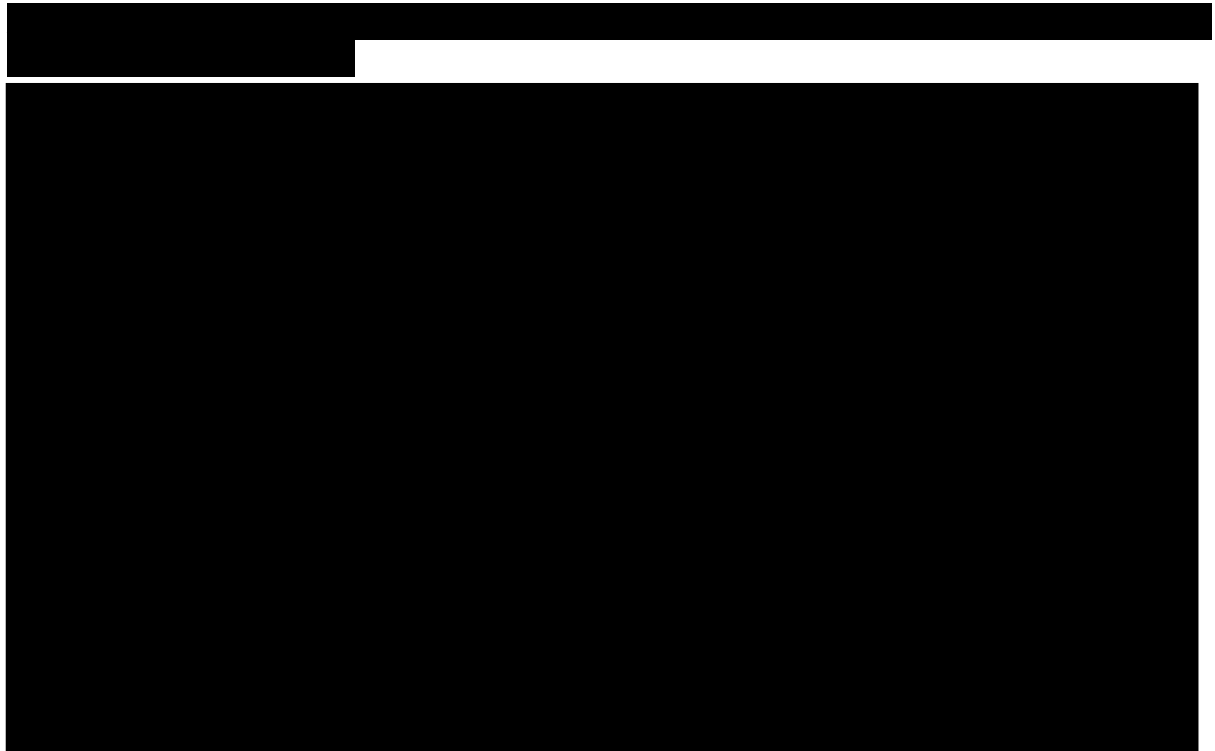
[Redacted]

[Redacted]

Abbreviation: CI = confidence interval; HRp = homologous recombination proficient; OS = overall survival
Source: Monk 2024⁸



Abbreviations: BRCAm = breast cancer mutation; CI = confidence interval; HRd = homologous recombination deficient; OS = overall survival
Source: Monk 2024⁸



Abbreviation: BRCAwt = breast cancer wild type; CI = confidence interval; HRd = homologous recombination deficient; OS = overall survival
Source: Monk 2024⁸

[REDACTED]

[REDACTED]

Abbreviations: BW = body weight; FSD = fixed starting dose; ISD = individualised starting dose; PC = platelet count
Percentage of patients at niraparib dose level by month. Percentages may not total 100 because of rounding.
(A) Subgroup A: 300-mg FSD, baseline BW ≥ 77 kg and PC $\geq 150,000/\mu\text{L}$ (n = 72). (B) Subgroup B: 300-mg ISD, baseline BW ≥ 77 kg and PC $\geq 150,000/\mu\text{L}$ (n = 34). (C) Subgroup C: 300-mg FSD, baseline BW < 77 kg or PC $< 150,000/\mu\text{L}$ (n = 243). (D) Subgroup D: 200-mg ISD (n = 122). Data cutoff date: May 17, 2019.
Source: Mirza 2023²²

[REDACTED]

[REDACTED]

Abbreviations: CI = confidence interval; FSD = fixed starting dose; ISD = individualised starting dose; HRD = homologous recombination deficient; HRp = homologous recombination proficient; PFS = progression free survival

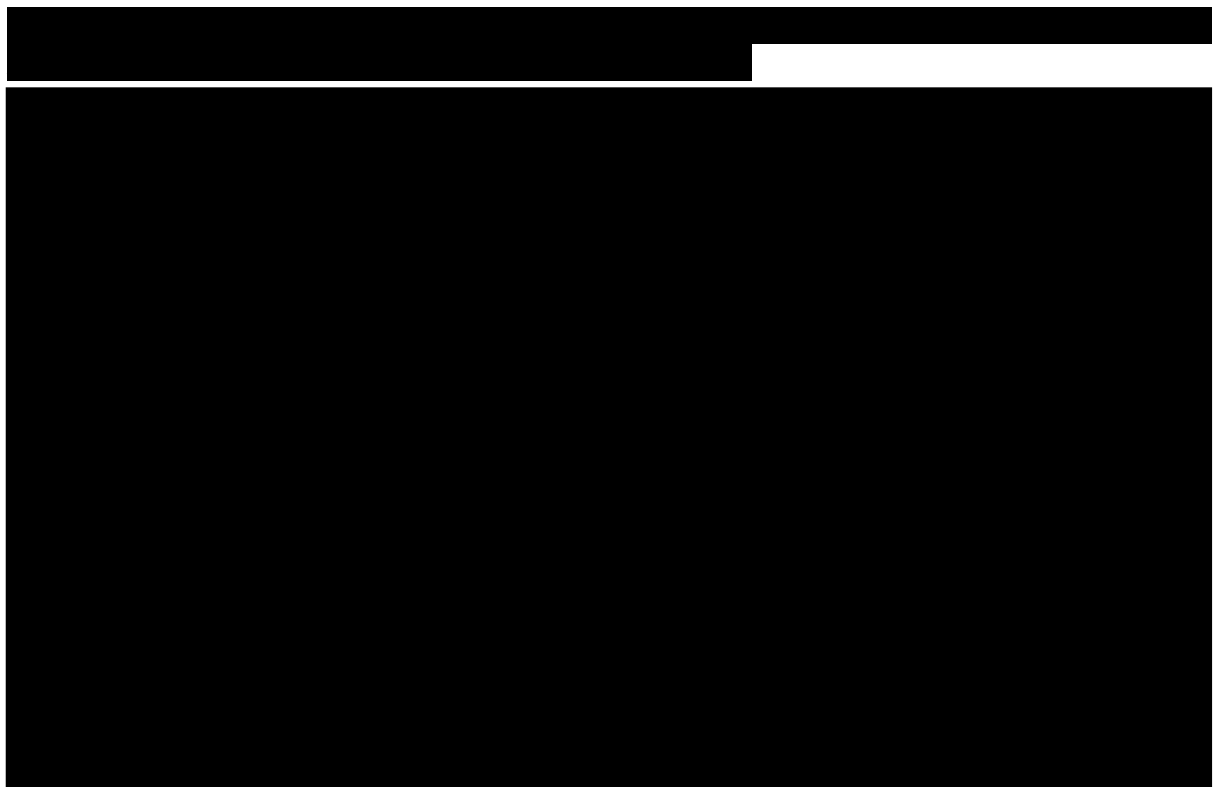
The original data cutoff date was 17 May 2019. The updated data cutoff date was 17 November 2019

Source: Mirza 2023²²

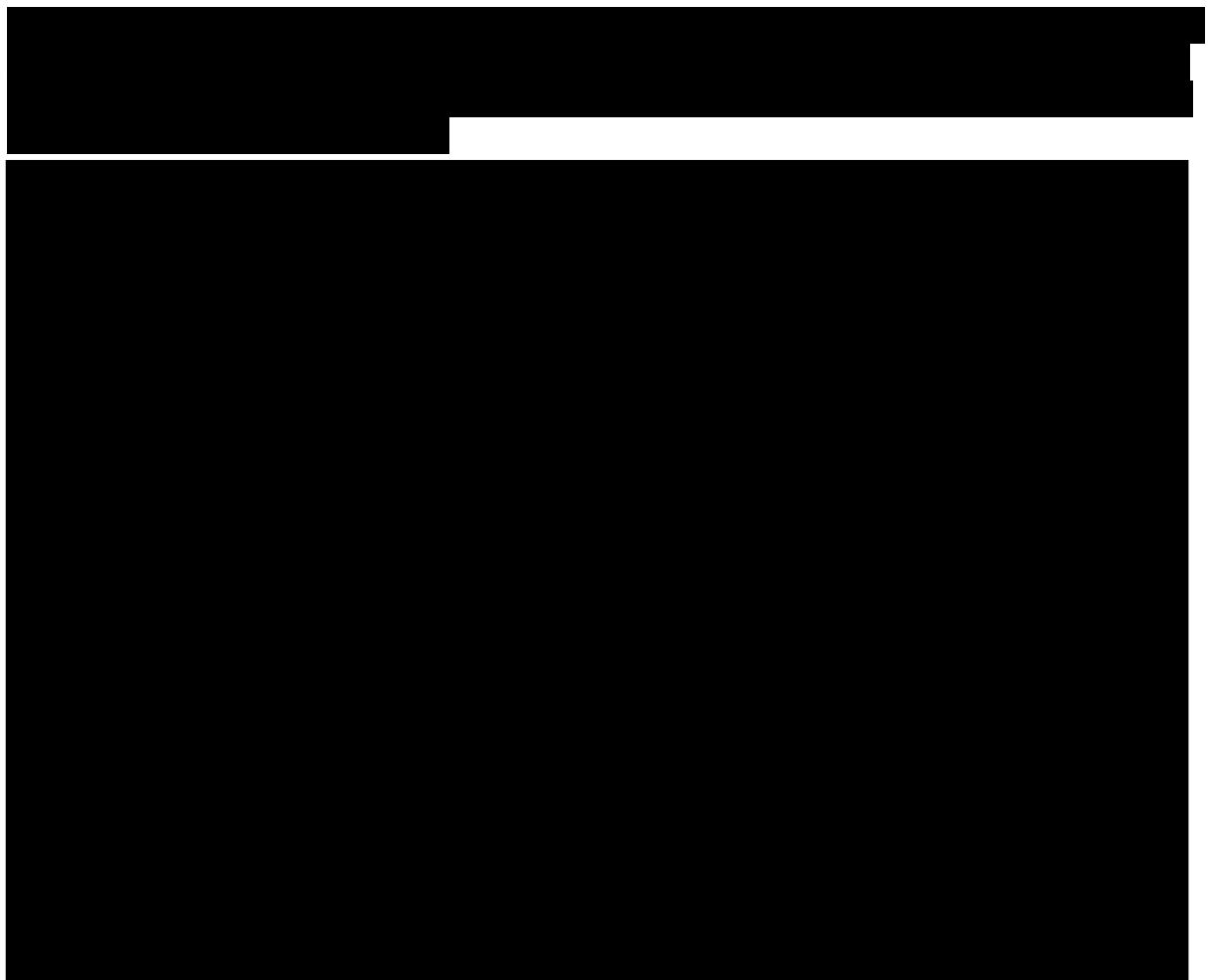


[REDACTED]

[REDACTED]



Abbreviations: KM = Kaplan Meier; PFS = progression-free survival



Abbreviations: KM = Kaplan Meier; NIRA = niraparib; PFS = progression-free survival

[REDACTED]

[REDACTED]

[Redacted]

[Redacted]

[REDACTED]

[REDACTED]

Abbreviations: BRCAm = breast cancer mutation; KM = Kaplan Meier; NIRA = niraparib; OS = overall survival; PFS = progression-free survival



Abbreviations: BRCAm = breast cancer mutation; KM = Kaplan Meier; NIRA = niraparib; OS = overall survival; PFS = progression-free survival

[Redacted]

[Redacted]

Abbreviations: CI = confidence interval; HR = hazard ratio

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Abbreviations: NIRA = niraparib; OLA = olaparib

[REDACTED]

[REDACTED]

[REDACTED]

Abbreviations: NIRA = niraparib; OLA = olaparib

[REDACTED]

[REDACTED]

[REDACTED]

Abbreviations: NIRA = niraparib; OLA = olaparib

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Abbreviations: KM = Kaplan Meier; NIRA = niraparib; PFS = progression-free survival

[REDACTED]

[REDACTED]

Abbreviations: KM = Kaplan Meier; NIRA = niraparib; PFS = progression-free survival

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Abbreviations: BRCAwt = breast cancer gene wild type; KM = Kaplan Meier; NIRA = niraparib; OS = overall survival; PFS = progression-free survival

[REDACTED]

[REDACTED]

Abbreviations: BRCAwt = breast cancer gene wild type; KM = Kaplan Meier; NIRA = niraparib; OS = overall survival; PFS = progression-free survival

[Redacted]

[Redacted]

Abbreviations: CI = confidence interval; HR = hazard ratio

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Abbreviations: NIRA = niraparib; OLA = olaparib

[REDACTED]

[REDACTED]

[REDACTED]

Abbreviations: NIRA = niraparib; RUCA = rucaparib

[REDACTED]

[REDACTED]

[REDACTED]

Abbreviations: NIRA = niraparib; RUCA = rucaparib

[REDACTED]

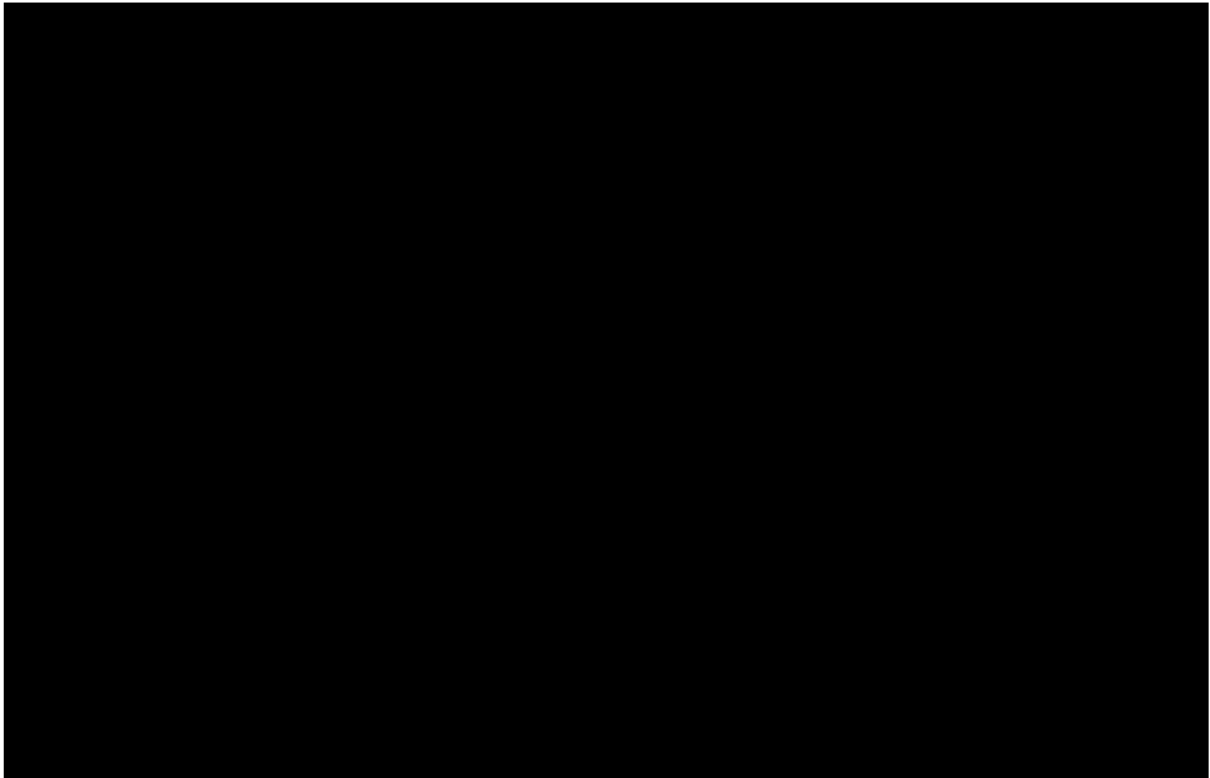
[REDACTED]

[REDACTED]

[REDACTED]

C5. Priority question. Within the CS, several figures (e.g., Figures 23 and 24) do not have a legible legend. Please can the company provide updated figures where the legend is clearly readable.

[REDACTED]



Abbreviations: BRCAm = breast cancer mutation; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; ITT = intent-to-treat; PFS-INV = progression-free survival investigator-assessed.

[REDACTED]

[REDACTED]

Abbreviations: BRCAm = breast cancer mutation; CI = confidence interval; HR = hazard ratio; ITT = intent-to-treat; PFS-INV = progression-free survival investigator-assessed.

Appendix

Updated Cost-effective Model Results

Base-case results

The total and incremental costs, QALYs, and LYG, along with the incremental cost per QALY and incremental Net Monetary Benefit (NMB) for the base case with PAS discount, are presented below in Table 16 for BRCAm and Table 17 for BRCAwt population. In the BRCAm population, niraparib compared to olaparib resulted in cost savings of [REDACTED] with the PAS price for niraparib. The health outcomes were largely equivalent with only a very marginal difference in QALYs of [REDACTED] due to nominal differences in AE incidence estimates applied. The resulting incremental NMB indicated niraparib to be highly cost-effective, amounting to [REDACTED] at a willingness-to-pay threshold (WTP) of £30,000 per QALY when including the niraparib PAS price discount.

For the BRCAwt population, niraparib compared with rucaparib resulted in cost savings of [REDACTED] when including the niraparib PAS price discount, with marginally lower incremental QALYs of [REDACTED] making niraparib dominant over rucaparib. The resulting incremental NMB was [REDACTED] at a WTP of £30,000 per QALY, when including the niraparib PAS price discount.

Table 16. Base-case results with niraparib PAS discount - BRCAm

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)	Incremental NMB at £20,000	Incremental NMB at £30,000
Niraparib	██████	8.21	████	██████	0.00	██████	Less costly, less effective	██████	██████
Olaparib	£128,104	8.21	6.27						

Abbreviations: ICER = incremental cost-effectiveness ratio; LYG = life years gained; QALYs = quality-adjusted life years; NMB = net monetary benefit

Table 17. Base-case results with niraparib PAS discount - BRCAwt

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)	Incremental NMB at £20,000	Incremental NMB at £30,000
Niraparib	██████	4.75	████	██████	0.00	██████	Less costly, more effective	██████	██████
Rucaparib	£ 117,230	4.75	3.50						

Abbreviations: ICER = incremental cost-effectiveness ratio; LYG = life years gained; QALYs = quality-adjusted life years; NMB = net monetary benefit

Probabilistic sensitivity analysis

Results from the PSA for both the BRCAm (vs. olaparib) and BRCAwt (vs. rucaparib) population base-case analyses are presented in Table 18 and Table 19, using the PAS price for niraparib. The results demonstrate good consistency with the deterministic analysis and show that niraparib remains a cost-effective treatment strategy versus olaparib and rucaparib, resulting in cost savings.

The cost-effectiveness plane for niraparib versus olaparib and versus rucaparib is presented in **Error! Reference source not found.** and

, respectively. At a willingness to pay threshold of £30,000, niraparib has a 100% probability of being cost-effective compared with olaparib and rucaparib. The cost-effectiveness acceptability curves of niraparib versus olaparib and versus rucaparib are not presented, since niraparib is cost-effective with 100% probability up to very large willingness to pay thresholds.

Table 18. Probabilistic base-case results with niraparib PAS discount – BRCAm

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)	Incremental NMB at £20,000	Incremental NMB at £30,000
Niraparib		8.42			0.00		Less costly, less effective		
Olaparib	£128,656	8.42	6.41						

Abbreviations: ICER = incremental cost-effectiveness ratio; LYG = life years gained; QALYs = quality-adjusted life years; NMB = net monetary benefit

Table 19. Probabilistic base-case results with niraparib PAS discount – BRCAwt

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)	Incremental NMB at £20,000	Incremental NMB at £30,000
Niraparib		4.78			0.00		Less costly, more effective		
Rucaparib	£ 117,264	4.78	3.52						

Abbreviations: ICER = incremental cost-effectiveness ratio; LYG = life years gained; QALYs = quality-adjusted life years; NMB = net monetary benefit

[REDACTED]

[REDACTED]

Abbreviations: ICER = incremental cost-effectiveness ratio; NIRA = niraparib; OLA = olaparib; QALY = quality-adjusted life year

[REDACTED]

[REDACTED]

Abbreviations: ICER = incremental cost-effectiveness ratio; NIRA = niraparib; QALY = quality-adjusted life year; RUCA = rucaparib

Deterministic sensitivity analysis

The results of the DSA for the 10 most influential parameters on incremental net monetary benefit are presented in **Error! Reference source not found.** for the BRCAm population (niraparib vs. olaparib) and in **Error! Reference source not found.** for the BRCAwt population (niraparib vs. rucaparib). The DSA outcomes indicate that the most influential parameters against olaparib included parameters determining PFS and TTDD for niraparib, the likelihood of AE discontinuations and treatment exposure for AE-related discontinuation for olaparib and niraparib RDI. Similarly, against rucaparib, the most influential parameters were the parameters determining the PFS parametric fit and TTDD for niraparib and the likelihood of AE discontinuations and treatment exposure for AE-related discontinuation for rucaparib.



Abbreviations: AE = adverse event; HCRU = healthcare resource use; KM = Kaplan-Meier; NIRA = niraparib; OLA = olaparib; PFS = progression-free survival; RDI = relative dose intensity

Note: PFS parametric fit P1 and P2 are the first and second coefficients of the parametric survival model. TTDD KM random sample is the random number used to vary, with the SE, the TTDD Kaplan-Meier curve.

[REDACTED]

[REDACTED]

[REDACTED]

Abbreviations: AE = adverse event; HCRU = healthcare resource use; KM = Kaplan-Meier; NIRA = niraparib; PFS = progression-free survival; RDI = relative dose intensity; RUCA = rucaparib
Note: PFS parametric fit P1 and P2 are the first and second coefficients of the parametric survival model. TTDD KM random sample is the random number used to vary, with the SE, the TTDD Kaplan-Meier curve.

Scenario analysis

Scenario analyses conducted showed that the base case analysis versus olaparib (BRCAm) and rucaparib (BRCAwt) is robust to variations in input parameters as outlined in Table 20 and Table 21. For the BRCAm population, greater than 10% variation from the base case INMB results was observed in scenarios where the PFS HR was changed ([REDACTED]), label-based TTDD was assumed, olaparib median TTDD was used, assumed SACT OS HR, and assumed SACT OS TTDD. For the BRCAwt population, a variation greater than 10% from the base case INMB was only observed in two scenarios: when RDI for rucaparib was included and when Bucher ITC HRs from the ITT population were used. In all scenarios, niraparib remained less costly compared to olaparib (BRCAm) and rucaparib (BRCAwt), with all resulting INMBs being positive.

Table 20. Results of scenario analyses – niraparib versus olaparib (BRCAm)

Scenario	Base case value/assumptions	Scenario analysis value/assumptions	Incremental Cost	Incremental QALY	Incremental NMB at £30,000
Base case	-	-	[REDACTED]	[REDACTED]	[REDACTED]
Time horizon	[REDACTED] years	20 years	[REDACTED]	[REDACTED]	[REDACTED]
Discount Rate	3.5%	1.5%	[REDACTED]	[REDACTED]	[REDACTED]

Scenario	Base case value/assumptions	Scenario analysis value/assumptions	Incremental Cost	Incremental QALY	Incremental NMB at £30,000
Median Age	Mean age PRIMA: [REDACTED] years	Median age from SACT data: 65 years	[REDACTED]	[REDACTED]	[REDACTED]
Alternative cure point	10 years	8 years to test application of earlier cure point based on UK advisory board feedback and aligned with approximate end of available follow-up from PRIMA	[REDACTED]	[REDACTED]	[REDACTED]
	10 years	12 years to test application of later cure point based on UK KOL feedback	[REDACTED]	[REDACTED]	[REDACTED]
PFS distribution	Gen. gamma	Lognormal	[REDACTED]	[REDACTED]	[REDACTED]
	Gen. gamma	1-knot normal spline	[REDACTED]	[REDACTED]	[REDACTED]
PFS HR	HR=1 (equivalence)	HR=[REDACTED] based on Bucher ITC HR of PRIMA vs SOLO-1	[REDACTED]	[REDACTED]	[REDACTED]
OS distributions	1-knot normal spline	Lognormal	[REDACTED]	[REDACTED]	[REDACTED]
	1-knot normal spline	Gen. gamma	[REDACTED]	[REDACTED]	[REDACTED]
Excess mortality vs general population	HR = 1.26	HR =1	[REDACTED]	[REDACTED]	[REDACTED]
TTDD	PRIMA TTDD - 90% of patients discontinuing at 36 months	SACT TTDD - 90% of patients discontinuing at 36 months	[REDACTED]	[REDACTED]	[REDACTED]
	PRIMA TTDD data - 90% of patients discontinuing at 36 months	SACT TTDD until 42 months and 38 months for NIRA and OLA, respectively, then assume all patients discontinue	[REDACTED]	[REDACTED]	[REDACTED]
	90% of patients discontinuing after stopping rule	100% of patients discontinue treatment according to product label-based stopping rules	[REDACTED]	[REDACTED]	[REDACTED]
Comparator TTDD	PFS combined with AE-related discontinuation from SOLO-1	Simple exponential models fitted through the median time on treatment estimates	[REDACTED]	[REDACTED]	[REDACTED]
Niraparib dosing	Individualised starting dose based on SACT data	Applies detailed 100/200/300mg dose per cycle based on PRIMA	[REDACTED]	[REDACTED]	[REDACTED]

Scenario	Base case value/assumptions	Scenario analysis value/assumptions	Incremental Cost	Incremental QALY	Incremental NMB at £30,000
	Individualised starting dose based on SACT data	Applies population specific mean dose calculated across the PRIMA data	██████	██████	██████
	Individualised starting dose based on SACT data	Applies the proportion of patients starting at 200 vs. 300mg based on PRIMA data	██████	██████	██████
	Individualised starting dose based on SACT data	Applies the proportion of patients starting at 200 vs. 300mg based on MONITOR-UK data	██████	██████	██████
Olaparib dosing	RDI not included	RDI = 96% as in NICE TA 1055	██████	██████	██████
Follow-up and monitoring	7-year stopping rule	Excludes stopping rule for follow-up and monitoring costs applied to patients who remain progression free for at least 7 years	██████	██████	██████
AEs	Grade 3+ incidence AEs from NIRA RWE (MONITOR-UK)	Use Grade 3+ incidence AEs from PRIMA	██████	██████	██████
Health state utility	██████ for progression-free and ██████ for progressed based PRIMA	0.81 for progression-free and 0.76 for progressed based on NICE TA962	██████	██████	██████
AE disutility	Include AE disutility	Exclude AE disutility	██████	██████	██████
Partitioned Survival model structure	3-health state PSM considering PF, PD and death	Uses 4-health state model structure including PFS2 and using 4-health state utilities - with slightly more conservative PFS2 curve for NIRA (gen gamma) and assuming PFS2 equivalence with OLA	██████	██████	██████
Partitioned Survival model structure	3-health state PSM considering PF, PD and death	Uses 4-health state model structure including PFS2 and using 4-state utilities - with slightly more optimistic PFS2 curve for NIRA (1-	██████	██████	██████

Scenario	Base case value/assumptions	Scenario analysis value/assumptions	Incremental Cost	Incremental QALY	Incremental NMB at £30,000
		knot hazard) and assuming PFS2 equivalence with OLA			
SACT OS HR	Assumed equivalence, HR = 1.00 for OS and PFS	Uses HR derived from SACT (■■■■) for NIRA vs OLA) to derive OLA OS curve and ■■■■ for NIRA vs OLA based on the Bucher ITC to derive the PFS curve	■■■■	■■■■	■■■■
SACT OS TTDD	Assumed equivalence, HR = 1.00 for OS and PFS TTDD niraparib: KM + exponential TTDD olaparib: Generated via PFS and AE discontinuation	Uses OS extrapolation for NIRA based on SACT (log-normal) This scenario used ■■■■ OS HR derived from SACT (used in SACT OS HR scenario); ■■■■ for NIRA vs OLA based on the Bucher ITC and SACT TTDD until 42 months and 38 months for NIRA and OLA, respectively, then assume all patients discontinued. These assumptions were combined with base case SACT dose distributions.	■■■■	■■■■	■■■■
95% Cured	100% cured	Assumes 95% of patients are cured after the 10 year cure point instead of 100%	■■■■	■■■■	■■■■
Life Tables	UK general population lifetables	Tests impact of alternative pre-COVID life tables	■■■■	■■■■	■■■■
Monitoring costs	Complete blood count: 2.67 Summary additional one-off monitoring cost (1 st cycle): £20.43	Explores impact of additional heart rate and blood pressure monitoring (extra consultant visit) within the first cycle	■■■■	■■■■	■■■■
Terminal care costs: unit cost	£9,248.28	Use alternative end of life costs based on PSSRU cancer costs for the last year of life	■■■■	■■■■	■■■■

Abbreviations: AE = adverse event; EoL = end of life; HR = hazard ratio; KOL = key opinion leader; NICE = National Institute for Health and Care Excellence; NIRA = niraparib; OS = overall survival; SACT = Systemic Anti-Cancer Therapy; PFS = progression-free survival; QALY = quality-adjusted life year; SACT = Systemic Anti-Cancer Therapy; TTDD = time to discontinuation or death.

Table 21. Results of scenario analyses – niraparib versus rucaparib (BRCAwt)

Scenario	Base case value	Scenario analysis value	Incremental Cost	Incremental QALY	Incremental NMB at £30,000
Base case	-	-			
Time horizon	years	20 years			
Discount Rate	3.5%	1.5%			
Median Age	Mean age PRIMA: years	Median age from SACT data: 70 years			
Alternative cure point	10 years	8 years to test application of earlier cure point based on UK advisory board feedback and aligned with approximate end of available follow-up from PRIMA			
	10 years	12 years to test application of later cure point based on UK KOL feedback			
PFS distribution	Gen. gamma	2-knot normal spline			
OS distributions	1-knot normal spline	Lognormal			
	1-knot normal spline	Gen. gamma			
TTDD	PRIMA TTDD - 90% of patients discontinuing at 36 months	SACT TTDD - 90% of patients discontinuing at 36 months			
	PRIMA TTDD - 90% of patients discontinuing at 36 months	SACT TTDD until 42 months, then assume all patients discontinue			
	90% of patients discontinuing	100% of patients discontinue			

Scenario	Base case value	Scenario analysis value	Incremental Cost	Incremental QALY	Incremental NMB at £30,000
	after stopping rule	treatment according to product label-based stopping rules			
Comparator TTDD	PFS combined with AE-related discontinuation from ATHENA-MONO	Simple exponential models fitted through the median time on treatment estimates			
Niraparib dosing	Individualised starting dose based on SACT data	Applies detailed 100/200/300mg dose per cycle based on PRIMA			
	Individualised starting dose based on SACT data	Applies population specific mean dose calculated across the PRIMA data			
	Individualised starting dose based on SACT data	Applies the proportion of patients starting at 200 vs. 300mg based on PRIMA data			
	Individualised starting dose based on SACT data	Applies the proportion of patients starting at 200 vs. 300mg based on MONITOR-UK data			
Rucaparib dosing	RDI not included	RDI = 88% as in NICE TA 1055			
Follow-up and monitoring	7-year stopping rule	Excludes stopping rule for follow-up and monitoring costs applied to patients who remain progression free for at least 7 years			
AEs	Grade 3+ incidence AEs from NIRA	Use Grade 3+ incidence AEs from PRIMA			

Scenario	Base case value	Scenario analysis value	Incremental Cost	Incremental QALY	Incremental NMB at £30,000
	RWE (MONITOR-UK)				
Health state utility	█ for progression-free and █ for progressed based PRIMA	0.81 for progression-free and 0.76 for progressed based on NICE TA962	█	█	█
AE disutility	Include AE disutility	Exclude AE disutility	█	█	█
Partitioned Survival model structure	3-health state PSM considering PF, PD and death	Uses 4-health state model structure including PFS2 and using 4-state utilities - with slightly more conservative PFS2 curve for NIRA (gen gamma) and assuming PFS2 equivalence with OLA	█	█	█
Partitioned Survival model structure	3-health state PSM considering PF, PD and death	Uses 4-health state model structure including PFS2 and using 4-state utilities - with slightly more optimistic PFS2 curve for NIRA (1-knot hazard) and assuming PFS2 equivalence with OLA	█	█	█
95% Cured	100% cured	Assumes 95% of patients are cured after the 10 year cure point instead of 100%	█	█	█
OS HR (vs age-sex general population mortality)	HR = 1.00	Applies 1.26 HR to life table estimates used for cured patients/survival curve	█	█	█

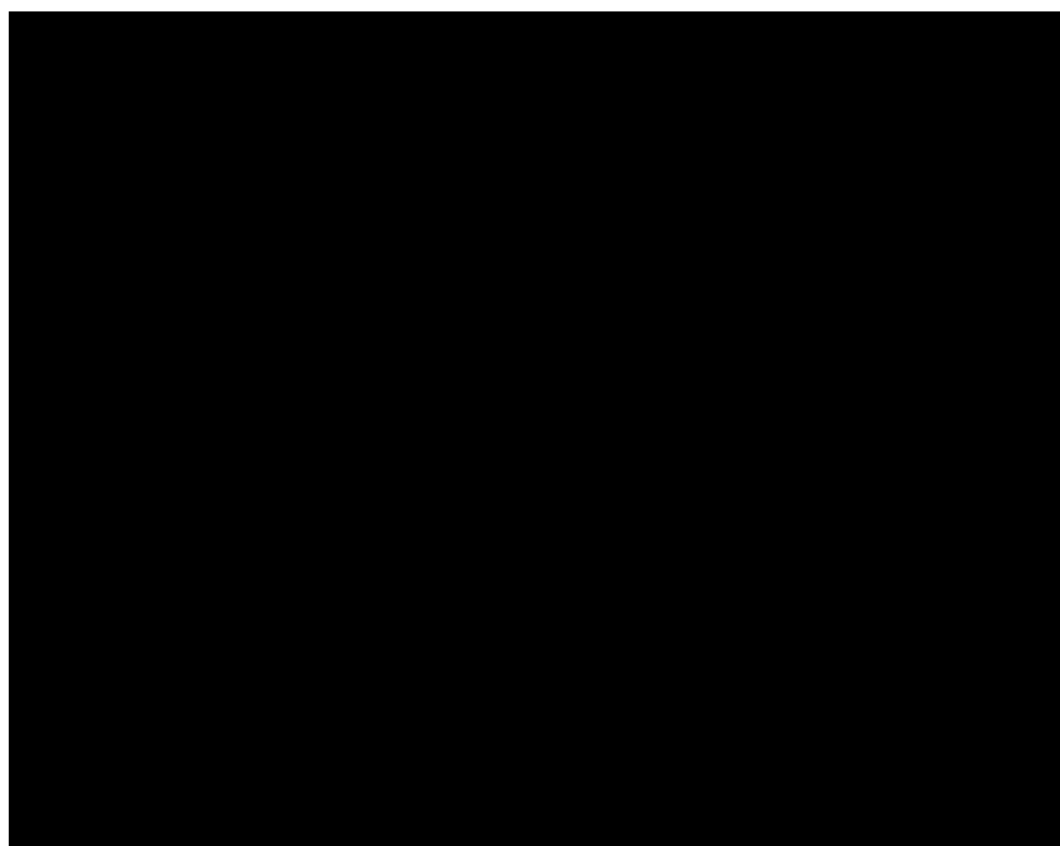
Scenario	Base case value	Scenario analysis value	Incremental Cost	Incremental QALY	Incremental NMB at £30,000
cured patients		capping in line with BRCAm population			
Life Tables	UK general population lifetables	Tests impact of alternative pre-COVID life tables			
Monitoring costs	Complete blood count: 2.67 Summary additional one-off monitoring cost (1 st cycle): £20.43	Explores impact of additional heart rate and blood pressure monitoring (extra consultant visit) within the first cycle			
Terminal care costs: unit cost	£9,248.28	Use alternative end of life costs based on PSSRU cancer costs for the last year of life			
Bucher ITT HRs NIRA vs RUCA	PFS HR: 1.00 (i.e. equivalence) OS HR: 1.00 (i.e. equivalence)	Applies Bucher ITC HRs for NIRA vs RUCA for PFS () and OS () based on ITT population analysis			
Bucher HRd HRs NIRA vs RUCA	PFS HR: 1.00 (i.e. equivalence) OS HR: 1.00 (i.e. equivalence)	Applies Bucher ITC HRs for NIRA vs RUCA for PFS () and OS () based on HRd population analysis			

Abbreviations: AE = adverse event; EoL = end of life; HR = hazard ratio; ITT = intention-to-treat; KOL = key opinion leader; NICE = National Institute for Health and Care Excellence; NIRA = niraparib; OLA = open label extension; OS = overall survival; PFS = progression-free survival; PSSRU = Personal Social Service Research Unit; QALY = quality-adjusted life year; SACT = Systemic Anti-Cancer Therapy; TTDD = time to discontinuation or death.

Additional Survival Analysis Inputs

BRCAm population – PRIMA PFS2

Second progression-free survival (PFS2, investigator-assessed (INV)) KM plots for the BRCAm subpopulation in the PRIMA study are shown in **Error! Reference source not found..**



Abbreviations: CI = confidence interval; HR = hazard ratio

AIC and BIC estimates for the PFS2 distributions for NIRA are shown in Table 22. The 3-knot normal and the 1-knot hazard spline models provided the best AIC and BIC statistics, respectively, although fairly marginal differences in statistical fit were broadly observed across the generalised gamma and spline models.

Table 22. AIC and BIC Estimates for Niraparib PFS2 Parametric Fits in BRCAm

Distribution	NIRA	
	AIC	BIC
Standard Parametric		
Exponential	919.0	922.0
Weibull (PH)	913.9	920.0
Gompertz	920.9	927.0
Log-logistic	902.0	908.0
Log-normal	896.5	902.5
Gamma	910.0	916.1
Generalized Gamma	887.6	896.6
Flexible Parametric Spline		
1-knot hazard	886.9	896.0
2-knot hazard	887.2	899.3
3-knot hazard	886.6	901.8
1-knot odds	887.5	896.6
2-knot odds	887.7	899.8
3-knot odds	886.6	901.7
1-knot normal	888.0	897.0
2-knot normal	886.7	898.8
3-knot normal	885.7	900.8

Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; NIRA = niraparib; PH = proportional hazard

Table 23 presents the PFS2 survival estimates for the niraparib curve for the BRCAm population.

Table 23. Niraparib PFS2 Survival Estimates in BRCAm

Comparat ors	Median PFS2 (months)	1-year	2-years	3-years	4-years	5-years	6- years
Niraparib	████	████	████	████	████	████	████

Abbreviations: NIRA = niraparib; PFS2 = Progression-free Survival to second progression

The expected proportion of patients alive and without second progression at 1 to 40-years were extracted for each niraparib parametric fit (Table 24), capped from below by the selected PFS model for niraparib (generalised gamma).

Table 24. Expected PFS2 for Niraparib Curves in BRCAm

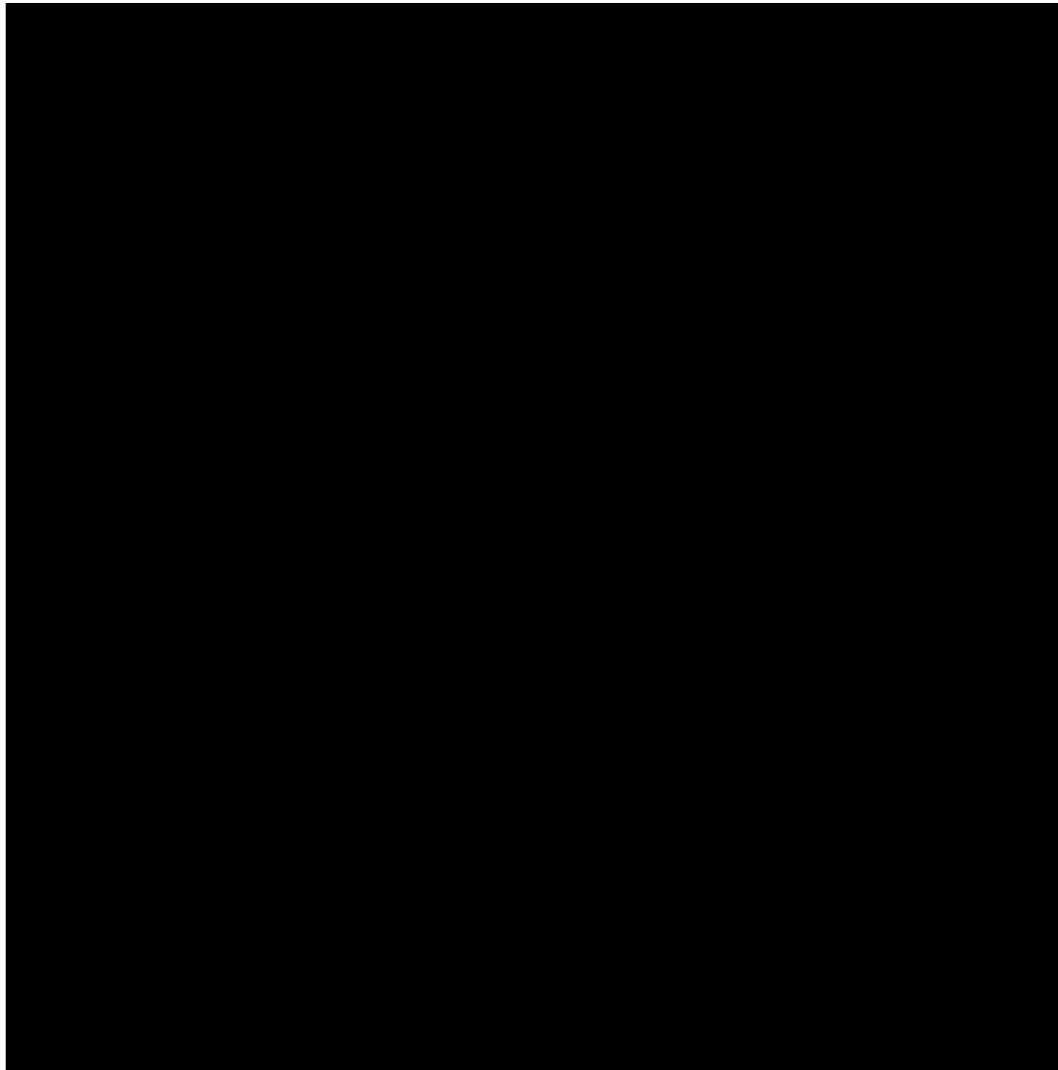
Distribution	1-year PFS2 prediction	5-year PFS2 prediction	10-year PFS2 prediction	15-year PFS2 prediction	20-year PFS2 prediction	30-year PFS2 prediction	40-year PFS2 prediction
NIRA Independent fit							
Exponential	████	████	████	████	████	████	████
Weibull (PH)	████	████	████	████	████	████	████
Gompertz	████	████	████	████	████	████	████
Log-logistic	████	████	████	████	████	████	████
Log-normal	████	████	████	████	████	████	████
Gamma	████	████	████	████	████	████	████
Generalized Gamma	████	████	████	████	████	████	████
1-knot hazard	████	████	████	████	████	████	████
2-knot hazard	████	████	████	████	████	████	████
3-knot hazard	████	████	████	████	████	████	████
1-knot odds	████	████	████	████	████	████	████
2-knot odds	████	████	████	████	████	████	████
3-knot odds	████	████	████	████	████	████	████
1-knot normal	████	████	████	████	████	████	████
2-knot normal	████	████	████	████	████	████	████
3-knot normal	████	████	████	████	████	████	████

Abbreviations: NIRA = Niraparib; PFS2 = Progression-free Survival to second progression; PH = Proportional Hazard

Based on clinical expert feedback received for niraparib PFS and OS expectations and the selected base case PFS and OS models (see Appendix J of the CS), a range of approximately █████ PFS2 at 10 years was considered most plausible for niraparib. Only the generalised gamma (████) and 1-knot normal spline models (████) produced 10-year PFS2 estimates between █████ and █████, with 1-knot hazard (████) and 1-knot odds (████) slightly above █████. However, as the 1-knot hazard and odds spline models provided slightly better visual fits to the data and were only marginally above the approximate █████ upper threshold, as well as the limited differences in statistical fit estimates between these models, two scenario analyses were conducted using the generalised gamma and 1-knot hazard models as lower and upper bound PFS2 extrapolations.

BRCAwt population – PRIMA PFS2

Second progression-free survival (PFS2, investigator-assessed (INV)) KM plots for the BRCAwt subpopulation in the PRIMA study are shown in **Error! Reference source not found..**



Abbreviations: CI = confidence interval; HR = hazard ratio

AIC and BIC estimates for the BRCAwt PFS2 distributions are shown in Table 25. The 3-knot normal spline model produced the lowest AIC, while the 1-knot odds model provided the lowest BIC. However, no substantial statistical fit differences were observed across the generalised gamma and spline models.

Table 25. AIC and BIC Estimates for Joint and Independent PFS2 Distribution Fits in BRCAwt

Distribution	NIRA	
	AIC	BIC
Standard Parametric		
Exponential	2076.3	2080
Weibull (PH)	2065.2	2072.7
Gompertz	2077.8	2085.2
Log-logistic	2012.8	2020.3
Log-normal	2009.0	2016.5
Gamma	2053.1	2060.5
Generalized Gamma	1990.8	2002.0
Flexible Parametric Spline		
1-knot hazard	1985.2	1996.4
2-knot hazard	1984.1	1999.0
3-knot hazard	1983.6	2002.2
1-knot odds	1987.2	1998.4
2-knot odds	1985.7	2000.6
3-knot odds	1983.7	2002.3
1-knot normal	1990.5	2001.8
2-knot normal	1983.7	1998.6
3-knot normal	1982.1	2000.8

Abbreviation: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; NIRA = Niraparib; PH = Proportional Hazard

Table 26 presents the PFS2 survival estimates for the niraparib curves for the BRCAwt population.

Table 26. PFS2 Survival Estimates in BRCAwt

Comparat ors	Median PFS2 (months)	1-year	2-years	3-years	4-years	5-years	6- years
Niraparib	████	████	████	████	████	████	████

Abbreviations: NIRA = niraparib; PFS 2 = Progression-free Survival to second progression

The expected proportion of second progression-free patients at 1 to 40 years are shown in Table 27, capped from below by the selected PFS model for niraparib (generalised gamma model).

Table 27. Expected PFS2 per Parametric Distribution for Niraparib Curves in BRCAwt

Distribution	1-year PFS2 prediction	5-year PFS2 prediction	10-year PFS2 prediction	15-year PFS2 prediction	20-year PFS2 prediction	30-year PFS2 prediction	40-year PFS2 prediction
NIRA Independent fit							
Exponential	████	████	████	████	████	████	████
Weibull (PH)	████	████	████	████	████	████	████
Gompertz	████	████	████	████	████	████	████
Log-logistic	████	████	████	████	████	████	████
Log-normal	████	████	████	████	████	████	████
Gamma	████	████	████	████	████	████	████
Generalized Gamma	████	████	████	████	████	████	████
1-knot hazard	████	████	████	████	████	████	████
2-knot hazard	████	████	████	████	████	████	████
3-knot hazard	████	████	████	████	████	████	████
1-knot odds	████	████	████	████	████	████	████
2-knot odds	████	████	████	████	████	████	████
3-knot odds	████	████	████	████	████	████	████
1-knot normal	████	████	████	████	████	████	████
2-knot normal	████	████	████	████	████	████	████
3-knot normal	████	████	████	████	████	████	████

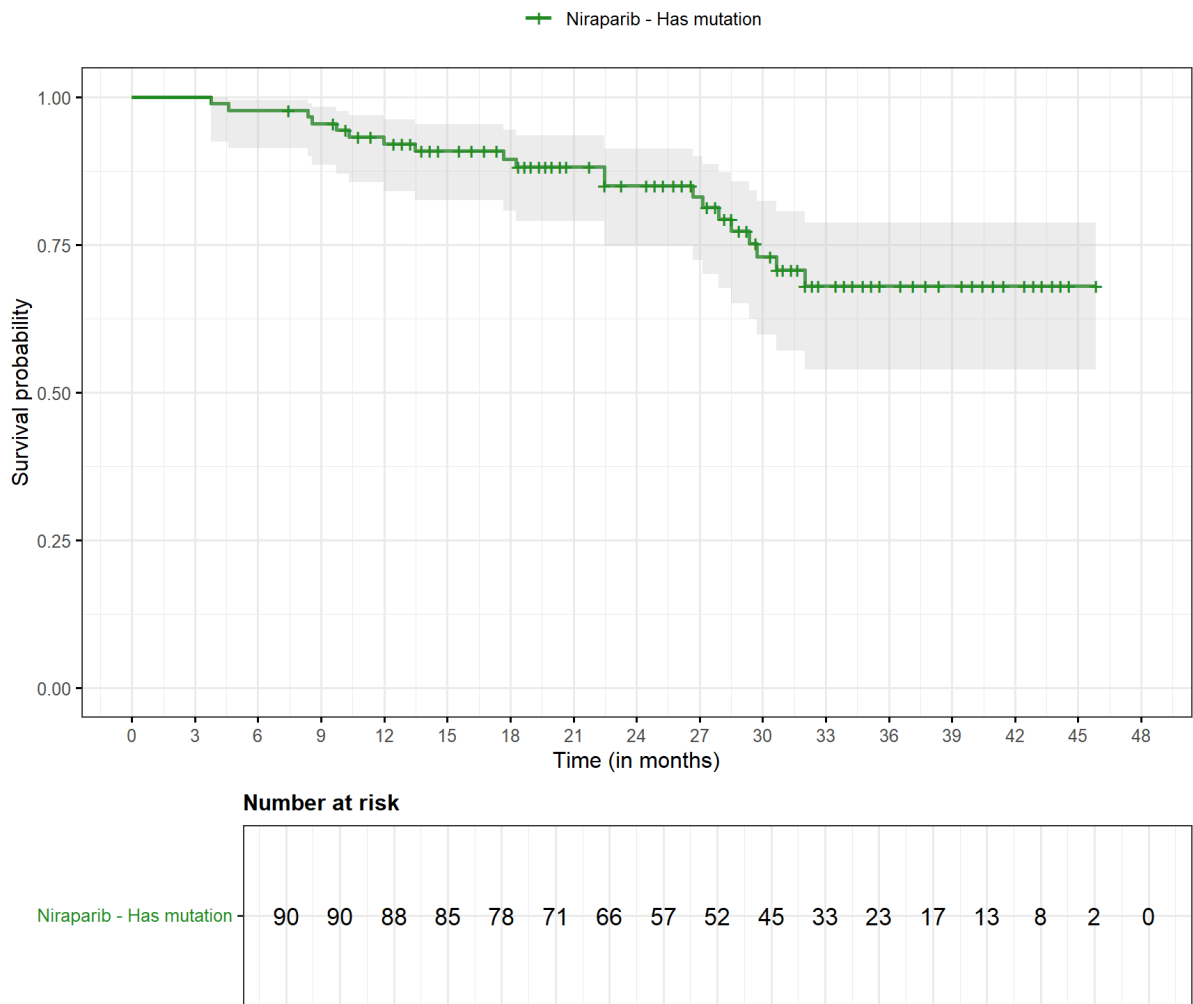
Abbreviations: NIRA: Niraparib; PFS2: Progression-free survival to second progression; PH: Proportional Hazard

Based on clinical expert feedback received for PFS and OS expectations at 10 years for the BRCAwt population (see Appendix J of the CS), models providing 10-year PFS2 estimates between █████ were considered most plausible. Among the fitted models, only the generalised gamma (████), 1-knot hazard spline (████), 1-knot odds spline (████) and 1-knot normal spline (████) provided estimates within this range at 10 years. Similar to the BRCAm population, the generalised gamma and 1-knot hazard spline models were explored in two scenario analyses as lower and upper bound PFS2 extrapolation for niraparib.

SACT OS (BRCAm)

The overall survival (OS) KM plot for niraparib for the BRCAm subpopulation in SACT is displayed in Figure 3.

Figure 3. KM Plot for Niraparib OS for the BRCAm Subpopulation in SACT



AIC and BIC estimates for the OS parametric models fitted to the niraparib SACT data are shown in Table 28, with 3-knot spline models excluded due to lack of convergence. The log-normal model produced the best statistical fit with the lowest AIC and lowest BIC; however, all AIC and BIC estimates for other parametric models were within 7 points of the log-normal, suggesting they provided a reasonable relative fit.

Table 28. AIC and BIC Estimates for Niraparib SACT OS Parametric Fits in BRCam

Distribution	NIRA	
	AIC	BIC
Standard Parametric		
Exponential	232.1	234.6
Weibull (PH)	229.8	234.8
Gompertz	231.3	236.3
Log-logistic	229.5	234.5
Log-normal	229.4	234.4
Gamma	229.6	234.6
Generalized Gamma	231.4	238.9
Flexible Parametric Spline		
1-knot hazard	231.7	239.2
2-knot hazard	232.3	242.3
1-knot odds	231.5	239.0
2-knot odds	231.8	241.8
1-knot normal	231.2	238.7
2-knot normal	231.3	241.3

Abbreviations: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion; NIRA = niraparib; PH = Proportional Hazard.

The predicted proportion alive between 1 to 40 years for the niraparib parametric models fitted to the SACT OS data is displayed in Table 29, considering general population background mortality and capped from below by the base case generalised gamma PFS model from PRIMA including a 10-year cure landmark point. All models converged with the base case PFS curve before 15 years.

Table 29. Expected OS per Parametric Distribution for Niraparib SACT Data in BRCam

Distribution	1-year OS prediction	5-year OS prediction	10-year OS prediction	15-year OS prediction	20-year OS prediction	30-year OS prediction	40-year OS prediction
NIRA Independent fit							
Exponential	████	████	████	████	████	████	████
Weibull (PH)	████	████	████	████	████	████	████
Gompertz	████	████	████	████	████	████	████
Log-logistic	████	████	████	████	████	████	████
Log-normal	████	████	████	████	████	████	████
Gamma	████	████	████	████	████	████	████
Generalized Gamma	████	████	████	████	████	████	████
1-knot hazard	████	████	████	████	████	████	████
2-knot hazard	████	████	████	████	████	████	████
1-knot odds	████	████	████	████	████	████	████
2-knot odds	████	████	████	████	████	████	████
1-knot normal	████	████	████	████	████	████	████
2-knot normal	████	████	████	████	████	████	████

Abbreviations: NIRA = niraparib; OS = overall survival; PH = Proportional Hazard.

As described in Appendix J of the CS, the following UK clinical expert feedback was collected on expectations for niraparib long-term OS:

- The first expert indicated OS expectations of around 28% for niraparib at 15 years
- The second expert suggested survival would be somewhere between log-normal and generalised gamma at 10 years █████ and 20 years █████ with a preference towards the log-normal model due to the PFS/OS crossing point at ~11 years, and suggesting OS may be closer to █████ at 10 years and █████ at 20 years.
- Although estimates presented for each parametric model were capped by adjusted general population mortality, the third clinical expert struggled to recommend a parametric model suggesting that 30-year OS predictions may be too optimistic in general due to the underlying age of the patient population.
- The fourth expert noted an expectation of 35-40% OS at 10 years, suggesting that OS of around 36% at 10 years and around 20% at 20 years would be reasonable, and stating a preference for spline models due to the PFS crossing point

As all SACT OS parametric models converged with the chosen PFS base case model before 15 years (and therefore produced equivalent OS thereafter), predictions at 10 years were compared with clinical expert feedback on 10-year OS expectations for niraparib, which ranged between approximately [REDACTED]. Only the exponential ([REDACTED]) and log-normal distributions ([REDACTED]) produced an estimate within this range OS at 10 years, with all remaining models providing estimates below the lower bound of clinical expert expectations. However, as the log-normal model provided a slightly better statistical fit and visual fit to the observed data, this model was utilised for scenario analysis exploring use of the SACT data for extrapolating niraparib OS.

Proportional Hazards Assumption Testing

This following sections present the results from testing the PH assumption on different study populations and outcomes.

ITT population – PRIME – OS

There was no evidence that the assumption of proportional hazards does not hold.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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]

ITT population – PRIME – PFS-BICR

There was evidence that the assumption of proportional hazards does not hold.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Table 30. Cox regression model with treatment and time interaction for PFS-BICR in the ITT population of PRIME

Model	Parameter	HR (95% CI)	P-Value

ITT population – ATHENA-MONO – PFS-BICR

There was some evidence that the assumption of proportional hazards does not hold.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Table 31. Cox regression model with treatment and time interaction for PFS-BICR in the ITT population of ATHENA-MONO

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]	[REDACTED]

HRd population – PRIME – PFS-BICR

There was no evidence that the assumption of proportional hazards does not hold.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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]

HRd population – ATHENA-MONO – PFS-BICR

There was no evidence that the assumption of proportional hazards does not hold.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Table 32. Cox regression model with treatment and time interaction for PFS-BICR in the HRd population of ATHENA-MONO

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]	[REDACTED]

HRd/BRCAwt population – PRIME – PFS-BICR

There was no evidence that the assumption of proportional hazards does not hold.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Table 33. Cox regression model with treatment and time interaction for PFS-BICR in the HRd/BRCAt population of PRIME

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]	[REDACTED]

HRd/BRCAwt population – ATHENA-MONO – PFS-BICR

There was no evidence that the assumption of proportional hazards does not hold.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Table 34. Cox regression model with treatment and time interaction for PFS-BICR in the HRd/BRCAt population of ATHENA-MONO

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]	[REDACTED]

BRCAm population – SACT – OS

There was evidence that the assumption of proportional hazards does not hold.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Table 35. Cox regression model with treatment and time interaction for OS in the BRCAm population of SACT

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]	[REDACTED]

BRCAm population – PRIME – PFS-BICR

There was evidence that the assumption of proportional hazards does not hold.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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]

BRCAm population – PRIMA – PFS-INV

There was no evidence that the assumption of proportional hazards does not hold.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Table 36. Cox regression model with treatment and time interaction for PFS-INV in the BRCAm population of PRIMA

Model	Parameter	HR (95% CI)	P-Value

BRCAm population – ATHENA-MONO – PFS-BICR

There was no evidence that the assumption of proportional hazards does not hold.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Table 37. Cox regression model with treatment and time interaction for PFS-BICR in the BRCAm population of ATHENA-MONO

Model	Parameter	HR (95% CI)	P-Value

BRCAm (ITT) – SOLO-1 – PFS-BICR

There was evidence that the assumption of proportional hazards does not hold.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Table 38. Cox regression model with treatment and time interaction for PFS-BICR in the BRCAm population of SOLO-1

Model	Parameter	HR (95% CI)	P-Value

BRCAm & high-risk population – SOLO-1 – PFS-INV

There was evidence that the assumption of proportional hazards does not hold.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Table 39. Cox regression model with treatment and time interaction for PFS-INV in the BRCAm & high-risk population of SOLO-1

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]	[REDACTED]

HRp population – PRIME – PFS-BICR

There was no sufficient evidence that the assumption of proportional hazards does not hold.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

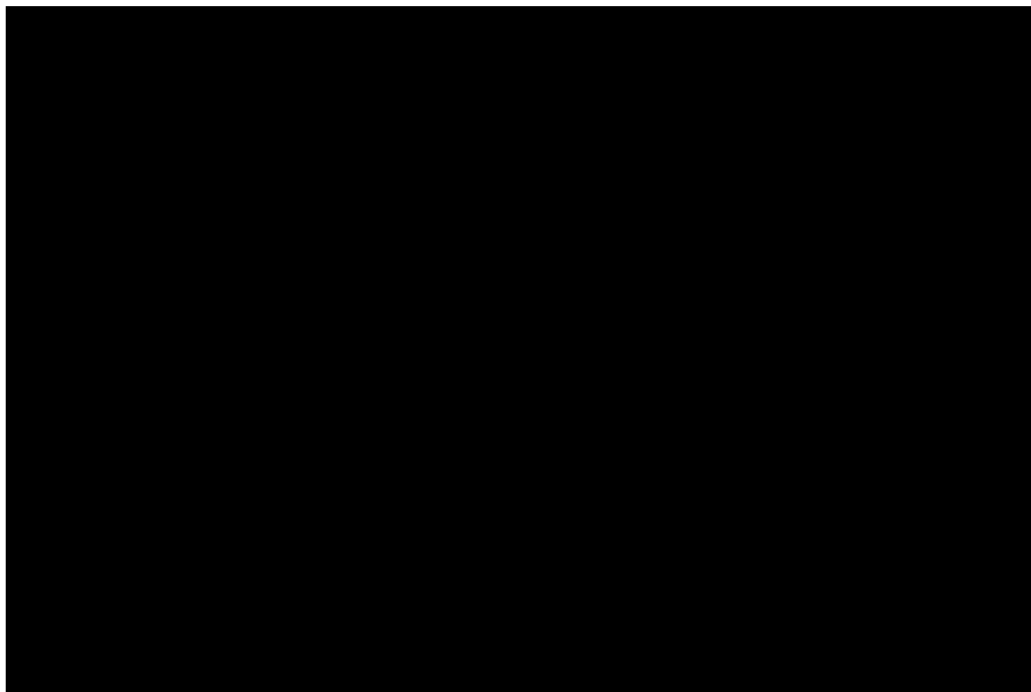


Table 40. Cox regression model with treatment and time interaction for PFS-BICR in the HRp population of PRIME

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]	[REDACTED]

HRp population – ATHENA-MONO – PFS-BICR

There was no sufficient evidence that the assumption of proportional hazards does not hold.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

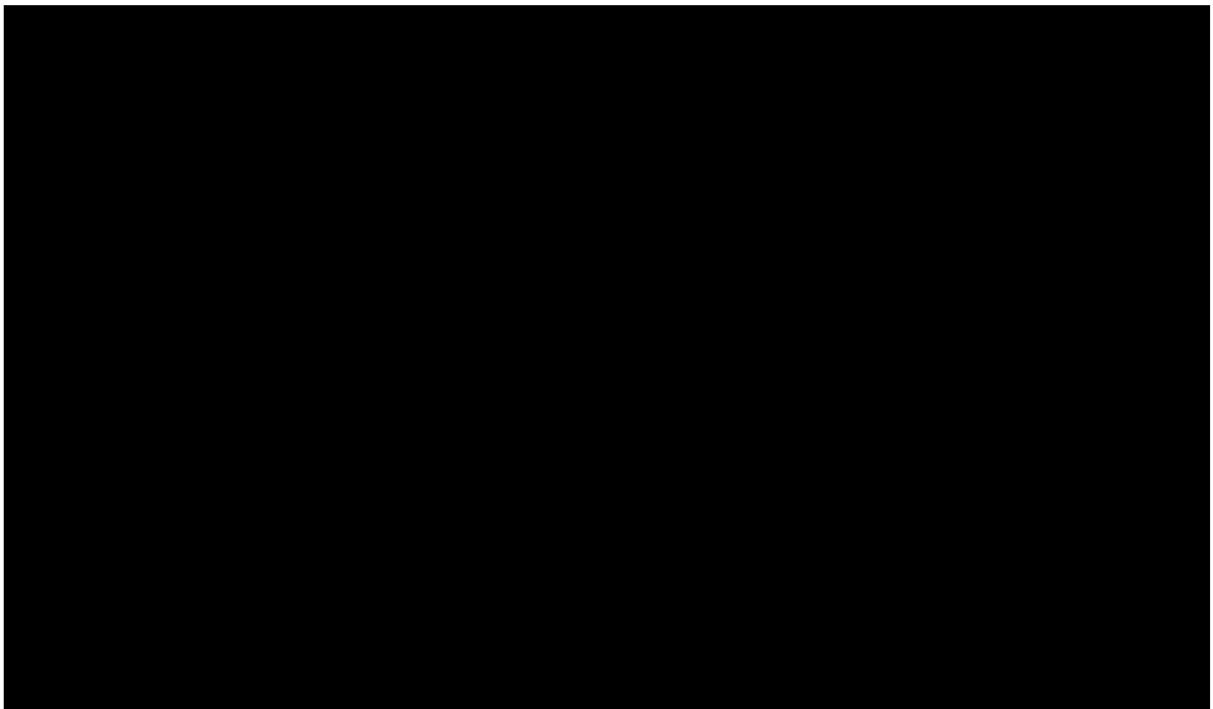
Table 41. Cox regression model with treatment and time interaction for PFS-BICR in the HRp population of ATHENA-MONO

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]	[REDACTED]

Kaplan-Meier Curves for Subgroups2024 CSG

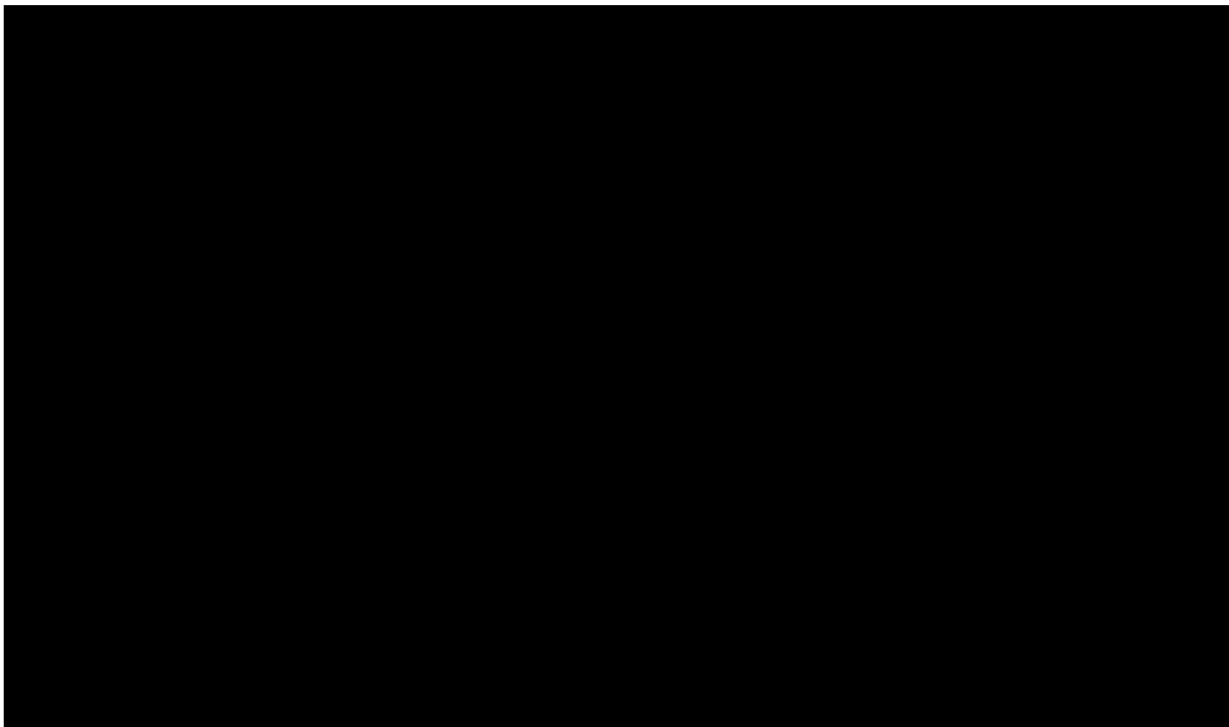
This section presents the KM curves for the requested biomarker subgroups.

HRd



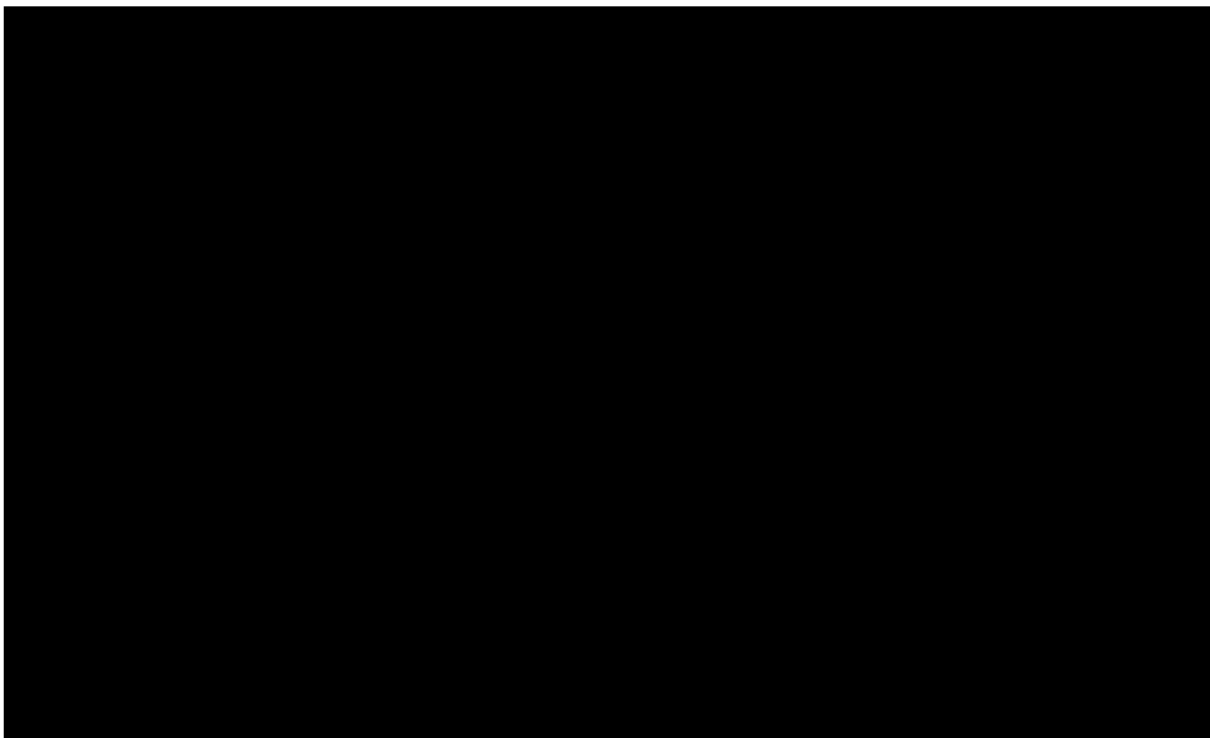
Abbreviations: CI = confidence interval; HR = hazard ratio
Source: GSK Data on File CSR 2019²³

[REDACTED]



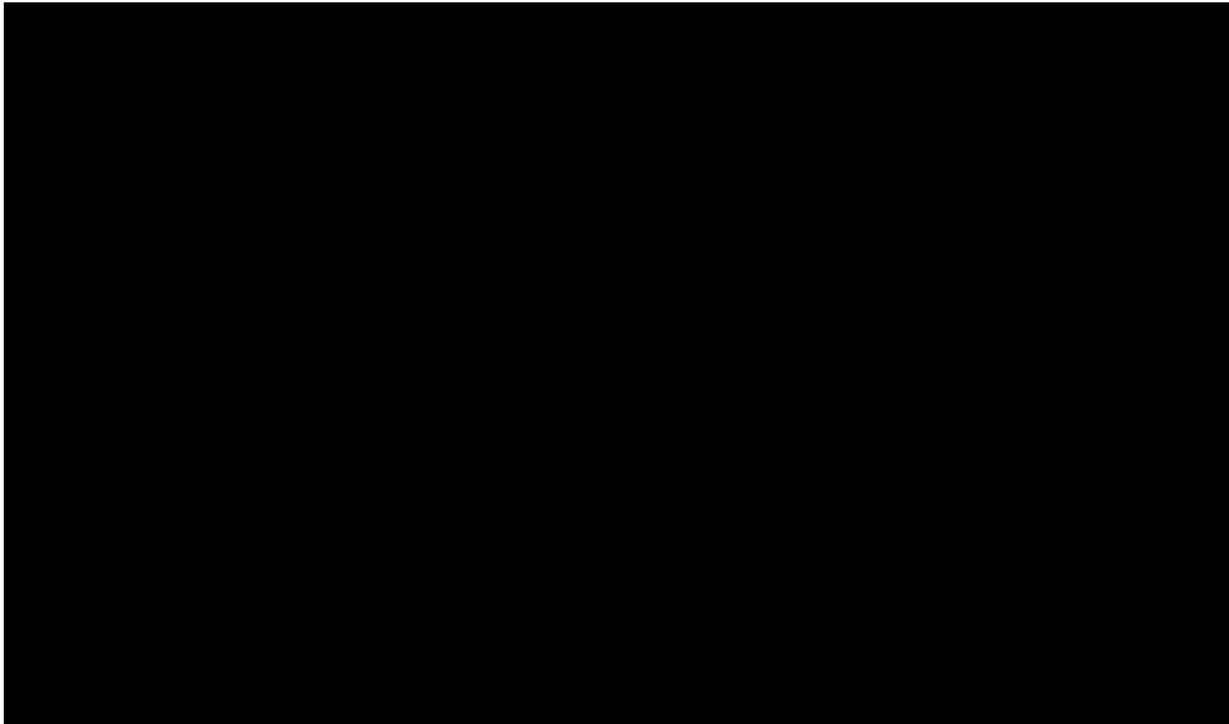
Abbreviations: CI = confidence interval; HR = hazard ratio
Source: GSK Data on File CSR 2024²¹

[REDACTED]



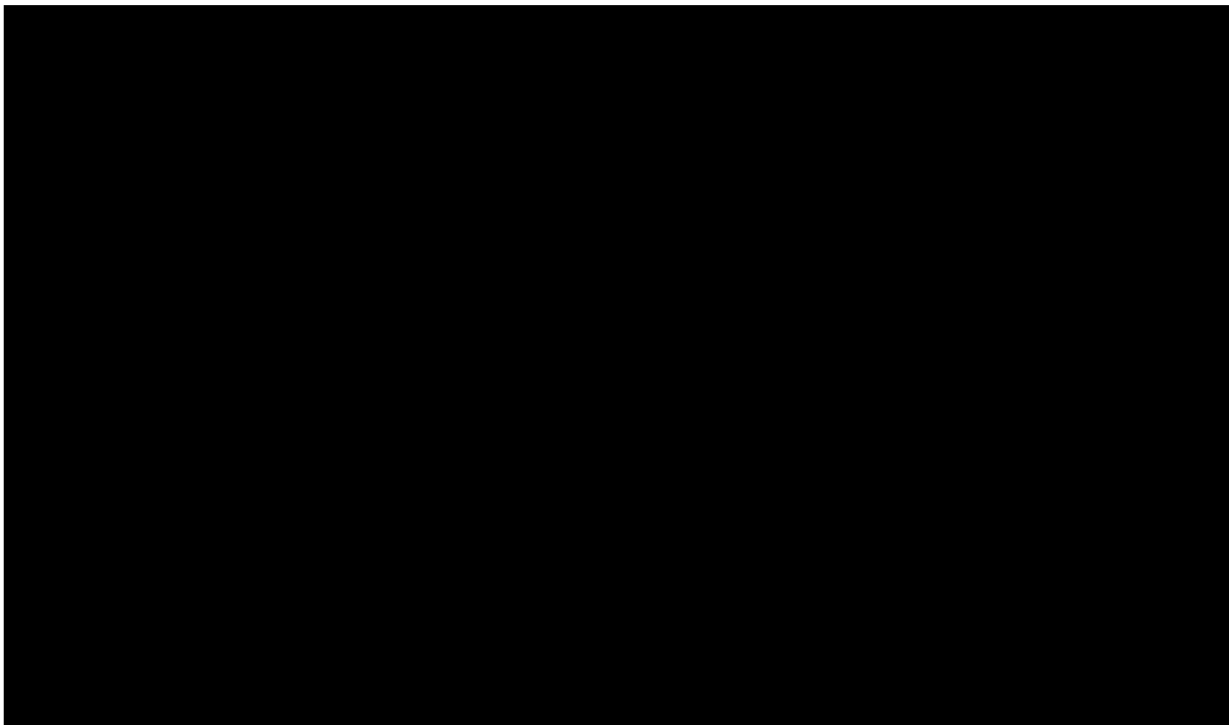
Abbreviations: CI = confidence interval; HR = hazard ratio
Source: GSK Data on File CSR 2024²¹

[REDACTED]



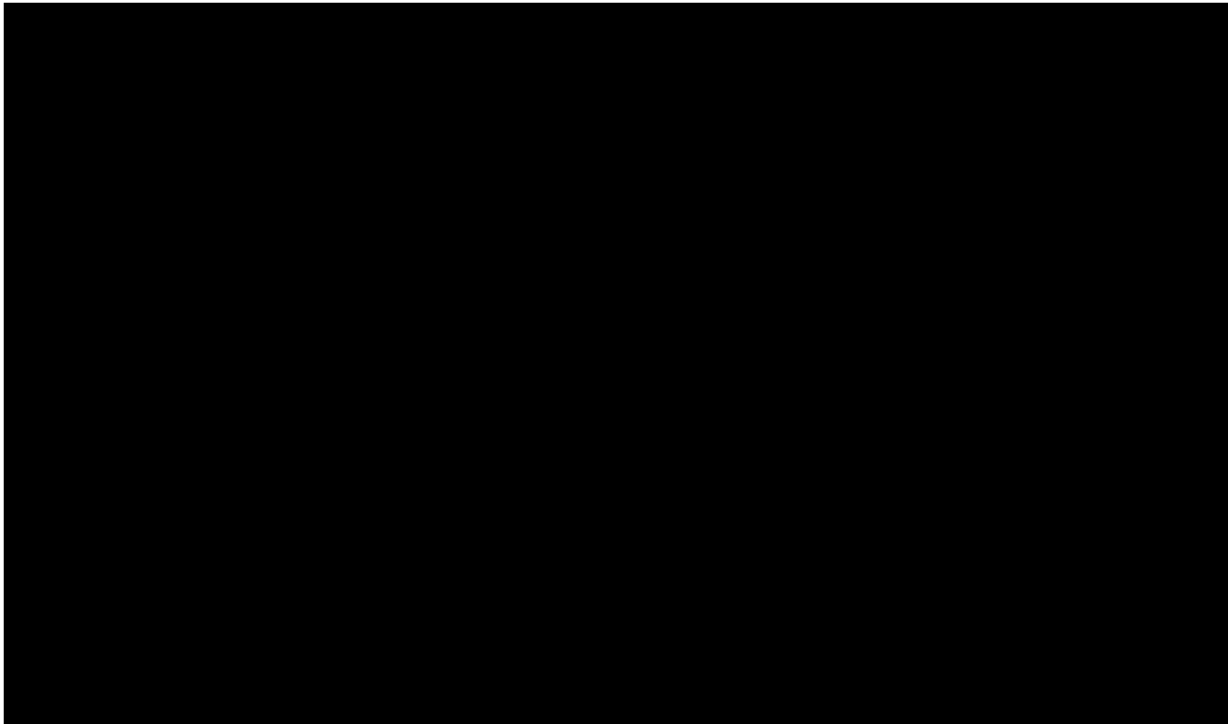
Abbreviations: CI = confidence interval; HR = hazard ratio
Source: GSK Data on File CSR 2024²¹

[REDACTED]



Abbreviations: CI = confidence interval; HR = hazard ratio
Source: GSK Data on File Final Analysis²¹

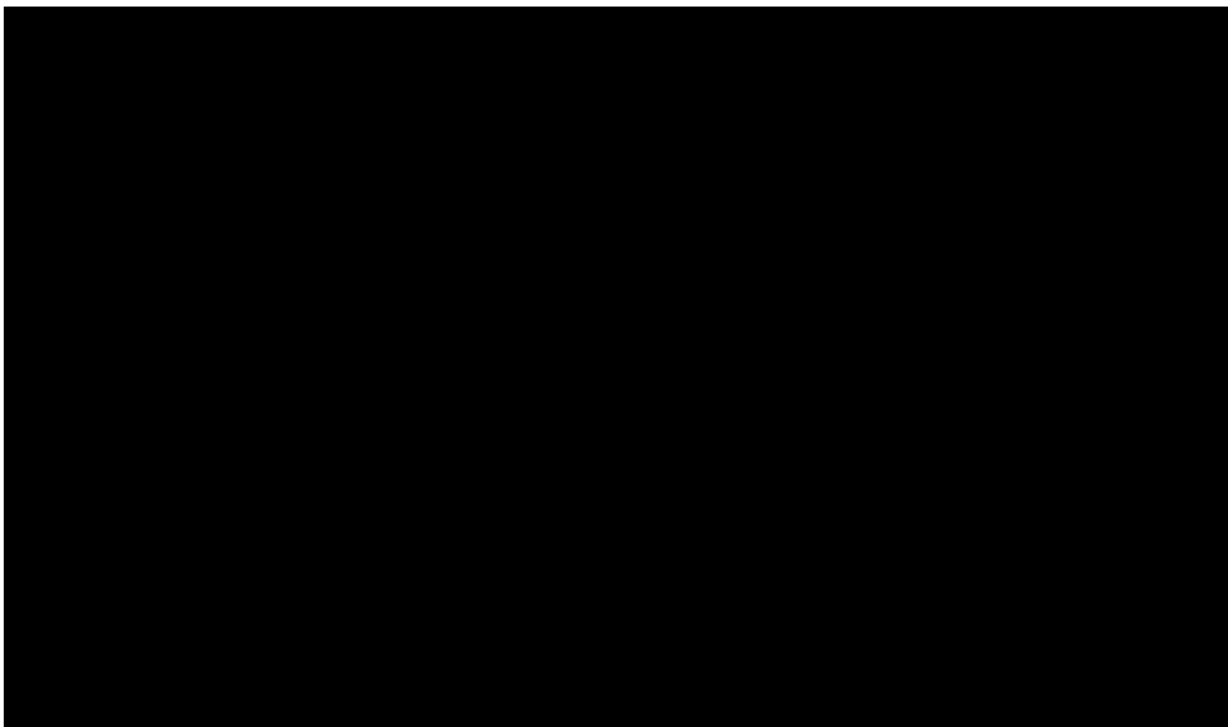
[Redacted]



Abbreviations: CI = confidence interval; HR = hazard ratio
Source: GSK Data on File CSR 2024²¹

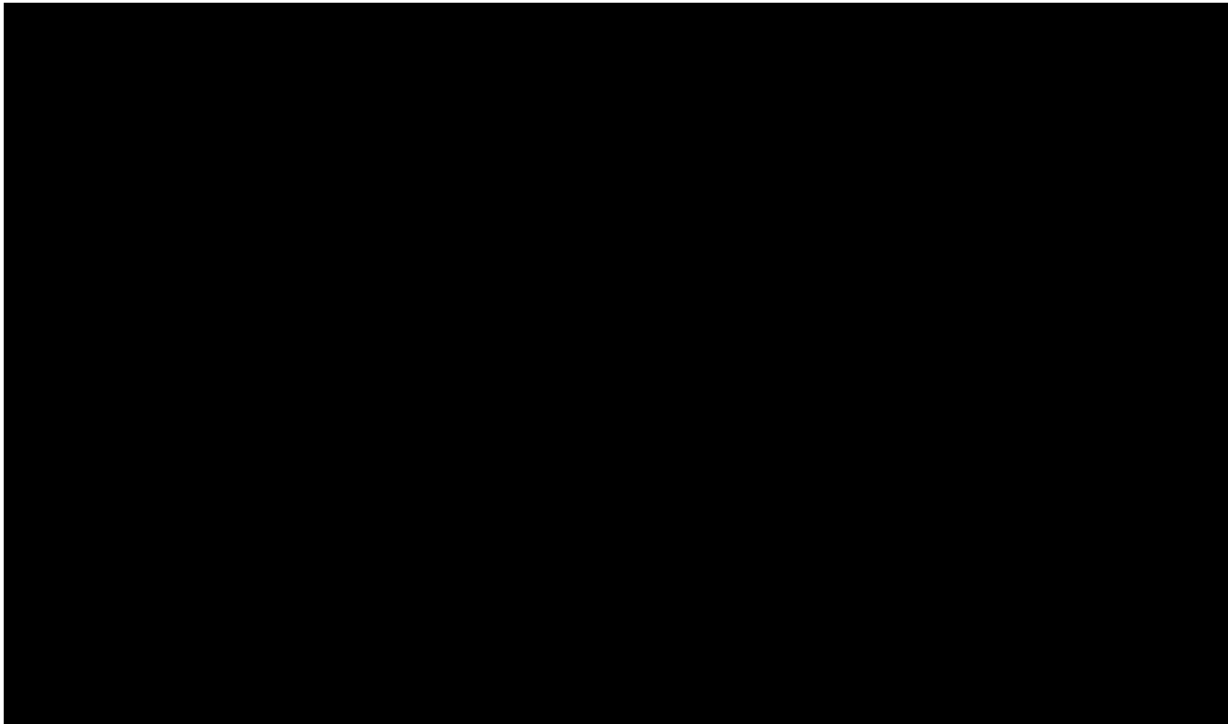
BRCAm

[Redacted]



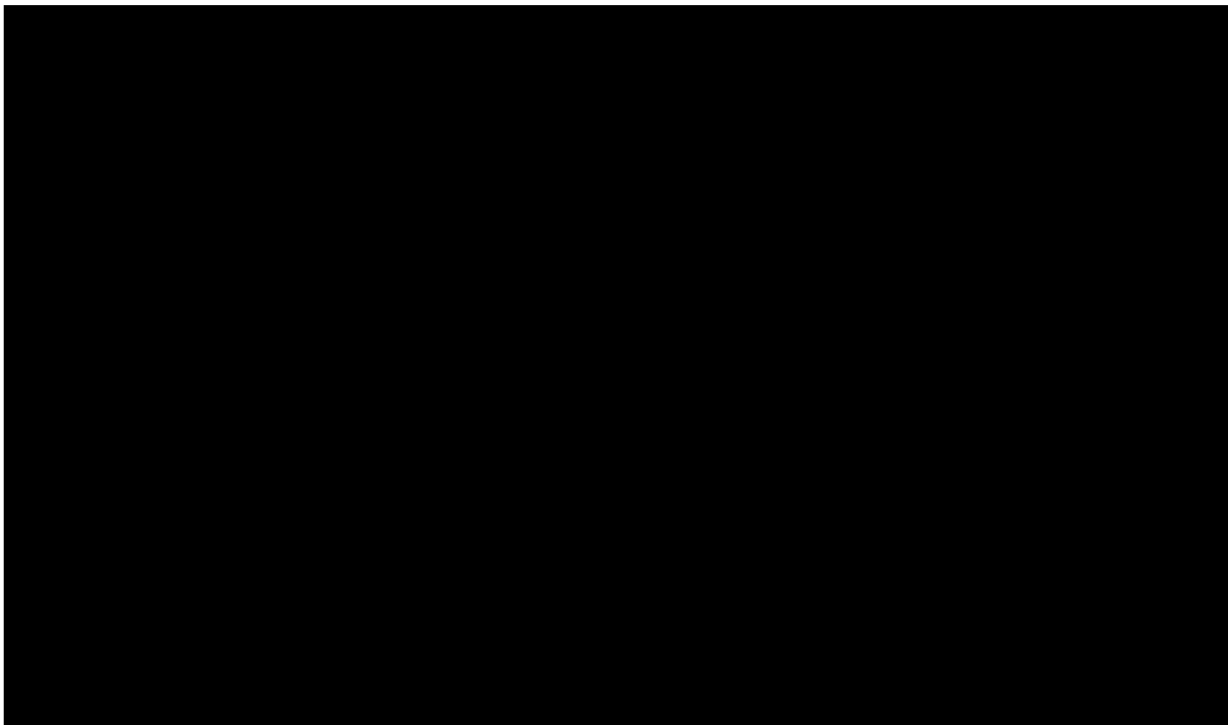
Abbreviations: CI = confidence interval; HR = hazard ratio
Source: GSK Data on File CSR 2019²³

[Redacted]



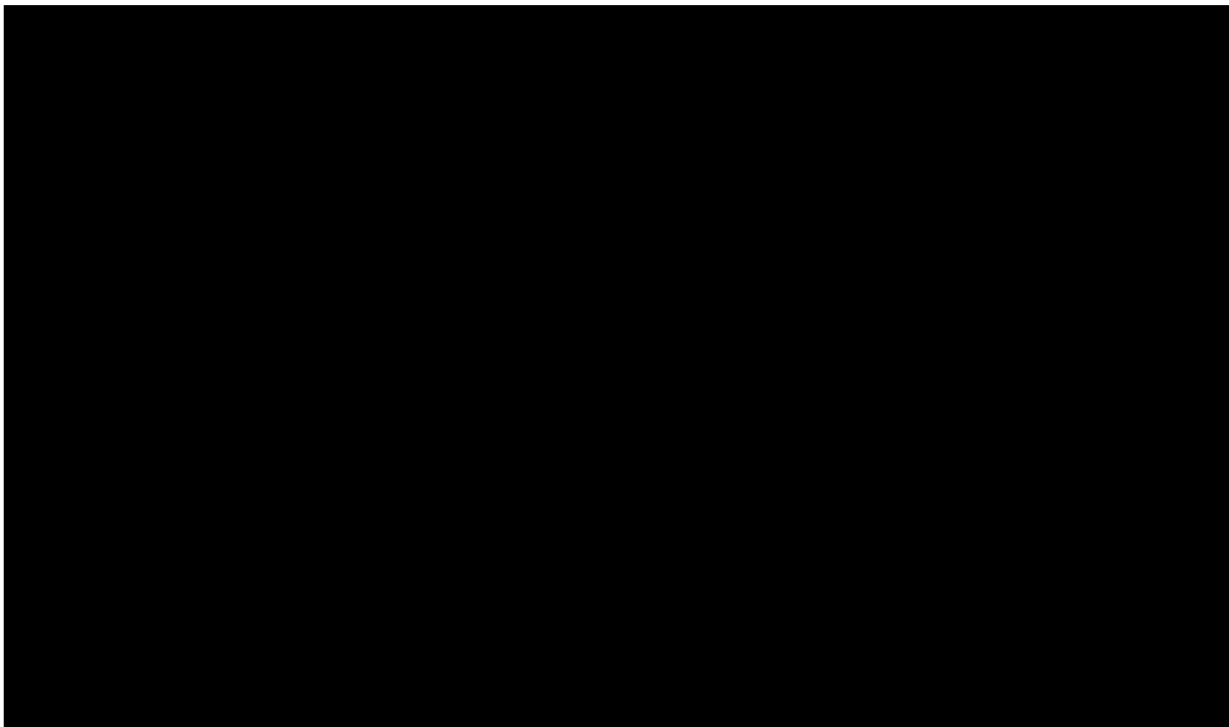
Abbreviations: CI = confidence interval; HR = hazard ratio
Source: GSK Data on File CSR 2024²¹

[Redacted]



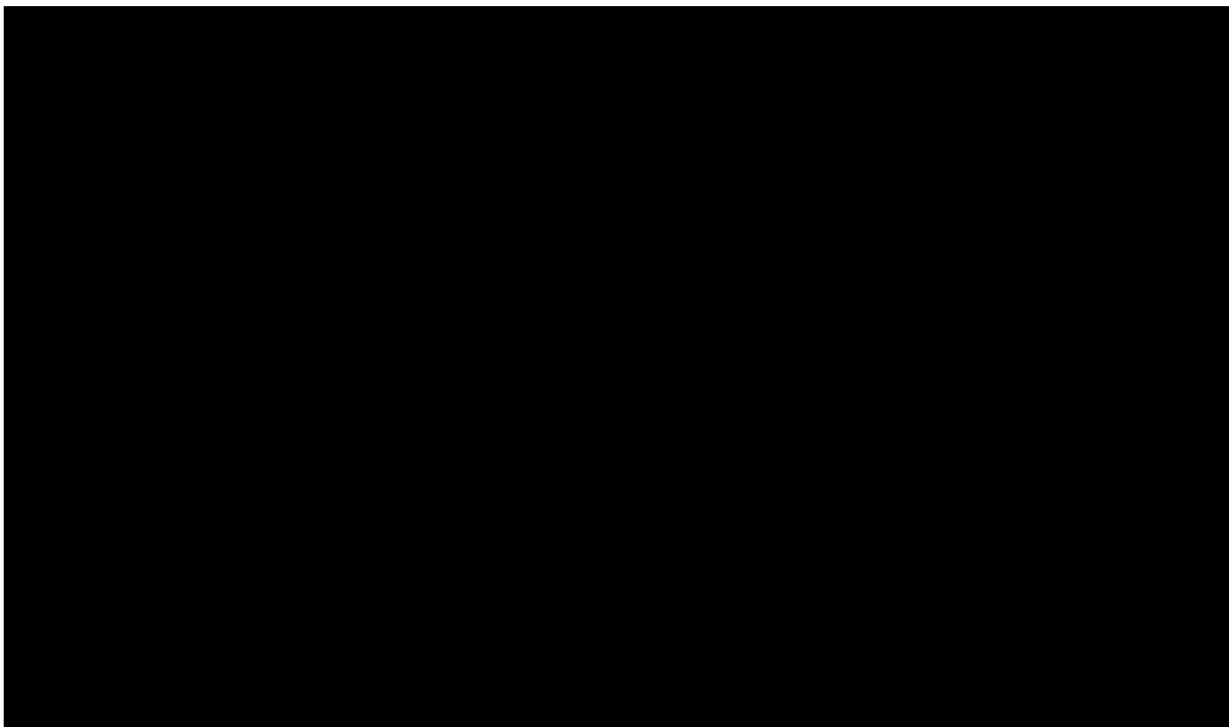
Abbreviations: CI = confidence interval; HR = hazard ratio
Source: GSK Data on File CSR 2024²¹

[Redacted]



Abbreviations: CI = confidence interval; HR = hazard ratio
Source: GSK Data on File CSR 2024²¹

[Redacted]



Abbreviations: CI = confidence interval; HR = hazard ratio
Source: GSK Data on File Final Analysis²¹

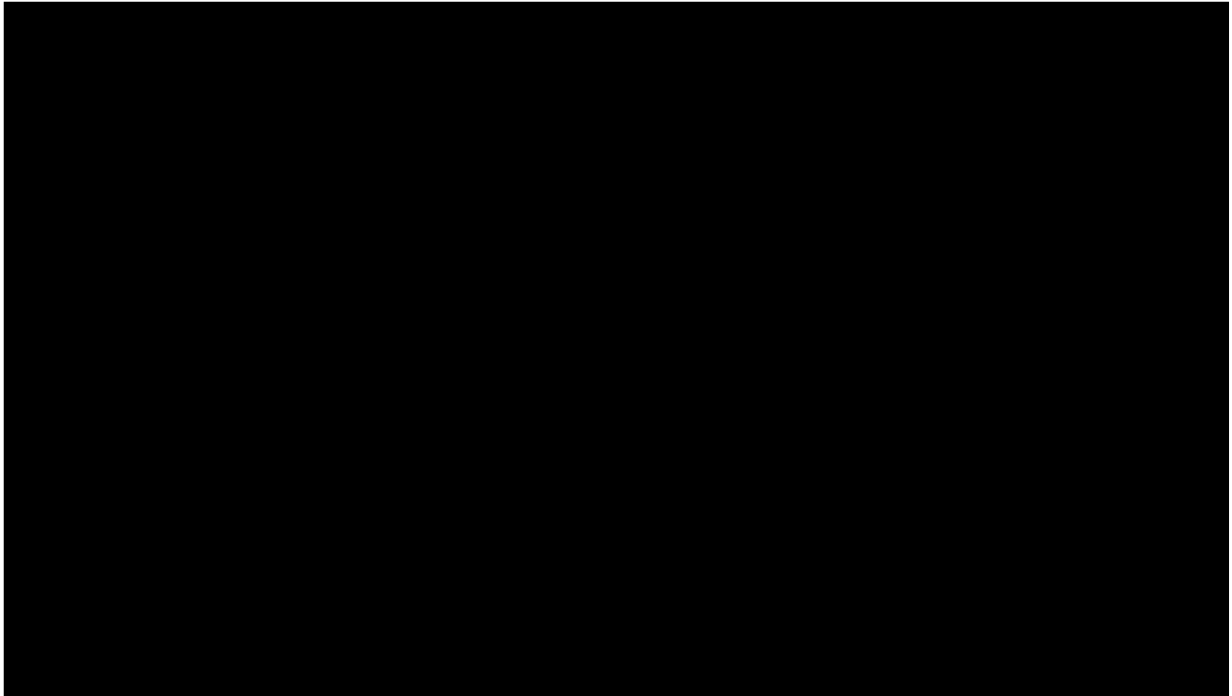
[REDACTED]

[REDACTED]

Abbreviations: CI = confidence interval; HR = hazard ratio
Source: GSK Data on File CSR 2024²¹

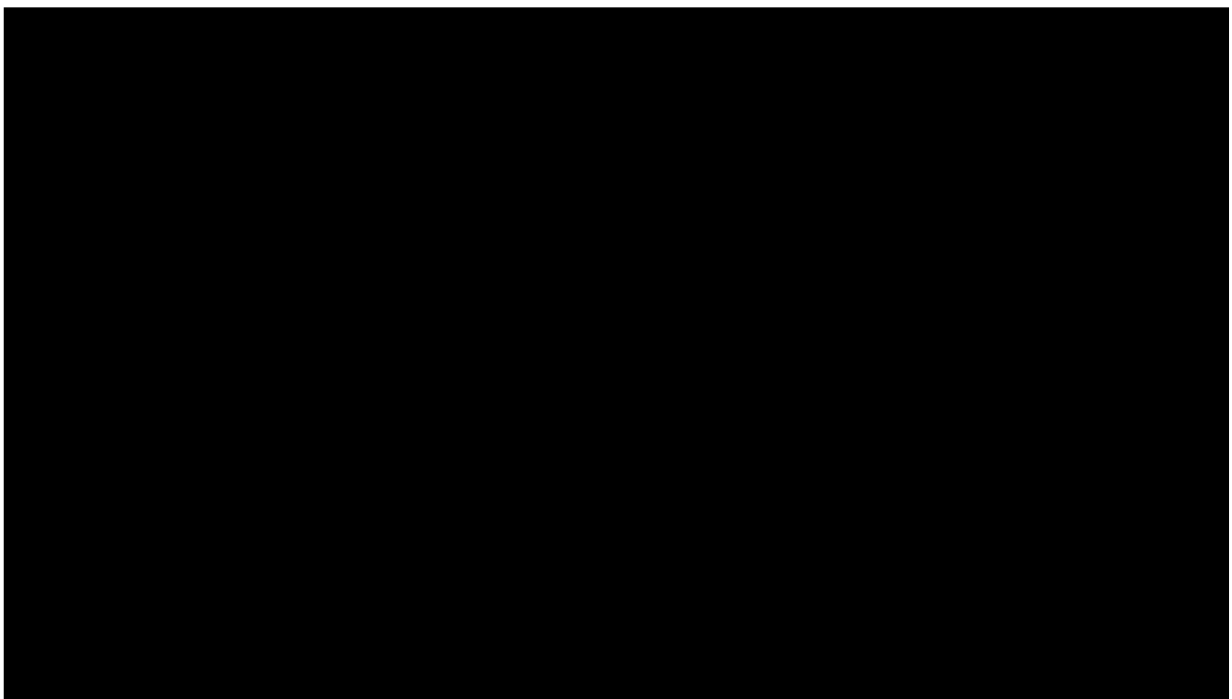
HRp

[REDACTED]



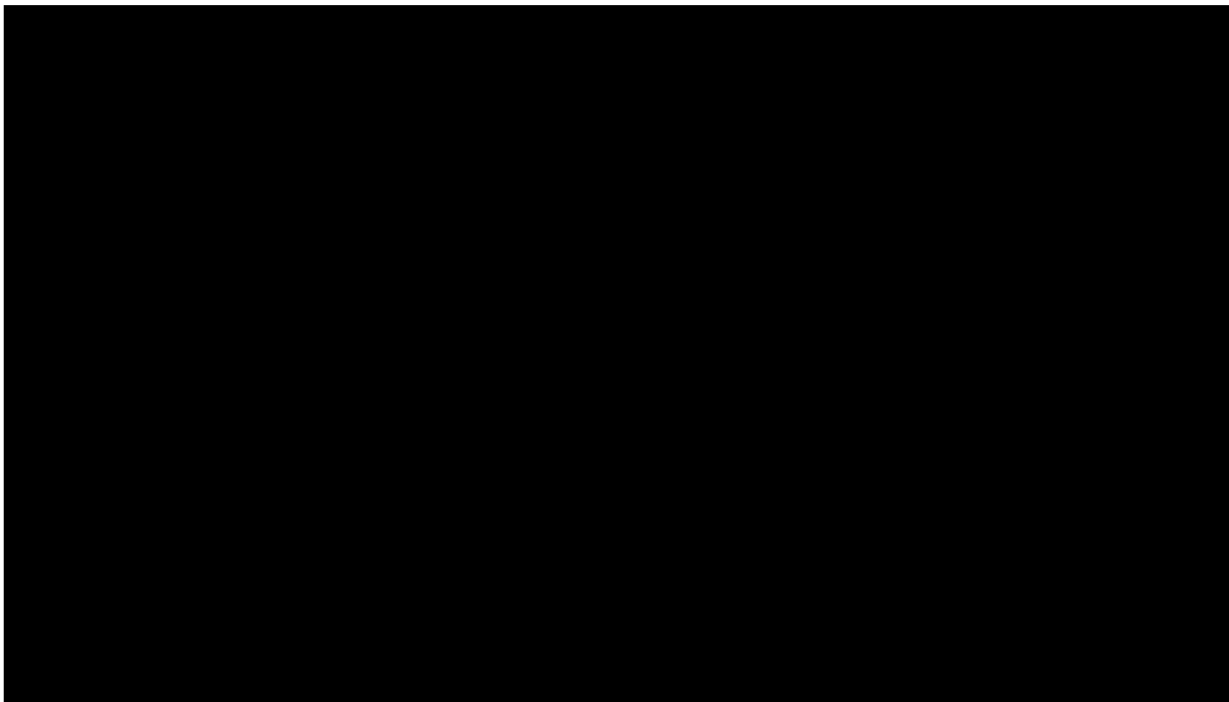
Abbreviations: CI = confidence interval; HR = hazard ratio
Source: GSK Data on File CSR 2019²³

[REDACTED]



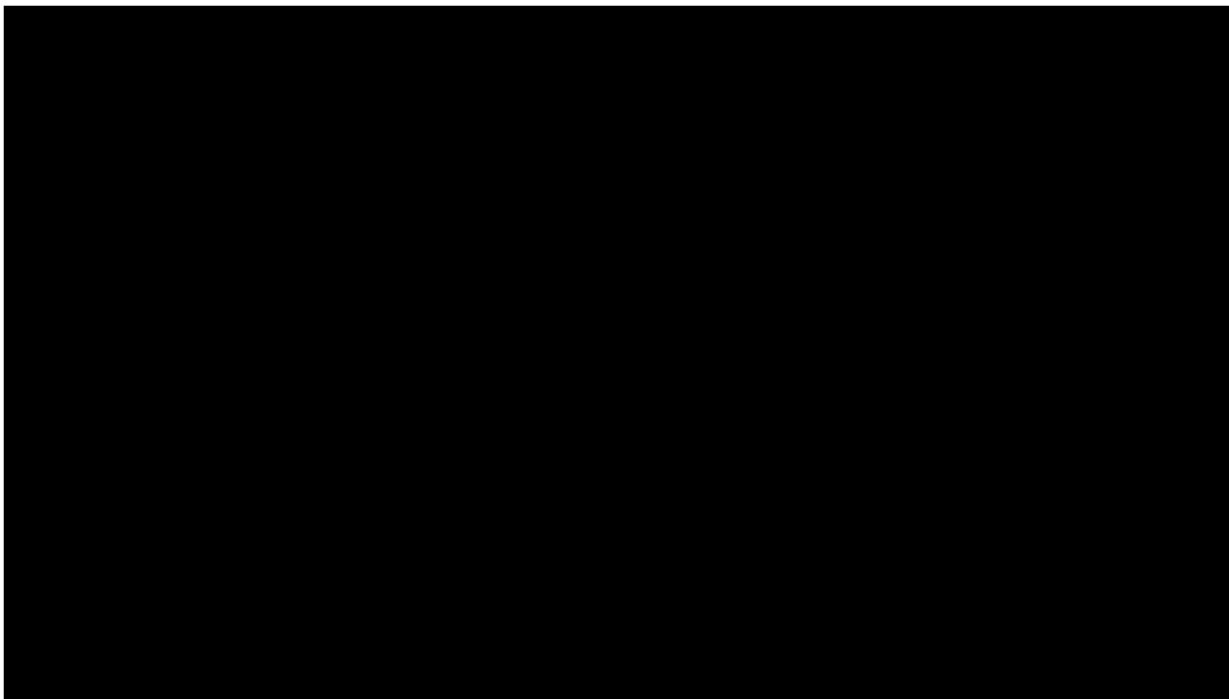
Abbreviations: CI = confidence interval; HR = hazard ratio
Source: GSK Data on File CSR 2024²¹

[Redacted]



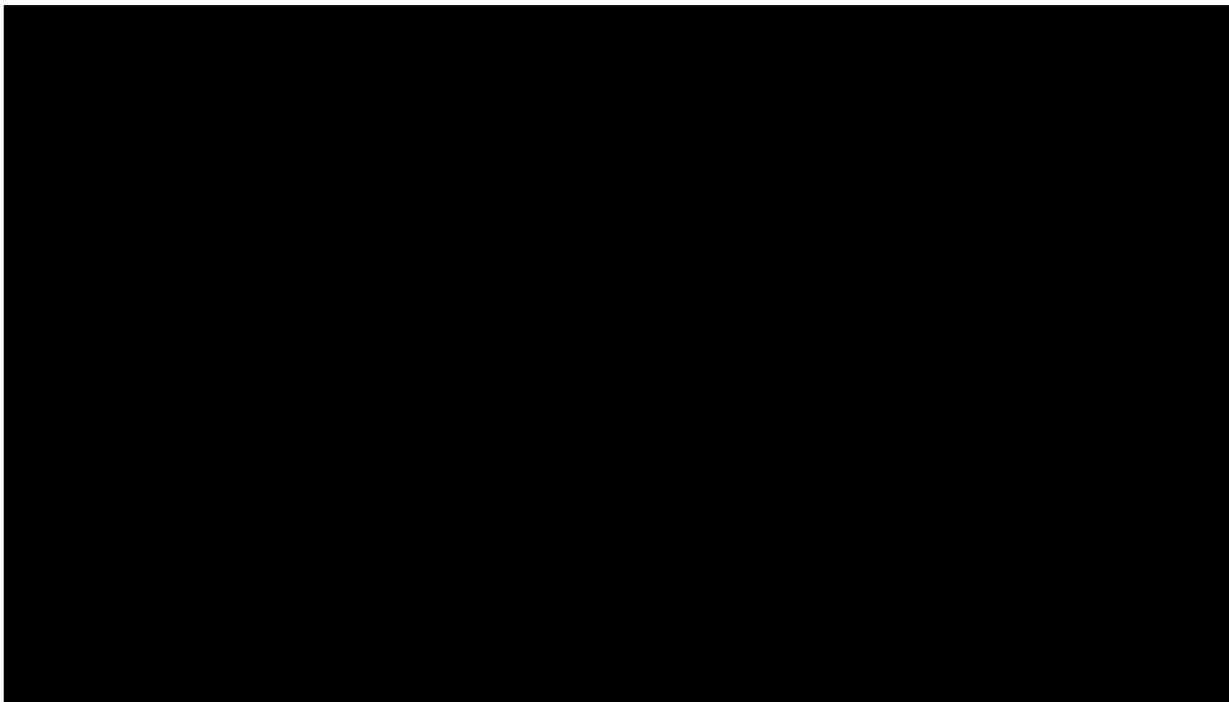
Abbreviations: CI = confidence interval; HR = hazard ratio
Source: GSK Data on File CSR 2024²¹

[Redacted]



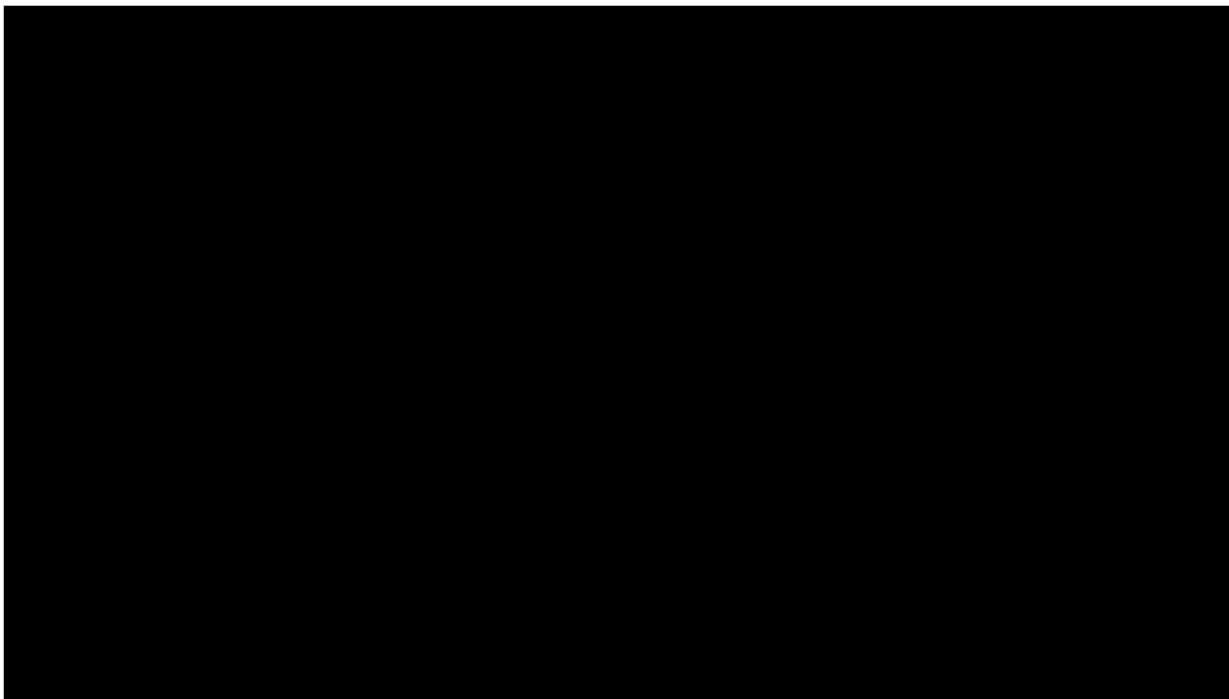
Abbreviations: CI = confidence interval; HR = hazard ratio
Source: GSK Data on File CSR 2024²¹

[REDACTED]



Abbreviations: CI = confidence interval; HR = hazard ratio
Source: GSK Data on File Final Analysis²¹

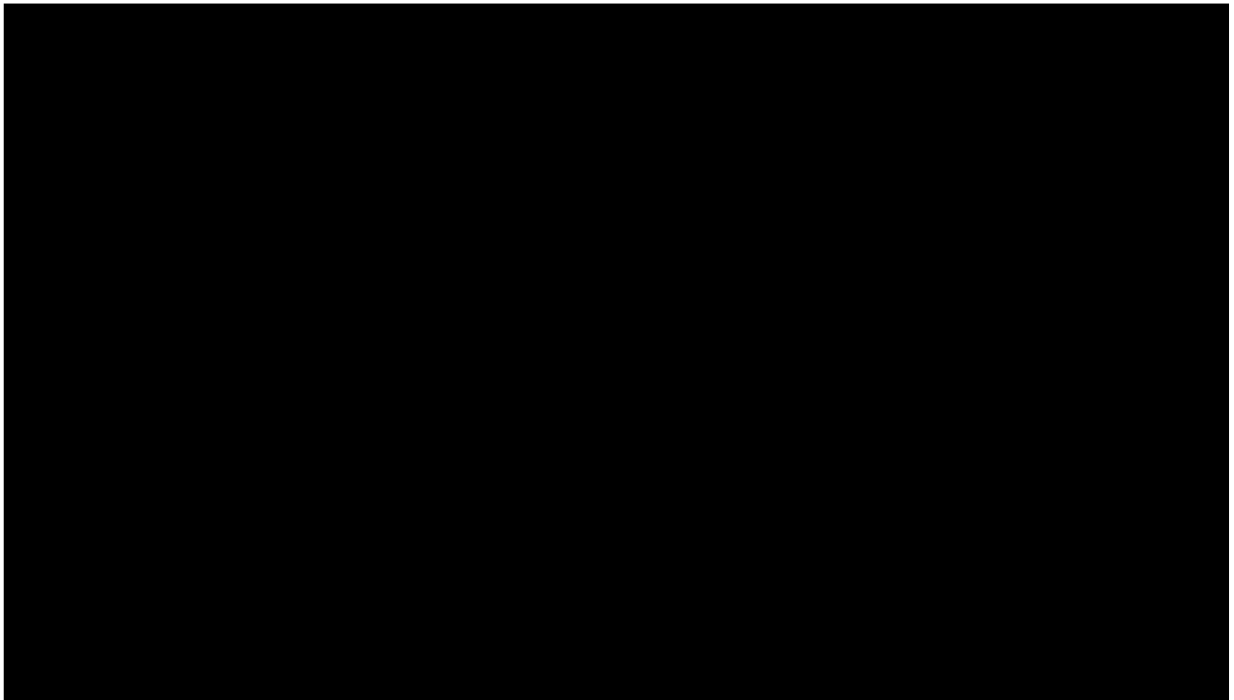
[REDACTED]



Abbreviations: CI = confidence interval; HR = hazard ratio
Source: GSK Data on File CSR 2024²¹

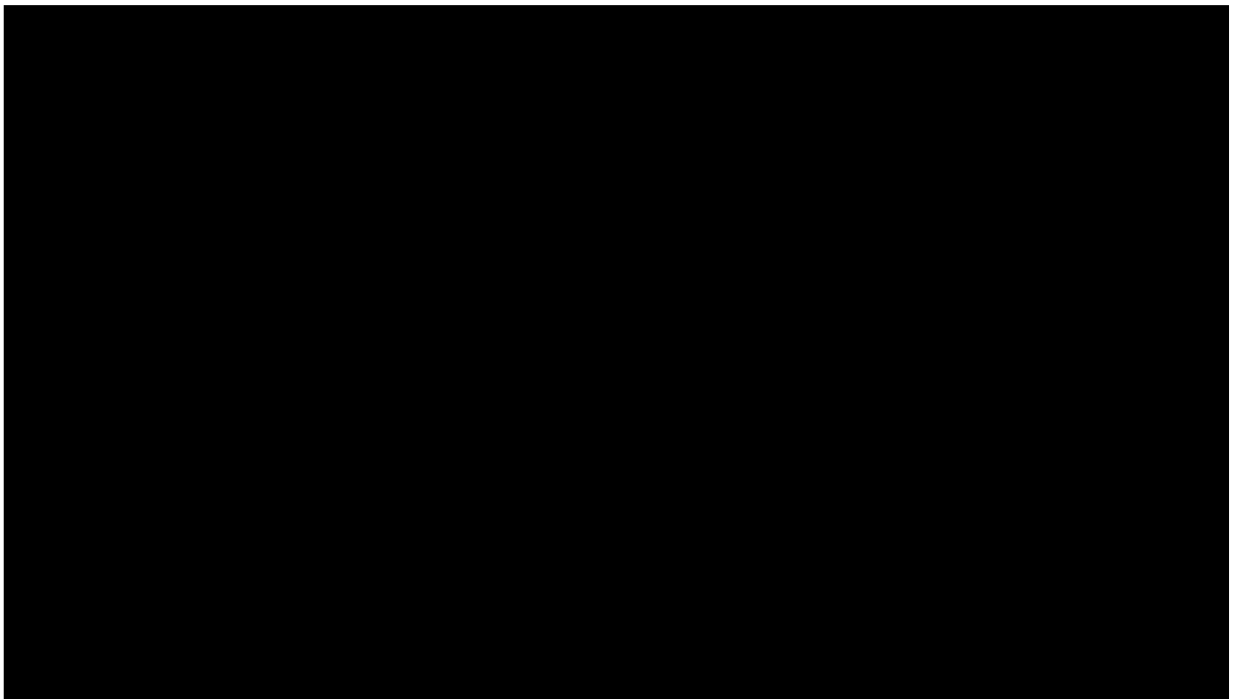
HRnd

[REDACTED]



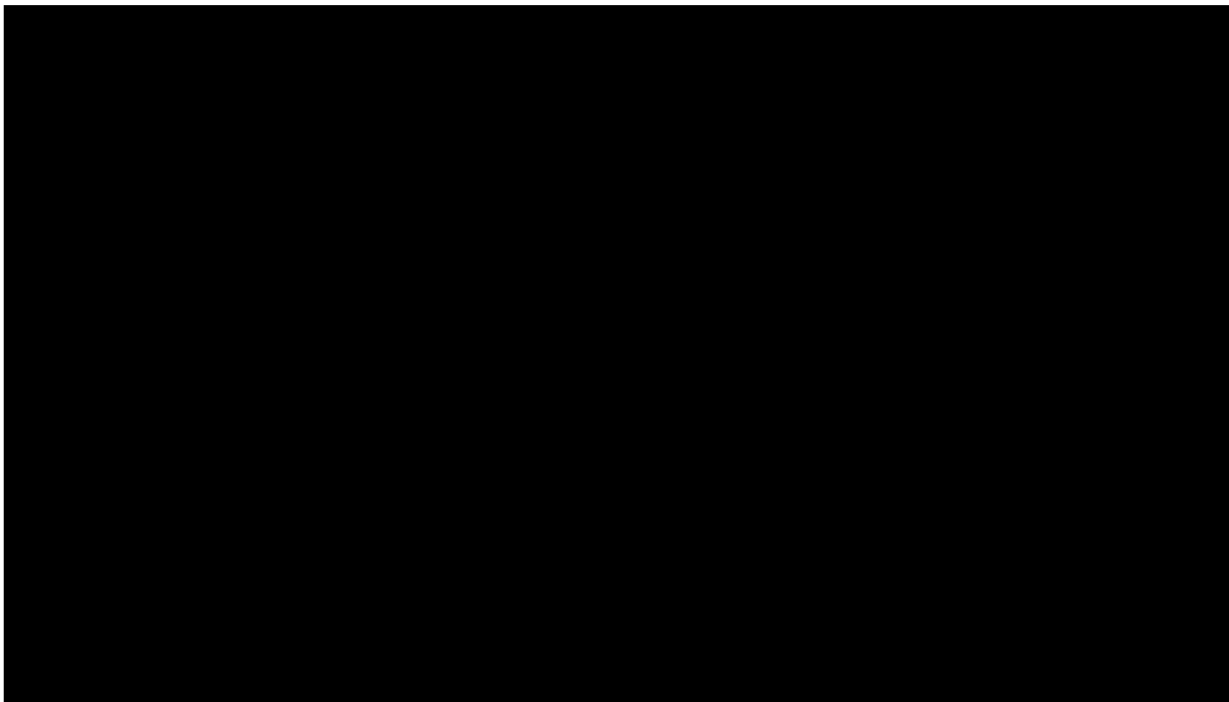
Abbreviations: CI = confidence interval; HR = hazard ratio
Source: GSK Data on File CSR 2019²³

[REDACTED]



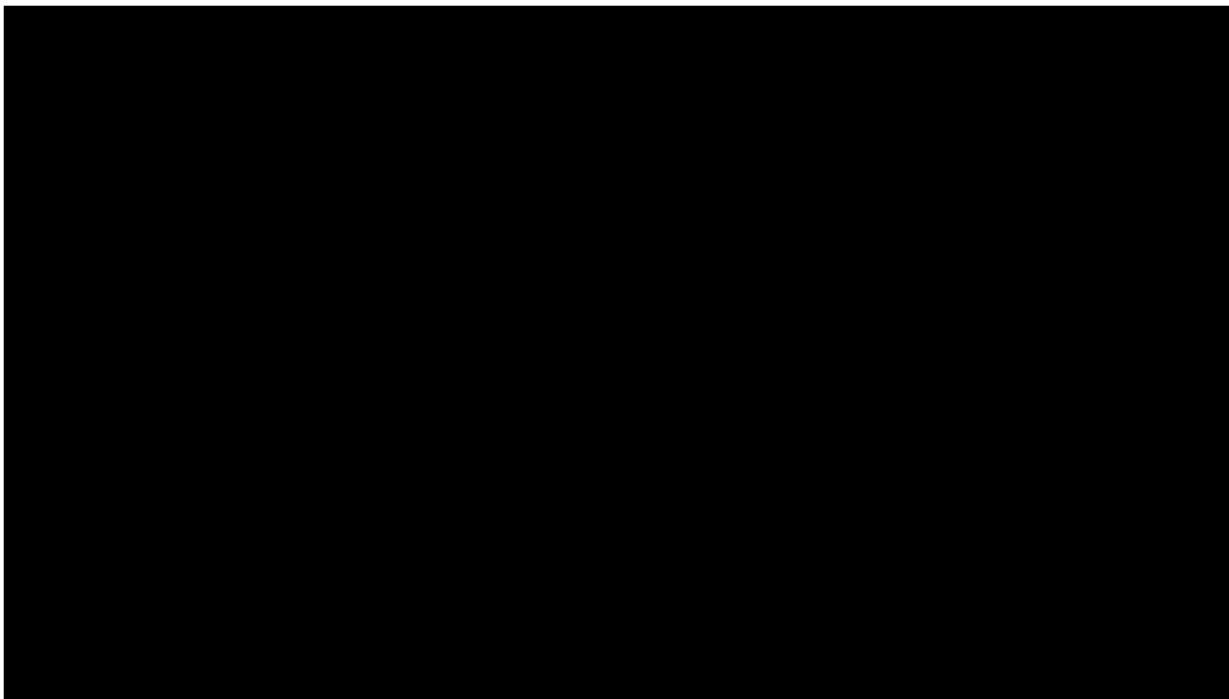
Abbreviations: CI = confidence interval; HR = hazard ratio
Source: GSK Data on File CSR 2024²¹

[Redacted]



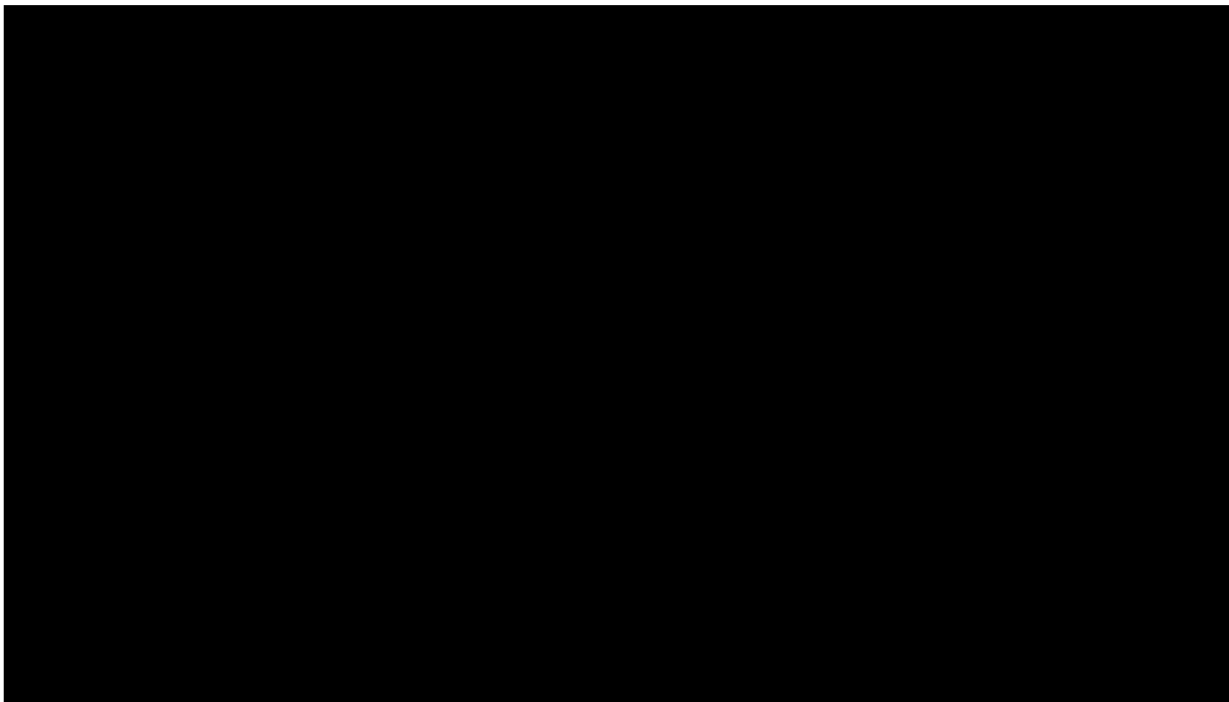
Abbreviations: CI = confidence interval; HR = hazard ratio
Source: GSK Data on File CSR 2024²¹

[Redacted]



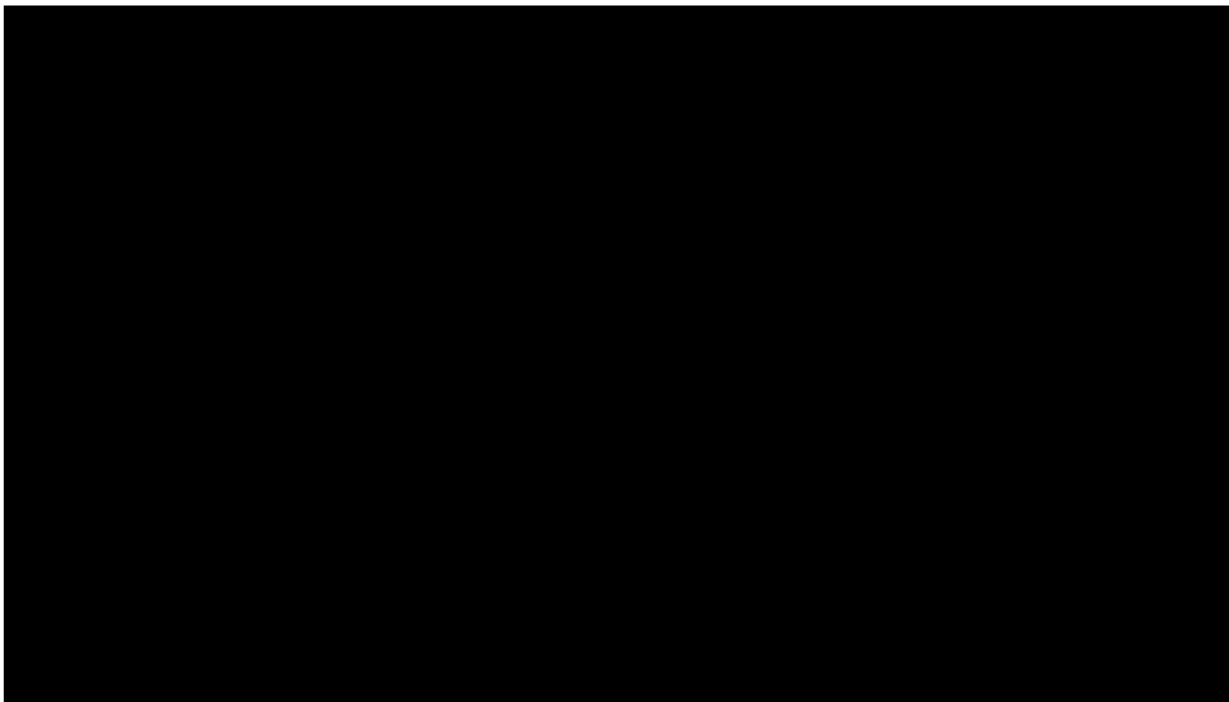
Abbreviations: CI = confidence interval; HR = hazard ratio
Source: GSK Data on File CSR 2024²¹

[Redacted]



Abbreviations: CI = confidence interval; HR = hazard ratio
Source: GSK Data on File Final Analysis²¹

[Redacted]



Abbreviations: CI = confidence interval; HR = hazard ratio
Source: GSK Data on File CSR 2024²¹

References

1. 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. Technology appraisal guidance [TA1055]*. 2025. 9 April 2025.
2. NHS England. National Cancer Drugs Fund List. 14 March 2025 2025;
3. National Institute for Health and Care Excellence. *Olaparib with bevacizumab for maintenance treatment of advanced high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer. Technology appraisal guidance [TA946]*. 2024. 17 January 2024.
4. Fujiwara K, Kristeleit R, Ghamande S, et al. 178O Rucaparib maintenance treatment in patients (pts) with newly diagnosed ovarian cancer (OC): Defining benefit according to disease risk subgroups within the phase III ATHENA–MONO study. *Annals of Oncology*. 2022;33(9):S1505-S1506.
5. O'Cearbhaill RE, Pérez-Fidalgo JA, Monk BJ, et al. Efficacy of niraparib by time of surgery and postoperative residual disease status: A post hoc analysis of patients in the PRIMA/ENGOT-OV26/GOG-3012 study. *Gynecol Oncol*. Jul 2022;166(1):36-43. doi:10.1016/j.ygyno.2022.04.012
6. Hettle R, McCrea C, Lee CK, Davidson R. Population-adjusted indirect treatment comparison of maintenance PARP inhibitor with or without bevacizumab versus bevacizumab alone in women with newly diagnosed advanced ovarian cancer. *Ther Adv Med Oncol*. 2021;13:17588359211049639. doi:10.1177/17588359211049639
7. Lorusso D, Mouret-Reynier MA, Harter P, et al. Updated progression-free survival and final overall survival with maintenance olaparib plus bevacizumab according to clinical risk in patients with newly diagnosed advanced ovarian cancer in the phase III PAOLA-1/ENGOT-ov25 trial. *Int J Gynecol Cancer*. Apr 1 2024;34(4):550-558. doi:10.1136/ijgc-2023-004995
8. Monk BJ, Barretina-Ginesta MP, Pothuri B, et al. Niraparib first-line maintenance therapy in patients with newly diagnosed advanced ovarian cancer: final overall survival results from the PRIMA/ENGOT-OV26/GOG-3012 trial. *Ann Oncol*. Nov 2024;35(11):981-992. doi:10.1016/j.annonc.2024.08.2241
9. Monk BJ, Parkinson C, Lim MC, et al. A Randomized, Phase III Trial to Evaluate Rucaparib Monotherapy as Maintenance Treatment in Patients With Newly Diagnosed Ovarian Cancer (ATHENA-MONO/GOG-3020/ENGOT-ov45). *J Clin Oncol*. Dec 1 2022;40(34):3952-3964. doi:10.1200/jco.22.01003
10. Li N, Zhu J, Yin R, et al. Treatment With Niraparib Maintenance Therapy in Patients With Newly Diagnosed Advanced Ovarian Cancer: A Phase 3 Randomized Clinical Trial. *JAMA Oncol*. Sep 1 2023;9(9):1230-1237. doi:10.1001/jamaoncol.2023.2283
11. Moore K, Colombo N, Scambia G, et al. Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. *N Engl J Med*. Dec 27 2018;379(26):2495-2505. doi:10.1056/NEJMoa1810858
12. Chase D, Perhanidis J, Gupta D, Kalilani L, Golembesky A, González-Martín A. Association of Multiple High-Risk Factors on Observed Outcomes in Real-World Patients With Advanced Ovarian Cancer Treated With First-Line Therapy. *JCO Clin Cancer Inform*. Jun 2023;7:e2200189. doi:10.1200/cci.22.00189
13. GlaxoSmithKline. Data on File PR-30-5017-C Baseline Characteristics. 2024.

14. Elattar A, Bryant A, Winter-Roach BA, Hatem M, Naik R. Optimal primary surgical treatment for advanced epithelial ovarian cancer. *Cochrane Database Syst Rev*. Aug 10 2011;2011(8):Cd007565. doi:10.1002/14651858.CD007565.pub2
15. González-Martín A, Harter P, Leary A, et al. Newly diagnosed and relapsed epithelial ovarian cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol*. Oct 2023;34(10):833-848. doi:10.1016/j.annonc.2023.07.011
16. Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. *CA Cancer J Clin*. Jan-Feb 2024;74(1):12-49. doi:10.3322/caac.21820
17. Kaul S, Diamond GA. Making sense of noninferiority: a clinical and statistical perspective on its application to cardiovascular clinical trials. *Prog Cardiovasc Dis*. Jan-Feb 2007;49(4):284-99. doi:10.1016/j.pcad.2006.10.001
18. Kim JH, Kim SI, Park EY, et al. Comparison of survival outcomes between olaparib and niraparib maintenance therapy in BRCA-mutated, newly diagnosed advanced ovarian cancer. *Gynecol Oncol*. Feb 2024;181:33-39. doi:10.1016/j.ygyno.2023.11.037
19. DiSilvestro P, Banerjee S, Colombo N, et al. Overall Survival With Maintenance Olaparib at a 7-Year Follow-Up in Patients With Newly Diagnosed Advanced Ovarian Cancer and a BRCA Mutation: The SOLO1/GOG 3004 Trial. *J Clin Oncol*. Jan 20 2023;41(3):609-617. doi:10.1200/jco.22.01549
20. GSK. Data on File Protocol PR-30-5017-C Table 2.5.1 and Table 2.5.2. 2025.
21. GlaxoSmithKline. *Final Overall Survival Analysis Clinical Study Report. A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study of Niraparib Maintenance Treatment in Patients with Advanced Ovarian Cancer Following Response on Front-Line Platinum-Based Chemotherapy*. 2024.
22. Mirza MR, González-Martín A, Graybill WS, et al. Prospective evaluation of the tolerability and efficacy of niraparib dosing based on baseline body weight and platelet count: Results from the PRIMA/ENGOT-OV26/GOG-3012 trial. *Cancer*. Jun 15 2023;129(12):1846-1855. doi:10.1002/cncr.34706
23. GlaxoSmithKline. *Niraparib PR-30-5017-c A phase 3, randomized, double-blind, placebo-controlled, multicenter study of niraparib maintenance treatment in patients with advanced ovarian cancer following response on front-line platinum-based chemotherapy – clinical study report*. 2019.

Single Technology Appraisal

Niraparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy (review of TA673) [ID6403]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1. Your name	██████████
2. Name of organisation	Ovarian Cancer Action
3. Job title or position	████████████████████
4a. Brief description of the organisation (including who funds it). How many members does it have?	Ovarian Cancer Action is the UK's ovarian cancer research charity. Ovarian Cancer Action funds research into early detection and better treatments, raises awareness of risk and symptoms to improve prevention and early diagnosis, and gives a voice to all those affected by ovarian cancer. Since 2006, Ovarian Cancer Action has funded over £12 million in research projects and launched the first ever dedicated centre of ovarian cancer research in Europe. Research is focussed on early detection and treatment of ovarian cancer to transform how long and how well women live after an ovarian cancer diagnosis. The charity raises funds through a variety of sources, the majority through individual public giving, philanthropic donations and charitable trusts and foundations. A small % is raised from gifts from corporate organisations including pharmaceuticals. It is not a membership organisation.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months If so, please state the name of the company,	AstraZeneca (olaparib) £10,000 Sponsorship of HHMT conference AstraZeneca (olaparib) £10,000 Update of Hereditary Cancer Risk Tool and campaign to raise awareness of genetic testing eligibility

Patient organisation submission

[Niraparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy (review of TA673)]

amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	Significant experience of day-to-day interactions with patients, their families and healthcare professionals (face-to-face, via telephone, email and written case studies). Consultation through email, phone, virtual meetings and surveys with patients and family members who volunteered to tell us about their experiences with ovarian cancer and its treatment. This included members of our Research Network. Previous direct consultation of patients for other NICE and SMC reviews. Quotes include those from patients not taking this medication, but who have given us insight into what living with ovarian cancer is like and their opinions on medications.

Living with the condition 6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	A diagnosis of ovarian cancer can be devastating, significantly affecting quality of life. The symptoms of the disease itself, the process of diagnosis, then treatment and anxiety over the high chances of recurrence, all impact patients and their families physically and mentally. The disease affects every aspect of their life – their relationships, work, family life and social life. Patients told us: “Before I was actually given my diagnosis, a consultant told me “you’re going to need to start on your bucket list”” “I didn’t sleep for months after being told I had advanced ovarian cancer” “When you have ovarian cancer you are not yourself - life revolves around the disease and in the very worst moments you have no interest in your family, friends and general life outside of the disease and what it is putting your body and mind through.” “Quality of life is poor – reasonable at best when on treatment. There is a desire to cram as much into life as possible due to not knowing what is going to happen next but being bound by the horrific side effects such as complete exhaustion, severe pain, nausea and vomiting and mouth ulcers that make it almost impossible to eat.” “[my diagnosis] has had a huge impact on my family. From being someone who never had a day's sick leave in 25 years of working to being someone who needed help to get upstairs and at times was in a wheelchair- it was a very difficult time for all of us.” “Ovarian cancer has taken away everything that makes me a woman.” “Catastrophic. Up to the point of diagnosis, I was a fit and healthy person who lived a very active life. It was devastating when I was diagnosed particularly knowing the survival rate and the fact that there is no absolute cure. Initially, physically I needed care around the clock but once chemo started it seemed to clear symptoms very quickly. The mental impact has been the hardest as the dreaded outcomes are never far away from my thoughts. I made the decision to give up work as life has become very precious and the only way I can deal with it, is to get normality back as much as possible. I am now back walking and playing tennis and leading an active life as much as possible.”

	“The impacts on my life were life changing and dramatic as I was so ill and could do so little while waiting and waiting for a proper diagnosis and to start some kind of treatment.” “Ovarian cancer not only limits the time a woman has to live, it also limits what a woman is able to do with the time she has left.” Living with the anxiety of recurrence is difficult: “It is a constant worry and overhang in your life. One’s attitude to life changes. What are you planning for? What time frame? There is so much uncertainty. I was ‘no evidence of disease’ after my first round of chemo and then the cancer came back. There is no way of knowing how long gaps in treatment will be. It is hard to stay optimistic and live in the present.” “Even when I’ve been NED, I’ve worried a lot about recurrence. Every twinge is a worry. For a long time I couldn’t sleep, I was getting two hours a night and I had to beg for sleeping tablets as I couldn’t function. What if I’m living my life and the cancer’s growing?” “The fear of recurrence featured heavily in my thoughts, especially at night, and it affected my sleep. When I did recur, I didn’t trust my body anymore. It took me a lot longer to get over the shock than the original diagnosis. I wasn’t sure if I could still be strong and positive. Having got over the fear of dying from the disease, these thoughts returned with a vengeance. Living with OC now, with me being NED for over 6 years feels different as I take a maintenance drug which is very effective. It’s my parachute.” “I think the biggest concern is not knowing if or when another relapse will come.” “Even once the treatment is over it’s not really the end, it’s always there, it’s always in the back of your mind.” “When you finish chemo, you feel like it’s taking the crutches away, it’s ‘what now’?” Ovarian cancer impacts the family and loved ones of the woman diagnosed: “Life for both the patient and carer becomes totally consumed by the disease – when the next hospital appointment will be, managing side effects, organising childcare, sleepless nights – it is a vicious circle that never seems to end.”

Current treatment of the condition in the NHS 7. What do patients or carers think of current treatments and care available on the NHS?	Patients told us about their experiences being treated for ovarian cancer using surgery and chemotherapy: "The standard current treatment for ovarian cancer is debilitating, requiring extensive surgery and gruelling repeated courses of chemotherapy. Many women like me are left with chronic bowel pain and disturbance (or a stoma) after surgery and the chemotherapy leaves women with multiple long-term effects including peripheral neuropathy, joint pains and fatigue, and many understandably suffer from a degree of post-traumatic stress disorder." "There were points where I couldn't even get up and go to the bathroom. I'm a really independent person and from somebody who's led a very full independent life, never having to depend on anyone for anything, all of a sudden my daughters are bathing me and I'm having to be carried to the bathroom." "During chemo treatment the emotional anxiety of having OC is heightened by the physical issues experienced with the chemo. Everyone's symptoms with chemo will be different but I found each of my six month cycles of chemo brutal, both physically and mentally. The times between treatment are easier - but again the worry of what the next blood test will show - has the CA125 increased? - is ever present. Waiting for scan results is agony." "For me personally after the initial diagnosis and first lot of treatment I thought there is just no way I can do that again. Chemotherapy is so tough." "I had such an awful time and my treatment journey wasn't very good. I suffered very badly from side effects. And with all of that, I reached a really dark place. Physically it bashed me and it broke me, but it nearly broke me mentally as well and emotionally, to the point where I wanted it all to end. I wanted life to end. It was my faith that grounded me and got me through that really dark portion, but also the love that surrounded me." We can see that the impact of chemotherapy on patients and family is extreme, and being able to extend the time between these treatments would benefit all.

8. Is there an unmet need for patients with this condition?	Niraparib being available at first line has improved the options available to women and should become part of standard practice. A choice of first line maintenance therapies should be available for all those diagnosed with ovarian cancer – enhancing choice enables those diagnosed with ovarian cancer to have an improved progression free survival which is important for a disease which reoccurs. Although PARP inhibitors all utilise the same mechanism of action, they do so in different ways and as such have different pharmacological profiles and side effects. Clinicians should be able to choose and adapt the maintenance therapy based on the specific needs and toxicity risks of each patient. Patients themselves need to have options for first-line maintenance therapies, with a range of options available in case of significant side effects. Giving a woman hope, through access to niraparib at first line, gives her whole family, and friends, hope too. Earlier access would allow women more, and better, quality time with friends and family, with fewer side effects than chemotherapy, with better mental health due to reduced anxiety. Patients and their families told us: “[We need] choice of treatment options rather than just being told which treatment you are being put on. Patients should be given more information to take away and read and assess before then consulting with your oncologist and deciding which path to go.” "I also am very concerned that treatment options in the UK depends on where in the UK a patient lives. That cannot be right. We are a NATIONAL health service." "I felt that the system was designed to assume that I have OC and I'll be ill for a short period of time and then I'll die from it, so there's no point investing any time or energy into any recovery or quality of life. It felt that I was forgotten about as there just wasn't anything in place to support me." There is a need for options for women at first line: "The awful news there's nothing else for you until it returns. I begged for something to keep it at bay."

Advantages of the technology 9. What do patients or carers think are the advantages of the technology?	Providing niraparib after first line chemotherapy allows families a period of stability which would be priceless to both the patient, their family and carers giving them good quality time together and a chance to do important things they wished to do before the patient became too unwell to do such things. Patients who have taken niraparib tell us: "I have been on both a PARP inhibitor - niraparib - and on Avastin. I felt positive knowing that there is data which shows that these maintenance treatments can keep the cancer at bay. And indeed they did do so in my case for some time." "AMAZING! Although I had issues with low platelets initially, once put on the right dose, I have no known side effects." "As niraparib is a tablet, we are freed up from endless time at a chemotherapy unit and have more time to enjoy life" "For any woman with recurrent ovarian cancer and their family, this period off chemotherapy whilst still relatively well, would be priceless." "Apart from the first three months on the PARP which was tough (side effects such as really bad nausea/fatigue etc) I live a wonderful, manageable life. I still have to manage the fatigue, and stress of living with cancer, but can plan short term things like holidays and trips with my family. I play tennis, I paint. I am able to celebrate important life events of my children e.g. my son going to Uni. Plan adventures with them. Share another Christmas. Build more memories with my children. Try and become a better person. Use my experiences of cancer and help others." "After chemo maintenance treatments are so much easier and one of the massive positives is that as a result of being on treatments is that your vitals are constantly being monitored and there is always someone to answer any issues/ problems/symptoms. This 'holds your hand' as you move to your new world of normal. Hugely positive. It's hard when you come off these treatments as then the fear of it returning kicks in." "[Maintenance treatments are] much needed alternatives for bodies that need a break from chemo as it can keep you stable especially if your situation is only controlled not cured." "As I've had two recurrences, progression free survival is of utmost importance to me."

	"For my whole family my diagnosis was painful and upsetting, including all the time taking me to treatment and seeing the side effects. I am now on a PARP inhibitor so have to go to the hospital less and this has really helped reduce the toll on my daughter." "Niraparib means I can get on with doing things and feeling healthy while at the same time knowing something is suppressing the tumours which feels more proactive than just waiting. I'm able to do things I couldn't do on chemo- travel, improve my Italian, go to the opera again." "I have been taking 200mg of Niraparib since September 2019 and am happy with the quality of life I am living. In fact if it hadn't been for COVID19, 2020 would have been a very busy year full of big family celebrations and a wedding in Slovakia. I feel very lucky to have been able to receive it." "Niraparib has massively improved my quality of life, both physically and mentally. We all feel my quality of life has improved considerably. I wish it had been available after my first line of chemo." "For me Niraparib has offered a life line from the daunting prospective of further rounds of chemo. I don't know how long it will work for but that's the nature of cancer treatments. It's very manageable and hasn't stopped me doing anything. Can get on with your life with minimal side effects. It had given me good and quality of life." "I have responded well to Niraparib, but could not be offered it until after my second line of chemotherapy. Perhaps being able to have it sooner would have prevented the need for a second line" Maintenance treatments, taken at home rather than at hospital, reduce the burden of travel and appointment time for not only the patient but for their carers/ family also: "For my whole family my diagnosis was painful and upsetting, including all the time taking me to treatment and seeing the side effects. I am now on a PARP inhibitor so have to go to the hospital less and this has really helped reduce the toll on my daughter." "Living in a more rural location, I had to travel in to hospital to have my treatment. This meant long car journeys to get to my chemotherapy every Tuesday, and once a month on a Wednesday too to meet with my oncologist. This was tiring for me but also for my support system who drove me and waited while I had my treatment." The anxiety over recurrence is felt by family/friends as well as the patient. Access to rucaparib at the earliest possible point of treatment provides women and their families to feel they are actively stopping the disease from progressing, and gives them more good quality time with their friends and family.

Disadvantages of the technology 10. What do patients or carers think are the disadvantages of the technology?	Ovarian Cancer Action has received numerous anecdotal comments and concerns regarding side effects of treatments. Adverse effects of treatment and health-related quality of life should certainly be considered as significant in any outcome assessments. Patients are concerned about any short- and long-term side effects of the treatments, as key for them is that the time are living with this disease is of good quality and enjoyable. It's imperative that treatments offer not only time but quality of life, and we understand that there are drawbacks to any treatment. Niraparib does cause some side effects including: anaemia, fatigue, nausea and decreased platelet count, however we're told these side effects are easier to deal with than those of regular chemotherapy and do tend to subside after the first few months of treatment. We asked our supporters about side effects and downsides to taking Niraparib: "Some minor nausea, but nothing significant. The main issue has been much increased photo sensitivity of my skin, meaning in I have to be particularly careful." "The only slight negative is the need to have bi monthly blood tests taken at the chemo unit and 3 monthly consultations with my oncologist, so it reminds me that I am living with cancer, and when taking it every night I think is there is a subconscious impact of this." "Constipation and insomnia are also an issue but it's a small price for me to pay for something that is giving me extra time with family" "The downsides of these treatments in my opinion are few." "I have a little bit of nausea and fatigue at the mo, but it's nothing like when I was on chemo and I am told those symptoms will abate as my body learns to tolerate the treatment." "I was put on a PARP inhibitor niraparib. Getting the dosage right was painful, I needed blood transfusion etc." "It would seem far better to offer Niraparib earlier if it is likely to prevent the need for further chemotherapy, which I found far more invasive and disruptive." In comparison to the whole-body impact of chemotherapy, these side effects have often been described to us as "more annoying than debilitating" so quality of life is better than the 'traditional' treatment women have already experienced. However, we know from our patient supporters that there is significant anxiety over what will happen if they do not tolerate the PARP inhibitor protocol they are on. Anecdotally we have heard from patients who are scared to tell

	their clinical teams about side effects they are experiencing for fear of being taken off the maintenance treatment they are on. Open discussion about dose-reduction (and the resulting efficacy) and options to address side-effects at the start of the treatment may help to alleviate this.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	

Other issues

13. Are there any other issues that you would like the committee to consider?	

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	• Ovarian cancer is a devastating disease for both patients and their families/ friends, with a poor prognosis for the many women diagnosed at a late stage. • Patients and their families face a great deal of anxiety over treatment itself, and whether the disease will recur (which it does for most). Maintenance treatments offer patients more time between chemotherapy treatments. • Ovarian Cancer Action supports new options being made available that can give women more good quality time with their families and friends. In order to improve survival rates we must ensure that more patients have access to the best available treatment, and at the earliest opportunity. These options are life-changing for the patients we see every day, offering hope for the future. • Making sure there are options for maintenance treatment gives patients and their clinicians the opportunity to choose the most suitable treatment based on the individual and their current health. • On the basis of patient feedback Ovarian Cancer Action believe that niraparib should continue to be available for this cohort, and should move to routine access.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - YES or NO

For more information about how we process your personal data please see our [privacy notice](#).

Patient organisation submission

[Niraparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy (review of TA673)]

Single Technology Appraisal

Niraparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy (review of TA673) [ID6403]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1. Your name	[REDACTED]			
2. Name of organisation	Ovacome Ovarian Cancer Charity			
3. Job title or position	[REDACTED]			
4a. Brief description of the organisation (including who funds it). How many members does it have?	Ovacome is the national UK ovarian cancer charity focused on providing support and information to anyone affected by ovarian cancer. This includes people who have either been diagnosed with the disease or think that they might be at risk, as well as their friends and family and healthcare professionals. We provide direct support to over 6,200 people each year and have 5,000 members. We have 16 members of staff. We are funded through charitable donations, trusts and foundations donations, community fundraising donations and earned income.			
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months?	Company	Amount Received	Date received	Funding for:
	GSK	£600.00	9/8/2024	Patient Advisory Board - UK Ovarian Cancer Patient Council
	MSD	£83,509.30	22/8/2024	Grant towards Health Equality work
	MSD	£83,509.30	10/1/2024 Deferred from	Grant towards Health Equality work

Patient organisation submission

[Niraparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy (review of TA673)]

[Relevant companies are listed in the appraisal stakeholder list.] If so, please state the name of the company, amount, and purpose of funding.			previous FY	
	GSK	£520.00	13/11/2024	UK Ovarian Cancer Patient Panel
	Pharma&	£9,060.00	6/12/2024	Donation
	GSK	£10,000.00	20/2/2025	Grant for delivery costs of six regionally based support and outreach events
	Abbvie	£10,000.00	27/3/2025	Project funding
	GSK	£375.00	16/4/2025	Recording of Expert Opinions for future use at GSK external meetings
	Abbvie	£465.00	1/5/2025	Meeting participation
	Pharma&	£13,015.00	9/5/2025	Donation
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No.			
5. How did you gather information about the experiences of	Knowledge and experience from providing support to those affected by ovarian cancer. With regards to this submission, we have also used feedback from members sought through the My Ovacom online forum.			

Patient organisation submission

[Niraparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy (review of TA673)]

patients and
carers to
include in your
submission?

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Ovarian cancer has a significant impact on quality of life. The majority of people are diagnosed at Stage III when it has already spread outside of the pelvis. This means they can experience symptoms impacting their health and quality of life, such as ascites. Treatment is therefore aimed at minimising the burden of the disease and maximising periods of wellness between treatments. As treatment lines are exhausted, those diagnosed fear being told there is no more treatment available to manage their ovarian cancer. The surgery undertaken is most usually a total abdominal hysterectomy and bilateral salpingo-oophorectomy. This operation can have long term effects on abdominal organs and particularly the bowel with associated continence issues. This may mean having manage a stoma, either short or long term. It will result in immediate surgical menopause. Associated issues include fatigue, possible chronic pain and changes to body image and function affecting sexuality. Long-term effects of chemotherapy treatment can include peripheral neuropathy which can limit both walking mobility and ability to drive. These physically and psychologically debilitating side effects can impact relationships, work and caring roles permanently. Living with ovarian cancer can be very isolating, due to its comparative rarity those diagnosed may not meet anyone else with the same condition or facing the same issues of managing their cancer as a chronic condition rather than aiming for a cure. Those diagnosed live with the anxiety of possible recurrence. The time after treatment whereby patients are under routine surveillance can be psychologically very hard to cope with. Our members report feeling adrift and as if they are waiting for their disease to return. Having a choice of maintenance treatment and continued input from oncology teams offers a significant psychological benefit as well as physical health benefits. There is currently one first-line PARPi routinely available for people with non-BRCA+/HRD ovarian cancer and this treatment would provide further options for these patients in the first line setting for whom rucaparib is unsuitable.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Our members express concerns regarding limited choices and availability of maintenance treatments. These include; • concerns about the availability of maintenance therapies and the uncertainty around whether or not they will be approved for routine clinical use. • concerns from our members who may be experiencing treatment side effects that effective alternative options may not be available. • concerns that treatment options are limited and lines of treatment to control the disease will be exhausted leaving palliative care only
8. Is there an unmet need for patients with this condition?	There is currently one first-line PARPi routinely available for people with non-BRCA+/HRD ovarian cancer and this treatment would provide further options for these patients in the first line setting for whom rucaparib is unsuitable.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	They are pleased to have a choice of maintenance therapy that is manageable in terms of administration and side effects. It enables good quality of life while receiving ongoing treatment and increases the time between lines of chemotherapy. Ongoing regular contact with oncology teams can be reassuring and have psychological benefits. Please see comments below from our members [please note, these may refer to niraparib for recurrent ovarian cancer]: <i>“Before starting I was aware all PARPS work better if BRCA + so very grateful there was a maintenance I could be offered, after chemo and surgery. It was a real plus.</i> <i>I was on Niraparib for 12 months with minimal side effects, I had a great quality of life, I travelled and I worked. I was really well, then slight progression at 12-month stage then taken off Niraparib and started other chemotherapy.</i> <i>I feel there’s not a lot for people that are BRCA – but grateful for the 12 months of Niraparib especially seeing how much it costs.</i> <i>I want you to know that it is really valued by a BRCA negative person.”</i> Another member describes the importance of choice: <i>“I was diagnosed with Stage 4 high grade serous ovarian cancer in [date] and was found to carry the BRCA2 gene. I had debulking surgery on [date] and chemotherapy before and after this.</i> <i>I started maintenance treatment with Olaparib from [date] but experienced significant side effects, particularly breathlessness, which led to this being discontinued. I then started on Niraparib in [date] and have continued to date.”</i> Another member describes quality of life: <i>“I am stage 4b HGSOC and had the standard treatment of carbo/taxol and debulking. have been on Niraparib since / for 15 months, I was never declared NED. Niraparib has been a life saver for me, it has really improved my quality of life. It has prolonged my life.</i>

	<i>I have experienced side effects with it but they have been manageable, it has led to some of my tumours / tumours reduction and I have been able to live as well as possible with my cancer whilst on Niraparib. So, I think it is a very good treatment for people in my case. I am HRD positive and I have quite a high score on the positive side of HRD, so that's what I wanted to say and I hope NICE will continue to fund Niraparib."</i>

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	They are aware there are side effects which are often manageable. Please see comment below from one of our members: <i>"2 side effects; One in first month grade 4 thrombocytopenia so stopped Niraparib for a couple of weeks then went from 300mg to 200mg and stayed on this dose.</i> <i>Second side effect: In Nov – 6 months into taking Niraparib, my blood pressure went up, which I was surprised by as I'd expected that to happen in the beginning. I wasn't aware that side effects can happen at any time. I had a really bad headache and checked my BP and saw it had gone up. It was very scary as I thought they'd take me off the treatment. It was manageable and they put me on blood pressure tablets without a break in Niraparib."</i> Another member describes: <i>"I've experienced very few side effects of Niraparib. The side effects that I do have are a cough and runny nose and some fatigue. I can't be sure though how much of the fatigue is due to the Niraparib and how much to having had a lot of cancer treatment, becoming less fit and just getting older.</i> <i>The dosage was reduced to 100mg on [date] due to neutropenia. I've also had a couple of breaks from taking Niraparib due to elevated liver enzymes, which have quickly resolved."</i>

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	We know that some people with ovarian cancer can struggle to access treatments if they don't fully understand treatment options and choices. This may include people with learning disabilities, people who have English as a second language or who have low levels of literacy. It is important that all patients have equal access to this treatment option where clinically appropriate, and that includes detailed understanding of risk-benefits. It is essential that all patients' information and support needs are assessed on an individual basis and that risk-benefit conversations take place in an appropriate and accessible manner. These should take into consideration patient preferences such as preferred language and preference for face to face, or over the phone appointments.

Other issues

13. Are there any other issues that you would like the committee to consider?	

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	• Ovarian cancer is frequently managed as a chronic condition rather than curative and therefore expanding the choice of maintenance therapies for this group of patients is vital. • For patients with advanced ovarian cancer knowing their cancer is likely to recur, having maintenance therapy which extends progression-free survival and continued input from oncology teams offers significant psychological as well as health benefits. • Niraparib is convenient in terms of administration, offering good quality of life for patients whose side effects are manageable. • For patients (particularly those who may have barriers to accessing information) it is essential that information and support needs are assessed on an individual basis and that risk-benefit conversations take place in an appropriate and accessible manner.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

Patient organisation submission

[Niraparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy (review of TA673)]

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - YES or NO

For more information about how we process your personal data please see our [privacy notice](#).

Single Technology Appraisal

Niraparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy (review of TA673) [ID6403]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1. Your name	██████████
2. Name of organisation	Target Ovarian Cancer
3. Job title or position	████████████████████
4a. Brief description of the organisation (including who funds it). How many members does it have?	Target Ovarian Cancer is the UK's leading ovarian cancer charity. We work to: • improve early diagnosis • fund life-saving research • provide much needed support to women with ovarian cancer We are the only national charity fighting ovarian cancer on all three of these fronts, across all four nations of the UK. We are the authority on ovarian cancer. We work with women, family members, and health professionals to ensure we target the areas that matter most for those living and working with Target Ovarian Cancer is funded through voluntary donations and some limited funding from manufacturers outlined below:
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.]	Yes GSK July 2025 £5,000 to support the development of patient information AstraZeneca August 2024 £400 honorarium for a speaking engagement

Patient organisation submission

[Niraparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy (review of TA673)]

If so, please state the name of the company, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	• Anecdotal feedback from patients and their families. • Calls to the Target Ovarian Cancer support line and questions and comments on our online communities • Survey of those who have accessed niraparib from the 1st line of treatment

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Around 6,900 women are diagnosed with ovarian cancer in England each year and two thirds are diagnosed at a late stage (stage III or IV) when the cancer is more difficult to treat. Survival rates for ovarian cancer trail those for many other cancers. Standard treatment involves surgery and chemotherapy, with chemotherapy either post-surgery or neoadjuvant. In the majority of cases the disease returns after first line treatment. At this point treatment is no longer curative and each further recurrence and subsequent round of platinum-based chemotherapy a woman goes through increases her chance of becoming platinum resistant; at which point very few treatment options remain and prognosis is extremely poor.

Patient organisation submission

[Niraparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy (review of TA673)]

	The prospect of recurrence casts a shadow over the lives of many women. Fears around recurrence are compounded by the knowledge that there are limited treatment options for ovarian cancer, particularly for the around 50 per cent who do not have a BRCA mutation or are not HRD positive. Patients are aware of the high level of recurrence for ovarian cancer so would welcome options that may prevent a recurrence or offer more time between lines of chemotherapy which has the potential to prolong platinum - sensitivity. Target Ovarian Cancer's Pathfinder research found that 60 per cent of those diagnosed with ovarian cancer report that it had a negative impact on their mental health. We also found high levels of unmet needs for support with patients reporting the need for support with feelings of isolation, issues relating to body image and sex and intimacy. <i>"It's completely affected me. Body image, anxiety. My personality has change"</i> Woman with ovarian cancer. There are also practical implications of debilitating treatments rendering individuals unable to work or take part in regular day-to-day life.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	<i>“The latest drugs offer hope and the chance that women with progressive disease can enjoy a better quality of life and longer survival. If new drugs are not made available, the current survival rates will continue to be dire in comparison with other cancers and this has to change. Women with ovarian cancer should be given the same right to life as those with other, more widely supported, cancers.”</i> Woman with ovarian cancer <i>“(there are) very limited options, with limited success. New treatments are urgently needed”</i> Woman with ovarian cancer Platinum-based chemotherapy is effective in maintaining stable disease and helping alleviate the impact of ovarian cancer symptoms. However, platinum-based chemotherapy will cause some side effects which women find difficult to manage, including tiredness and fatigue, hair loss, nausea and vomiting, and tingling and numbness in the fingers and toes. When Target Ovarian Cancer surveyed those who had accessed 1st line niraparib 97 per cent agreed that being able to access a PARP inhibitor after 1st line chemotherapy was important to them with 84 per cent of those being strongly agree
8. Is there an unmet need for patients with this condition?	Yes patients who do not have a BRCA variation or who are not HRD positive currently only have one option of PARP inhibitor available to them in routine commissioning

9. What do patients or carers think are the advantages of the technology?	Effective treatment Patients are often aware of the poor outcomes associated with ovarian cancer accessing a maintenance treatment they feel they are giving themselves the best possible chance or preventing a recurrence. For some patients this has meant valuable time with their loved ones <i>More time is an exponential benefit for ovarian cancer sufferers. For me it's made the difference of leaving teenagers to make it in the world on their own to now young men ready for this challenge-</i> Woman who has accessed niraparib from the 1st line of treatment <i>Taking niraparib is the best chance of keeping my cancer at bay & giving me the best chance to live longer. It's the golden ticket so to speak.</i> Woman who has accessed niraparib from the 1st line of treatment <i>Eternally grateful to be able to have this drug on the NHS. I am aware of the monthly cost and that makes me even more humble. Anything that can give other women the same opportunity the better.</i> Woman who has accessed niraparib from the 1st line of treatment Emotional/mental health impact. Patients report that the hope given to them by being able to access a maintenance treatment has a beneficial impact on their mental health. The prospect of recurrence can have an impact of the mental health so being able to access a maintenance treatment allows valuable time to recover from chemotherapy allowing patients to resume some normality and live their lives as fully as possible <i>'The hope that it's keeping the disease at bay. I've been on it for 15 months, still NED albeit with rising CA125.'</i> Woman who has accessed niraparib from the 1st line of treatment <i>'Taking a tablet you feel you are doing something to keep your cancer away which is so much better than chemo you can get on with your life. I have had no real side effects.'</i> Woman who has accessed niraparib from the 1st line of treatment

	<i>'To be offered a maintenance drug was a positive action that helped me so much. It helped keep me NED for 12 months'.</i> Woman who has accessed niraparib from the 1st line of treatment <i>'I felt I was doing the best for myself by taking them... Comforting almost that I was able to somehow try and suppress the cancer from returning'</i> Woman who has accessed niraparib from the 1st line of treatment Mode of delivery – niraparib is given in tablet form allowing women to easily continue treatment in their own home and greatly reducing hospital visits. It also reduces the need for women to live their life around their hospital appointments and treatment. <i>Feels very 'unmedical' not going to the hospital all the time, almost like being normal! Kept my cancer away for almost 4 years</i> Woman who has accessed niraparib from the 1st line of treatment Choice – Niraparib gives another option for maintenance treatment following first line treatment. There is currently one option in routine commissioning for first line maintenance for women who do not have a BRCA mutation or are not HRD positive. It is vital that there is a choice of PARP inhibitors are available as side effects from one type may not be tolerated

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Patients have shared that they have faced a range of side effects, some of these have been mitigated by a dose reduction. Side effects need to be managed between patients and their clinical team; some patients are able to make changes to cope with the side effects and some are not able to tolerate treatment due to them. <i>'Usual side effects but I'd rather have side effect I can manage than not having a good chance of living longer.'</i> Woman who has accessed niraparib from the 1st line of treatment <i>'Commenced on higher dose originally, required a blood transfusion but once titrate down to 100mg have been fine, some nausea but tolerable.'</i> Woman who has accessed niraparib from the 1st line of treatment <i>'Side effects can be hard to manage and have resulted in quite a few lifestyle changes.'</i> Woman who has accessed niraparib from the 1st line of treatment <i>'I had more side effects than with any of the chemotherapy drugs I have had. I had to stop taking it because of abnormal liver function so many times I was off it more than on it. Also the nausea and vomiting were difficult to cope with'</i> Woman who has accessed niraparib from the 1st line of treatment <i>'Initially it caused me huge anxiety so had to reduce the dose. It also gave me hypertension so now having to treat that separately. Joint pain is also a side effect although difficult to know if that's from the medication or surgical menopause.'</i> Woman who has accessed niraparib from the 1st line of treatment

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Those who do not have a BRCA variation or are not HRD positive currently only have one option available to them in routine commissioning so any treatments that offers patients choice would be welcomed

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	

Other issues

13. Are there any other issues that you would like the committee to consider?	

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	• Choice – Many women welcome the opportunity to be involved in making decisions about their care and treatments they receive, and feel they are able to take some control at what is a very uncertain time. Choice is also important so that there are alternate options when side effects are not tolerated • Mental health benefit – patients report that being able to access a maintenance treatment from the first line offers hope and the potential to resume more normal activities • Mode of delivery Niraparib is given in tablet form allowing women to easily continue treatment in their own home and greatly reducing hospital visits. It also reduces the need for women to live their life around their hospital appointments and treatment. • Effectiveness of treatment – Patients are often aware of the poor outcomes associated with ovarian cancer by accessing a maintenance treatment they feel they are giving themselves the best possible chance or preventing a recurrence. For some patients this has meant valuable time with their loved ones.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - YES or NO

For more information about how we process your personal data please see our [privacy notice](#).

Single Technology Appraisal

Niraparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy (review of TA673) [ID6403]

Clinical expert statement

Information on completing this form

In [part 1](#) we are asking for your views on this technology. The text boxes will expand as you type.

In [part 2](#) we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Clinical expert statement

Niraparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy (review of TA673) [ID6403]

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See [Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals](#) (section 3.2) for more information.

The deadline for your response is **5pm on 24 October 2025**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received, 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 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.

Clinical expert statement

Niraparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy (review of TA673) [ID6403]

Part 1: Treating ovarian, fallopian tube and peritoneal cancer and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Jonathan A Ledermann
2. Name of organisation	University College London and UCL Hospitals, London
3. Job title or position	Professor of Medical Oncology and Honorary Consultant in Medical Oncology
4. Are you (please tick all that apply)	☒ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with ovarian, fallopian tube and peritoneal cancer ? ☒ A specialist in the clinical evidence base for ovarian, fallopian tube and peritoneal cancer or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

Clinical expert statement

Niraparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy (review of TA673) [ID6403]

8. What is the main aim of treatment for ovarian, fallopian tube and peritoneal cancer ? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	The treatment aim in newly diagnosed advanced ovarian, fallopian tube or peritoneal cancer is to provide patients with longer time before subsequent treatment is needed, and to improve the duration of overall survival.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Given that niraparib is used in patients who have responded to surgery/chemotherapy, a clinically significant response is a delay to tumour progression, and consequently the time until subsequent treatment is needed.
10. In your view, is there an unmet need for patients and healthcare professionals in ovarian, fallopian tube and peritoneal cancer ?	Over the last 25 years there has been little change in the time to disease progression after front line treatment of ovarian cancer with surgery and chemotherapy. The only exception to this has been the addition of bevacizumab to the treatment of some patients, extending the mean time to progression by about 3.5 months in a sub-population of patients at high risk of recurrence. These data, available from clinical trials published in 2011 resulted in a median survival of about 36 months in patients in this treatment group who were able to receive bevacizumab. This 'best' survival' figure has remained a consistently poor outcome of treatment, and it applies to most patients who have advanced disease. The clinical trials with PARP inhibitors were designed to improve this result, extending the time to disease progression.
11. How is ovarian, fallopian tube and peritoneal cancer currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	The guidelines for treatment largely follow the international guidelines from ESMO, the European Society of Medical Oncology with adjustments according to approvals in the NHS. The BGCS (British Gynaecological Cancer Society) Guidelines essentially mirror the ESMO guidelines. Current guidelines for advanced disease stages (about 75% of cases) consist of three components: firstly a decision about the timing of cytoreductive surgery before or after the start of chemotherapy, secondly a chemotherapy phase with standard drugs (carboplatin and paclitaxel) with or without the addition of bevacizumab depending on clinical risk factors of progression, and a third maintenance phase-whether to use drugs beyond chemotherapy. This component has changed considerably in the last 5 years as it is now clear that there is great variety of biological behaviour in high-grade cancers, the commonest subtype. This

Clinical expert statement

	biology principally revolves around knowing whether the tumour has an impaired ability to repair double-strand breaks of DNA (HR deficiency, or HRD). Such tumours are susceptible to treatment with PARP inhibitors (PARPi) that exploit the presence of HRD in the tumour. The greatest degree of HRD is seen in tumours with a BRCA mutation, approximately 20-25% of all high-grade tumours, but also in a further 25% that have HRD without a BRCA mutation. Since the publication of clinical trials with PARPi in 2018 and 2019, and their subsequent licensing, there have been major improvements in progression-free survival in these subgroups of patients using PARPi. These drugs are also being used in tumours that do not exhibit HRD by current tests, but here the effect of PARPi is less marked. As a consequence of this, the ESMO guidelines (updated in 2023) and ESMO-ESGO-ESP consensus statements (2024) have categorised high-grade tumours into three groups; BRCA, HRD+/BRCA wild-type/ and non-HRD (also called HRP). Maintenance therapy options are recommended within each of the groups using either PARPi, alone, or combined with bevacizumab, or Bevacizumab alone. Thus, most patients are now recommended one of these three maintenance options.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	Currently, niraparib is used within the NHS Cancer drugs fund and is available, according to the result of the pivotal phase III (PRIMA) trial and its licence for any patient with high grade ovarian cancer in response, or without evidence of progression after front line chemotherapy/surgery. The testing of patients for a BRCA mutation both germline and tumour as well as tumour testing for HRD has become part of routine practice, as recommended in the guidelines above. Thus, the option to continue to have access to the technology will not change current practice. All patients with ovarian cancer are treated within a network of specialised centres by physicians familiar with this sub-specialty of oncology. The use of the technology is already established within all centres, and in addition there is access to home blood testing and blood pressure monitoring,

Clinical expert statement

	currently funded by the company that is very popular with patients and treating doctors. It has led to a substantial reduction in travelling by patients, the implementation in many centres of telemedicine clinics reducing the size of clinics and the dispatch of drugs by mail.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? - Do you expect the technology to increase length of life more than current care? - Do you expect the technology to increase health-related quality of life more than current care?	The current use of PARPi has substantially increased progression-free survival. This was the primary endpoint for the trial. In an updated analysis there was a more than doubling of the progression free survival at 5 years (22% versus 12% in the total population and 35% versus 16% in the HRD positive group). High levels of cross over to PARPi at relapse in the control arm made it difficult to show an overall survival benefit. If this technology became unavailable progression-free survival with first line treatment would revert to pre-PARPi times. The best old results from studies in 2011 with bevacizumab did not measure PFS at 60 months but overall survival can be estimated from the GOG218 trial (not ICON7 which reflects UK practice) and is less than 25% at 60 months. Thus, PFS would be less. It should be noted that although there were no OS differences in the PRIMA trial the OS at 5 years was around 44% in the overall population and 56% in the HRD subgroup. Whilst the population in PRIMA only includes responding patients at the time of randomisation, overall survival in the VELIA trial with veliparib that included all patients from the time of diagnosis was around 50%. Veliparib is a PARPi that has not been taken forward for licensing. Thus, the inclusion of PARPi into clinical practice means that approximately twice as many patients will be alive at 5 years compared with previous trials that were performed in the pre-PARPi era. From the perspective of a patient an approximate 50% reduction in the risk of progression with twice as many patients progression-free at 5 years is clinical result that would be welcomed by all.

Clinical expert statement

Niraparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy (review of TA673) [ID6403]

	Such differences over this prolonged period were not measured in the QoL questions used in this trial that focussed more on experiences in treatment and control groups while on treatment.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Niraparib has the greatest effect in patients with BRCA mutations and those with HRD. It should be noted that measurement of HRD is based on a Genomic Instability score, determined largely through measurement of genomic scarring. Generally patients with BRCA mutations have higher HRD scores than those with BRCA- wild type tumours but there is overlap in both directions, so that some patients with BRCA-wild-type tumours may have a higher score than another patient with a BRCA mutation. About 50% patients have a score that has been defined as a negative 'cut-off' (for the Myriad MyChoice assay- the test performed in clinical trials, it represents the 95% CI around scores from BRCAmutated tumours). It is unfortunately that this scoring has been interpreted as a categorical variable positive and negative as there are patients either side of the cut-off whose outcome on PARPi may differ from the predicted HRD score. In trials of both niraparib and rucaparib the PFS was improved in the HRD negative (HRP) group and consequently rucaparib has already been approved in this HRD negative or unknown group in situations where bevacizumab is not appropriate (NICE TA1055). The results with niraparib are very similar to those of rucaparib.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	Healthcare professionals treating ovarian cancer all have experience in using niraparib according to its licensed indication and approval via the Cancer Drugs Fund.

Clinical expert statement

Niraparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy (review of TA673) [ID6403]

16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	The use of niraparib will be largely confined to patients with a BRCA mutation or BRCA-Wild type HRD positive who do not require bevacizumab or for whom bevacizumab is not appropriate. As with rucaparib (TA1055) there is a place for maintenance therapy with PARPi in some patients in the HRD negative/unknown group. For those that do need bevacizumab, the combination of olaparib and bevacizumab can be used (PAOLA-1 trial). The use of bevacizumab is mainly based on the patient's risk of relapse as defined by the subgroup analysis of ICON7 and subsequent adoption by the Cancer Drugs Fund and latterly routine commissioning.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	Yes, the quality-of-life measurements are focussed on comparing toxicities, measured in a different way to CTCAE measurements during the course of treatment (up to 36 months). It compares quality of life differences between placebo and active drug. The key measurement in this trial (primary endpoint) is Progression-free survival. The trial including a group of patients that were at high risk of progression/relapse and the primary PFS analysis and recent re-analysis after 5 years follow up has shown substantial clinically meaningful differences between the two groups. As stated in section 13 we are now recording 5-year survival outcomes in patients offered PARPi far greater than was seen in the pre-PARP era.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? Is the technology a 'step-change' in the management of the condition?	See comment above. Differences in 5-year PFS rates and actual PFS at 5 years in the niraparib group are values that have not been observed in a population of patients with high risk of recurrence

Clinical expert statement

Niraparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy (review of TA673) [ID6403]

Does the use of the technology address any particular unmet need of the patient population?	
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The main side effects are haematological with thrombocytopenia and neutropenia often occurring in the first two cycles of treatment. Clinicians are aware of this and the need to monitor more closely during this time. For the majority of patients toxicity is manageable with occasional drug holidays in some or dose reductions. Cessation of treatment due to adverse events occurred in about 12 % of patients. Severe toxicity with Acute Myeloid Leukaemia or Myelodysplastic syndrome occurred in 2.3% patients in the treatment arm and 1.6% in the control arm.
20. Do the clinical trials on the technology reflect current UK clinical practice? - If not, how could the results be extrapolated to the UK setting? - What, in your view, are the most important outcomes, and were they measured in the trials? - If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? - Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Niraparib is currently used in the UK according to the clinical trials and licensed indications. The adoption of niraparib into standard practice will allow the continuation of this therapy. Extension of progression-free survival and overall survival data for both arms that exceed previous studies in advanced ovarian cancer in the pre-PARPi era. Surrogate outcome measures were not used in this study No new adverse effects are apparent. The use of this drug has enabled healthcare staff to be better able to manage the side effects due to their familiarity with the drug
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	The only evidence to add to the formal evaluations of this drug is to consider the outcome of patients in the prePARPi and PARPi eras. Surgery and chemotherapy use are similar and even with the use of bevacizumab the overall survival of patients recruited to the PRIMA study is better than that seen with historic trials

Clinical expert statement

Niraparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy (review of TA673) [ID6403]

22. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA673?	The overall survival data are now published and a further PFS analysis has been performed with 5 years of follow up
23. How do data on real-world experience compare with the trial data?	I have not seen large-scale real-world data with long-term follow up in this group of patients
24. NICE considers whether there are any equality issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why.	None

Clinical expert statement

Niraparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy (review of TA673) [ID6403]

More information on how NICE deals with equalities issues can be found in the [NICE equality scheme](#).

[Find more general information about the Equality Act and equalities issues here.](#)

Clinical expert statement

Niraparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy (review of TA673) [ID6403]

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Maintenance treatment with niraparib significantly extends progression-free survival in a high-risk group of patients with advanced ovarian cancer.
- The beneficial effects are greatest in patients who have a tumour with a BRCA mutation but are also substantial in HRD positive BRCA- wild-type tumours.
- The benefit in HRD negative (HRP) tumours is modest and short-lived but can improve PFS particularly if bevacizumab is not appropriate.
- The survival results at 5 years in the pivotal PRIMA trial are higher than has been seen in trials in the pre-PARPi era and the inclusion of niraparib maintenance represents a new and highly positive outcome result for patients with advanced ovarian cancer.
- The side effects of this oral drug are manageable with few patients needing to cease treatment due to adverse effects,

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our [privacy notice](#).

Clinical expert statement

Niraparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy (review of TA673) [ID6403]

Single Technology Appraisal

Ovarian cancer (advanced)- Niraparib (maintenance, after platinum chemotherapy) (review of TA673) Appraisal [ID6403]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In [part 1](#) we are asking you about living with Ovarian Cancer or caring for a patient with Ovarian cancer The text boxes will expand as you type.

In [part 2](#) we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Patient expert statement

Ovarian cancer (advanced)- Niraparib (maintenance, after platinum chemotherapy) (review of TA673) Appraisal [ID6403]

Please use this questionnaire with our [hints and tips for patient experts](#). You can also refer to the [Patient Organisation submission guide](#). **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

Thank you for your time.

We reserve the right to summarise and edit comments, 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 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.

Patient expert statement

Ovarian cancer (advanced)- Niraparib (maintenance, after platinum chemotherapy) (review of TA673) Appraisal [ID6403]

Part 1: Living with this condition or caring for a patient with Ovarian Cancer

Table 1 About you, Ovarian cancer, current treatments and equality

1. Your name	Gillian Nunn
2. Are you (please tick all that apply)	☒ A patient with advanced ovarian cancer ☒ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with Ovarian Cancer ? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Ovarian Cancer Action
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and do not wish to complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and do not wish to complete this statement ☒ I agree with it and will be completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement after attending the expert

Patient expert statement

Ovarian cancer (advanced)- Niraparib (maintenance, after platinum chemotherapy) (review of TA673) Appraisal [ID6403]

	engagement teleconference ☐ I have completed part 2 of the statement but was not able to attend the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with ovarian cancer If you are a carer (for someone with Ovarian Cancer) please share your experience of caring for them	I have lived with this condition for ten years. I was diagnosed Figo stage 4 High Serous OC in October 2015. I recurred in January 2018.I have had 2 cycles of chemotherapy and 2 radical debulking surgeries. Following my first chemo cycle I was on Avastin for 18 cycles. Since September 2018, I have been taking Niraparib. It took 4 months to get the dosage correct – moving from 300 mg to 100mg after platelets drop and 2 transfusions Initially I was told I did not carry the BRCA gene. However, genetic profiling confirmed that I am BRCA 1 positive. Both of my children inherited this mutation; my daughter developed breast cancer at the age of 36 with high risk of developing ovarian cancer. My experience of living with this condition has changed over the years. Physically I coped better than expected with surgeries and chemotherapies, but of course there were times I felt very unwell. The knowledge that I had what is considered “a silent killer”, and an incurable disease, weighed heavily on my mental health, particularly when Avastin did not prevent recurrence. I had some

Patient expert statement

Ovarian cancer (advanced)- Niraparib (maintenance, after platinum chemotherapy) (review of TA673) Appraisal [ID6403]

	counselling, which helped me come to terms with both diagnoses, and the management of negative thoughts of recurrence. Since being on Niraparib, knowing its potential to help resist recurrence has eased my anxiety and that of my family significantly. In terms of side effects from Niraparib, I suffer with constipation, mouth ulcers and an itchy skull in sunshine. I have bi-monthly bloods to assess overall blood count and CA125 levels. I'm always on tenterhooks awaiting my CA125 level. I have an annual CT scan and have 'scanxiety' when awaiting results. One element that never goes away is that you may have a positive scan showing recurrence.
7a. What do you think of the current treatments and care available for ovarian cancer on the NHS? 7b. How do your views on these current treatments compare to those of other people that you may be aware of?	I have no personal experience of current treatments (except Niraparib) and care, it being 7 years since the recurrence, but I garner some information from current Facebook Groups (Ovarian Cancer Community and PARP Inhibitors – Drugs and Trials) and news/www. It seems to me that nothing in the past ten years, except for the availability of Niraparib for on the NHS for specific patients like me. This was a significant step forward. Patients find the current regimes both toxic, frightening, and invasive.
8. If there are disadvantages for patients of current NHS treatments for ovarian cancer (for example, how they are given or taken, side effects of treatment, and any others) please describe these	I know that OC patients continue to have many physical issues with the toxicity of chemotherapy and maintenance therapy. Many are unable to, or choose not to, continue Maintenance therapy because of this.

Patient expert statement

Ovarian cancer (advanced)- Niraparib (maintenance, after platinum chemotherapy) (review of TA673) Appraisal [ID6403]

9a. If there are advantages of Niraparib over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? 9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? 9c. Does Niraparib to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these	a) Yes. I believe that at least having the opportunity to try a proven maintenance drug after first line chemo has the potential to minimise the worry of recurrence for many people and could improve their mental health and longevity. b) Being able to take an oral drug at home is a huge advantage over having intravenous Avastin. I believe the availability of Niraparib to a wider patient base would give people more hope of survival and minimise thoughts of recurrence. C) Yes -If Avastin is given, this is intravenously back at the chemo unit which can influence morale, and a sense of not moving forward.
10. If there are disadvantages of Niraparib over current treatments on the NHS please describe these. For example, are there any risks with Niraparib? If you are concerned about any potential side effects you have heard about, please describe them and explain why	I don't think that there are disadvantages per se to Niraparib over current treatments/strategies, but I am aware that for some the side effects are too extensive to continue, but there are risk factors (developing bone marrow disease), albeit rare. Is it possible that taking it for a long period of time is more likely to lead to bone marrow problems? Side effects I have heard most about most are fatigue, racing heartbeat, dizziness, cough, mouth ulcers. All have the capacity to impact on wellbeing but can be managed. .

Patient expert statement

Ovarian cancer (advanced)- Niraparib (maintenance, after platinum chemotherapy) (review of TA673) Appraisal [ID6403]

11. Are there any groups of patients who might benefit more from Niraparib or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	I am not aware of any specific groups of people who might benefit less, although a poor level of general fitness could exclude some people e.g. older and more frail patients.
12. Are there any potential equality issues that should be taken into account when considering ovarian cancer and Niraparib? Please explain if you think any groups of people with this condition are particularly disadvantaged Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	I am aware that some socioeconomic groups, Black women and ethnic minorities are considered to be at a disadvantage from receiving timely interventions and treatments. I understand that geographical location is a bit of a lottery and has an impact too. Possibly interaction with other prescribed drugs may be an issue.
13. Are there any other issues that you would like the committee to consider?	The toxicity side of Niraparib and it's side effects and risks are apparent, but the opportunity to take it should be given, as I believe the benefit to mental health is highly significant through reduction in anxiety of recurrence.

Patient expert statement

Ovarian cancer (advanced)- Niraparib (maintenance, after platinum chemotherapy) (review of TA673) Appraisal [ID6403]

	I understand 100mg is the correct efficacy for me/my body. I think it's important that patients understand that being on a lower dose of Niraparib does not mean the drug won't work as well.

Patient expert statement

Ovarian cancer (advanced)- Niraparib (maintenance, after platinum chemotherapy) (review of TA673) Appraisal [ID6403]

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Niraparib is effective for me – I consider it an ‘elixir of life’
- Taking Niraparib gives patients some peace of mind regarding fear of recurrence
- Niraparib does have side effects, but most are manageable
- Niraparib has a small risk of developing bone marrow disease
- Oral medication is preferable to intravenous drugs

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see [NICE's privacy notice](#).

Patient expert statement

Ovarian cancer (advanced)- Niraparib (maintenance, after platinum chemotherapy) (review of TA673) Appraisal [ID6403]

Single Technology Appraisal

Niraparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy (review of TA673) [ID6403]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In [part 1](#) we are asking you about living with advanced ovarian, fallopian tube and peritoneal cancer or caring for a patient with advanced ovarian, fallopian tube and peritoneal cancer. The text boxes will expand as you type.

In [part 2](#) we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Patient expert statement

Niraparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy (review of TA673) [ID6403]

Please use this questionnaire with our [hints and tips for patient experts](#). You can also refer to the [Patient Organisation submission guide](#). **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

Thank you for your time.

We reserve the right to summarise and edit comments, 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 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.

Patient expert statement

Niraparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy (review of TA673) [ID6403]

Part 1: Living with this condition or caring for a patient with advanced ovarian, fallopian tube and peritoneal cancer

Table 1 About you, advanced ovarian, fallopian tube and peritoneal cancer, current treatments and equality

1. Your name	Rachel Downing
2. Are you (please tick all that apply)	☐ A patient with advanced ovarian, fallopian tube and peritoneal cancer? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with advanced ovarian, fallopian tube and peritoneal cancer ? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Target Ovarian Cancer
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☒ I agree with it and do not wish to complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and do not wish to complete this statement ☐ I agree with it and will be completing
5. How did you gather the information included in your statement? (please tick all that apply)	☐ I am drawing from personal experience

Patient expert statement

	☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement after attending the expert engagement teleconference ☐ I have completed part 2 of the statement but was not able to attend the expert engagement teleconference ☒ I have not completed part 2 of the statement
6. What is your experience of living with advanced ovarian, fallopian tube and peritoneal cancer ? If you are a carer (for someone with advanced ovarian, fallopian tube and peritoneal cancer) please share your experience of caring for them	
7a. What do you think of the current treatments and care available for advanced ovarian, fallopian tube and peritoneal cancer on the NHS? 7b. How do your views on these current treatments compare to those of other people that you may be aware of?	
8. If there are disadvantages for patients of current NHS treatments for advanced ovarian, fallopian tube and peritoneal cancer (for example, how they are given or taken, side effects of treatment, and any others) please describe these	
9a. If there are advantages of Niraparib over current treatments on the NHS please describe these. For example, the effect on your quality of life,	

Patient expert statement

your ability to continue work, education, self-care, and care for others? 9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? 9c. Does Niraparib help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these	
10. If there are disadvantages of Niraparib over current treatments on the NHS please describe these. For example, are there any risks with Niraparib ? If you are concerned about any potential side effects you have heard about, please describe them and explain why	
11. Are there any groups of patients who might benefit more from Niraparib or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	
12. Are there any potential equality issues that should be taken into account when considering advanced ovarian, fallopian tube and peritoneal cancer and Niraparib ? Please explain if you think any groups of people with this condition are particularly disadvantage	

Patient expert statement

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	

Patient expert statement

Niraparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy (review of TA673) [ID6403]

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see [NICE's privacy notice](#).

Patient expert statement

Niraparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy (review of TA673) [ID6403]

Niraparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy (review of TA673) [ID6403]

STA Report

Source of funding

This report was commissioned by the NIHR Evidence Synthesis Programme as project number NIHR176617.

Title:	Niraparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy (review of TA673) [ID6403]
Produced by:	BMJ Technology Assessment Group (BMJ-TAG)
Authors:	Steve Edwards, Director of Health Technology Assessment, BMJ-TAG, London Ben Burgess, Senior Clinical Evidence Analyst, BMJ-TAG, London Kate Ennis, Senior Health Economist, BMJ-TAG, London Victoria Wakefield, Principal Clinical Evidence Analyst, BMJ-TAG, London Archie Walters, Senior Health Economist, BMJ-TAG, London
Correspondence to:	Steve Edwards, BMJ-TAG, BMJ Group, 5th Floor, 90 Whitfield Street, London W1T 4EZ, UK.
Date completed:	23 September 2025
Source of funding:	This report was commissioned by the NIHR Evidence Synthesis Programme as project number NIHR176617.
Declared competing interests of the authors	No competing interests were declared which affect the impartiality of this report. BMJ Technology Assessment Group (BMJ-TAG) and the editorial team of The BMJ work independently to one another. The views and opinions expressed in this report are those of the BMJ-TAG.
Acknowledgments:	The EAG would like to thank Dr Sundar Santhanam, Consultant Oncologist, Nottingham University Hospital NHS Trust, Nottingham; Professor Sean Kehoe, Professor of Gynaecological Cancer, Churchill Hospital, Oxford; and Dr Kalliopi Michoglou, Medical Oncologist, Cambridge University Hospitals NHS Foundation Trust, Cambridge for providing clinical advice throughout the project, and for providing feedback on the clinical sections of the report.
Rider on responsibility for report:	The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.
Report reference:	Steve Edwards, Ben Burgess, Kate Ennis, Victoria Wakefield, Archie Walters. Niraparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy (review of TA673): A Single Technology Appraisal. BMJ Technology Assessment Group, 2025.

Copyright is retained by GSK for Figures 1-11, 14-15, 17, and 20-24; and content reproduced in Tables 24, 57-60, 62, 64-65, 67-70, and 73-74.

Contribution of authors:

Steve Edwards	Critical appraisal of the company's submission; validated the statistical analyses; provided feedback on all versions of the report. Guarantor of the report
Benjamin Burgess	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; cross checking of company's search strategies; and drafted the summary, background and clinical results sections
Victoria Wakefield	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; cross checking of company's search strategies; and assisted with drafting the clinical results sections
Kate Ennis	Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections
Archie Walters	Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections

All authors read and commented on draft versions of the EAG report.

Table of Contents

Table of Contents.....	4
List of Tables	8
List of Figures	14
List of Abbreviations	16
1 Executive summary	19
1.1 Overview of the EAG's key issues.....	19
1.2 Overview of key model outcomes.....	20
1.3 EAG's key issues.....	21
1.4 Secondary issues identified by the EAG	28
1.5 Company's modelling errors identified by the EAG	28
1.6 Summary of EAG's preferred assumptions and resulting ICER	29
1.7 Outline of confidential comparator or subsequent treatment prices.....	33
2 Background	34
2.1 Introduction.....	34
2.2 Background.....	34
2.3 Critique of the company's definition of the decision problem	36
2.3.1 Population	44
2.3.2 Intervention.....	46
2.3.3 Comparators.....	46
2.3.4 Outcomes	48
2.3.5 Subgroups.....	49

3	Clinical effectiveness.....	51
3.1	Critique of the methods review.....	51
3.2	Critique of trials of the technology of interest.....	54
3.2.1	PRIMA trial	55
3.2.2	PRIME trial.....	60
3.3	Critique of the clinical effectiveness analysis and interpretation	66
3.3.1	Primary outcome.....	66
3.3.2	Secondary outcomes.....	72
3.3.3	Safety.....	76
3.3.4	Health-related quality of life	78
3.4	Critique of indirect treatment comparisons.....	78
3.4.1	Trials informing the indirect treatment comparison	78
3.4.2	Statistical methods and performed indirect treatment comparisons	87
3.4.3	Indirect treatment comparison results: niraparib and olaparib	93
3.4.4	Indirect treatment comparison results: niraparib and rucaparib	96
3.4.5	Indirect treatment comparison results: assumptions of equivalence	102
3.5	Conclusions of the clinical effectiveness section.....	106
3.5.1	Summary of EAG's core findings	110
4	Cost effectiveness	114
4.1	Critique of the review of cost effectiveness evidence	115
4.2	Critique of the submitted economic evaluation.....	116
4.2.1	NICE reference case checklist	116

4.2.2	Population	117
4.2.3	Modelling approach and model structure	119
4.2.4	Treatment effectiveness	122
4.2.5	Treatment discontinuation	147
4.2.6	Adverse Events	152
4.2.7	Health-related quality of life	153
4.2.8	Resource use and costs	155
5	Cost effectiveness results	163
5.1.1	BRCam subgroup.....	163
5.1.2	BRCawt subgroup.....	165
5.1.3	Company's sensitivity analyses	167
5.2	EAG additional analyses	170
5.2.1	Model validation and face validity check.....	170
5.2.2	EAG's exploratory analyses using the company's base case.....	171
5.2.3	EAG preferred assumptions	175
5.2.4	Scenario analyses using EAG's preferred assumptions.....	180
5.3	Decision Modifiers.....	185
5.3.1	QALY weighting for severity	185
5.3.2	Uncaptured benefits	185
5.3.3	Health inequalities	185
5.4	Confidential comparator and subsequent treatment prices.....	186
5.5	Conclusions of the cost effectiveness sections	186

6	References	189
7	Appendices.....	193
7.1	Price sources for treatments included in the confidential appendix	193

List of Tables

Table 1. Summary of key issues	19
Table 2. Issue 1: Positioning of niraparib	21
Table 3. Issue 2: Consideration of HRD status	22
Table 4. Issue 3: Indirect treatment comparisons performed using disparate trials	23
Table 5. Issue 4: Insufficient evidence for assumptions of clinical equivalence.....	24
Table 6. 4a: Data to inform treatment comparisons in the model for the BRCAm population	25
Table 7. Issue 4b: Data to inform treatment comparisons in the model for the BRCAwt population (HRd/BRCAwt and HRp/BRCAwt).....	26
Table 8. Issue 5: Time to treatment discontinuation and implementation of stopping rules.....	27
Table 9. Summary of the EAG's preferred assumptions and resulting ICER in the BRCAm population, deterministic	29
Table 10. EAG base case results for BRCAm population.....	30
Table 11. Summary of the EAG's preferred assumptions and resulting ICER in the BRCAwt population, deterministic	31
Table 12. EAG base case results, BRCAwt with HRd/BRCAwt HR for overall survival applied	32
Table 13. EAG base case results , BRCAwt with HRp/BRCAwt HR for overall survival applied.....	32
Table 14. Summary of decision problem	37
Table 15. Summary of EAG's critique of the methods implemented by the company to identify evidence relevant this appraisal	52
Table 16. Trials identified through the systematic literature review.	54
Table 17. EAG's summary of the design, conduct and analysis of the PRIMA trial.	58
Table 18. EAG's summary of the design, conduct and analysis of the PRIME trial.....	63

Table 19. Hazard ratios reported for investigator-assessed progression-free survival from the PRIMA and PRIME trials.....	67
Table 20. Hazard ratios reported for blinded independent central review progression-free survival from the PRIMA and PRIME trials.	70
Table 21. Hazard ratios reported for overall survival from the PRIMA and PRIME trials.	72
Table 22. Hazard ratios reported for progression-free survival on the second line of therapy from the PRIMA and PRIME trials.	75
Table 23. Hazard ratios reported for time to first subsequent treatment from the PRIMA and PRIME trials.	75
Table 24. Grade 3+ adverse event incidence (reproduced from Table 42 of company's submission). 77	
Table 25. Baseline characteristics BRCam population from the PRIMA trial and the high-risk BRCam population from the SOLO-1 trial.	79
Table 26. Baseline characteristics for the PRIME and ATHENA-MONO trials for the ITT population. .	81
Table 27. Baseline characteristics for the PRIMA and ATHENA-MONO trials for the ITT populations.	85
Table 28. Bucher analyses performed by the company and provided in the company's submission..	87
Table 29. Bucher analyses requested by the EAG at the clarification stage.....	88
Table 30. Bucher analyses performed by the EAG and company comparing niraparib to rucaparib. .	90
Table 31. Bucher analyses performed by the EAG and company comparing niraparib to olaparib. ...	90
Table 32. Results of Bucher analyses for investigator-assessed progression-free survival and blind independent central review progression-free survival performed by the company and the EAG for the comparison of rucaparib to placebo.	92
Table 33. Results of Bucher analyses for investigator assessed progression free survival performed by the company and the EAG for the comparison of niraparib to olaparib.	93
Table 34. Results of Bucher analyses for overall survival performed by the company and the EAG for the comparison of niraparib to olaparib.....	94

Table 35. Results of Bucher analyses for second progression free survival performed by the company and the EAG for the comparison of niraparib to olaparib.	95
Table 36. Results of Bucher analyses for time to first subsequent treatment performed by the company and the EAG for the comparison of niraparib to olaparib.	95
Table 37. Results of Bucher analyses for investigator-assessed progression-free survival and blind independent central review progression-free survival performed by the company and the EAG for the comparison of niraparib to rucaparib.....	97
Table 38. Results of Bucher analyses for overall survival performed by the company and the EAG for the comparison of niraparib to rucaparib.....	99
Table 39. Results of Bucher analyses for second progression free survival performed by the company and the EAG for the comparison of niraparib to rucaparib.	99
Table 40. Results of Bucher analyses for time to first subsequent treatment performed by the company and the EAG for the comparison of niraparib to rucaparib.	101
Table 41. Results of non-inferiority analyses using the method of Kaul and Diamond (2007) for the ITCs performed by the company.....	103
Table 42. Results of non-inferiority analyses using the Monte-Carlo simulations for the ITCs performed by the company.	105
Table 43. EAG-derived hazard ratios from Bucher ITCs that are used within the economic model (a $HR < 1$ favours niraparib, and a $HR > 1$ favours the comparator).	109
Table 44. Company's base case results for the BRCAm population	114
Table 45. Company's base case results for the BRCAwt population	115
Table 46. Summary of the company's economic systematic literature review.....	116
Table 47. NICE reference case checklist.....	117
Table 48. Baseline characteristic informing the company model.....	118
Table 49. Median age of patients in PRIMA versus SACT data for niraparib.....	119

Table 50. Overview of company's survival curve selection by outcome and population.....	124
Table 51. EAG-derived hazard ratios from Bucher ITCs, as described in Section 3 of EAG report (a HR<1 favours niraparib, and a HR>1 favours the comparator)	126
Table 52. Estimates of overall survival for the BRCAm population, applying EAG derived HRs for both PFS and OS	135
Table 53. Landmark estimate of PFS in the BRCAwt population from key clinical trials compared to model predicted PFS	140
Table 54. Median PFS for BRCAwt population from key trials compared to model-predicted.....	140
Table 55. EAG derived hazard ratios for OS for the comparison of niraparib to rucaparib, BRCAwt population.....	143
Table 56. Estimates of overall survival for the BRCAwt population, applying EAG-derived HRs for the HRd/BRCAwt and HRp/BRCAwt populations	146
Table 57. Grade 3+ AE incidence included in the model (reproduced from Table 42 in the CS)	152
Table 58. Health state utility values (reproduced from Table 45 in the CS).....	154
Table 59. Adverse event disutilities (reproduced from Table 43 in the CS)	154
Table 60. One-off adverse event disutility (reproduced from Table 44 in the CS)	155
Table 61. Dosing distribution at baseline and relative dose intensities	156
Table 62. Acquisition costs per model cycle (reproduced from Table 49 in the CS)	157
Table 63. Drug administration costs used in company base model	158
Table 64. Health state resource use and frequencies (reproduced from Table 50 in the CS).....	159
Table 65. Health care resource use per health state per cycle (reproduced from Table 52 in the CS)	159
Table 66. AE unit and treatment costs.....	159

Table 67. Distribution of subsequent treatments applied in the economic model – base case (PRIMA) (reproduced from Table 55 in the CS).....	160
Table 68. Summary of subsequent treatment costs (reproduced from Table 58)	161
Table 69. Terminal care costs (reproduced from Table 59 in the CS).....	161
Table 70. Updated subsequent treatment costs (reproduced from Table 13 in the company's response to clarification questions).....	163
Table 71. Company's base case results (post clarification) – BRCAm subgroup	164
Table 72. Company's base case results (post clarification) – BRCAwt subgroup	166
Table 73. Company scenario analysis – niraparib versus olaparib (BRCAm subgroup) (extracted from Table 22 of the company's clarification response)	169
Table 74. Company scenario analysis – niraparib versus rucaparib (BRCAwt subgroup) (extracted from Table 23 of the company's clarification response)	169
Table 75. Summary of EAG's exploratory analyses using company's base case	172
Table 76. Results of EAG's exploratory analyses using the company's base case, BRCAm population (deterministic).....	174
Table 77. Results of EAG's exploratory analyses using the company's base case, BRCAwt population (deterministic).....	174
Table 78. Results using the EAG's preferred model assumptions in the BRCAm population, deterministic	176
Table 79. EAG base case results for BRCAm population.....	177
Table 80. Results using the EAG's preferred model assumptions, BRCAwt population.....	178
Table 81. EAG base case results, BRCAwt with HRd/BRCAwt HR for overall survival applied	179
Table 82. EAG base case results, BRCAwt with HRp/BRCAwt HR for overall survival applied	179
Table 83. Summary of EAG's scenario analyses using the EAG preferred assumptions.....	180

Table 84. Results of EAG’s exploratory analyses using EAG’s preferred assumptions, BRCAm population (deterministic only)	182
Table 85. Results of EAG’s exploratory analyses using EAG’s preferred assumptions, BRCAw population (deterministic only)	184
Table 86. Source of the confidential prices used in the confidential appendix.....	193

List of Figures

Figure 1. Proposed positioning of niraparib within UK clinical practice (reproduced from Figure 5 of the CS).....	36
Figure 2. Trial design for the PRIMA trial (reproduced from Figure 7 of the CS).....	56
Figure 3. Trial design for the PRIME trial (reproduced from Figure 15 of the CS).....	62
Figure 4. Forest plot of investigator-assessed progression-free survival by subgroup, using data from the final analysis of the PRIMA trial with a cut-off 8 April 2024 (reproduced from Figure 14 of CS)...	69
Figure 5. Forest plot of blinded independent central review progression-free survival, from the PRIME trial, by subgroup (reproduced from Figure 19 of CS).	72
Figure 6. Forest plot of overall survival by subgroup, using data from the final analysis of the PRIMA trial with a cut-off 8 April 2024 (reproduced from Figure 50 of CS).....	74
Figure 7. Company model, reproduced from Figure 28 in CS).....	120
Figure 8. Progression-free survival in company's base case for the BRCam population (generalised gamma, long-term remission assumption), produced from the company's model.....	128
Figure 9. Progression-free survival in company's base case for the BRCam population (generalised gamma, no long-term remission assumption), produced from the company's model.....	128
Figure 10. Progression-free survival using EAG preferred analysis for the BRCam population (generalised gamma, long-term remission assumption applied)	130
Figure 11. Overall survival in company's base case for the BRCam population (one-knot normal spline), including base-case PFS extrapolation constraint. Produced from the company's model....	131
Figure 12. Comparison of overall survival data from SACT for BRCam patients: niraparib versus olaparib	133
Figure 13. Overall survival using EAG preferred analysis for the BRCam population (HRs applied to estimate olaparib PFS and OS).....	135
Figure 14. Progression-free survival in the company's base case for the BRCAwt population (generalised gamma, long-term remission assumption), produced from the company's model	137

Figure 15. Progression-free survival in company's base case for the BRCAwt population (generalised gamma, no long-term remission assumption), produced from the company's model.....	137
Figure 16. Progression-free survival based on EAG analysis of BRCAwt population (generalised gamma, long-term remission assumption applied) with HR applied to estimate rucaparib.....	139
Figure 17. Overall survival in company's base case for the BRCAwt population (one-knot hazard spline), including base-case PFS extrapolation constraint. Produced from the company's model....	142
Figure 18. Overall survival for niraparib and rucaparib, applying EAG derived HR for HRd/BRCAwt population to baseline niraparib BRCAwt (all) curve.....	144
Figure 19. Overall survival for niraparib and rucaparib, applying EAG derived HR for HRp/BRCAwt population to baseline niraparib BRCAwt (all) curve.....	145
Figure 20. Time to treatment discontinuation used in the company base for niraparib and olaparib, BRCAM population. Reproduced from Figure 34 of the CS	148
Figure 21. Time to treatment discontinuation used in the company base for niraparib and niraparib, BRCAwt population. Reproduced from Figure 35 of the CS	149
Figure 22. Time to treatment discontinuation from SACT data for niraparib and olaparib, BRCAM population. Produced from the company's economic model	151
Figure 23. Scatterplot of PSA estimates on a cost-effectiveness plane, niraparib versus olaparib - BRCAM subgroup (Figure 20 of the company's clarification response document)	165
Figure 24. Scatterplot of PSA estimates on a cost-effectiveness plane, niraparib versus rucaparib - BRCAwt subgroup (Figure 21 of the company's clarification response document)	167
Figure 25. Tornado plot using net monetary benefit – niraparib versus olaparib (BRCAM subgroup)	168
Figure 26. Tornado plot using net monetary benefit – niraparib versus rucaparib (BRCAwt subgroup)	168

List of Abbreviations

1L	First line
2L	Second line
3L+	Third line or later
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BRCAm	Breast cancer gene mutation
BRCAwt	Breast cancer gene wild type
BSA	Body surface area
CA-125	Cancer antigen 125
CDF	Cancer Drugs Fund
CI	Confidence interval
CR	Complete response
CRF	Case report form
CS	Company submission
CT	Computed tomography
EAG	External Assessment Group
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EED	Economic Evaluation Database
eMIT	Electronic market information tool
EORTC-QLQ-C30	European Organisation for the Research and Treatment of Cancer 30-item core quality of life questionnaire
EORTC-QLQ-OV28	European Organisation for the Research and Treatment of Cancer 28-item quality of life questionnaire for ovarian cancer
EQ-5D-3L	European Quality of Life 5 Dimensions 3 Level Version
EQ-5D-5L	European Quality of Life 5 Dimensions 5 Level Version
FIGO	International Federation of Gynaecology and Obstetrics
FOSI	Functional Assessment of Cancer Therapy-Ovarian Symptom Index
fpNMA	Fractional polynomial network meta-analysis
HR	Hazard ratio
HRD	Homologous recombination deficiency
HRd	Homologous recombination deficient
HRnd	Homologous recombination not defined
HRQoL	Health-related quality of life
HRp	Homologous recombination proficient
HTA	Health Technology Assessment
ICER	Incremental Cost Effectiveness Ratio
ICS	Interval cytoreductive surgery

IDS	Interval debulking surgery
IPD	Individual patient data
ITT	Intent to treat
KM	Kaplan-Meier
LOH	Loss of heterozygosity
LY	Life year
MAIC	Matching adjusted indirect comparison
MHRA	Medicines and Healthcare products Regulatory Agency
ML-NMR	Multi-level network meta-regression
NA	Not applicable
NACT	Neoadjuvant chemotherapy
NHB	Net health benefit
NHS	National Health Service
NMB	Net monetary benefit
NICE	National Institute for Health and Care Excellence
NR	Not reported
OS	Overall survival
PAS	Patient access scheme
PARPi	Poly(ADP-ribose) polymerase inhibitor
PBC	Platinum-based chemotherapy
PCS	Primary cytoreductive surgery
PDS	Primary debulking surgery
PFS	Progression-free survival
PFS2	Progression-free survival on the second line of therapy
PFS-BICR	Blinded independent central review-assessed progression-free survival
PFS-INV	Investigator-assessed progression-free survival
PLD	Pegylated liposomal doxorubicin
PR	Partial response
PS	Performance status
PSSRU	Personal Social Services Research Unit
QALY	Quality-Adjusted Life Year
QIC	Quasi-information criteria
RCT	Randomised controlled trial
RWE	Real world evidence
SACT	Systemic anti-cancer therapy
SE	Standard error
SLR	Systematic literature review
SmPC	Summary of product characteristics
STA	Single Technology Appraisal
STC	Simulated treatment comparison

SW	South-west
TA	Technology appraisal
TFST	Time to first subsequent treatment
TTD	Time to treatment discontinuation
UK	United Kingdom
ULN	Upper limit of normal
WTP	Willingness to pay

1 Executive summary

This summary provides a brief overview of the key issues identified by the external assessment group (EAG) as being potentially important for decision-making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Section 1.3 explains the key issues in more detail. Secondary issues and modelling errors identified by the EAG are explored in Sections 1.4 and 1.5. Background information on the condition, technology and evidence, and non-key issues are presented in later sections of the EAG report.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1 Overview of the EAG's key issues

Table 1. Summary of key issues

ID	Summary of issue	Impact on results	Report sections
1	Positioning of niraparib	Unknown	Section 2.3.3
2	Consideration of HRD status	Unknown	Section 4.2.7.4 to 4.2.7.10
3	Indirect treatment comparisons performed using disparate trials	Unknown	Section 3.4
4	Insufficient evidence for assumptions of clinical equivalence	Large	Section 3.4.5 and Section 4.2.4
4a	Data to inform treatment comparisons in the model (BRCAm population)	Large	Section 4.2.4
4b	Data to inform treatment comparisons in the model (BRCAwt, HRd/BRCAwt and HRp/BRCAwt populations)	Large	Section 4.2.4
5	Time to treatment discontinuation and implementation of stopping rules	Medium	Section 4.2.5

Abbreviations: BRCAm, Breast cancer gene mutation; BRCAwt, Breast cancer gene wild type; EAG, External Assessment Group; HRD, homologous recombination deficiency; HRd, homologous recombination deficient; HRp, homologous recombination proficient.

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are the use of Bucher ITC results to inform relative treatment effectiveness between niraparib and the included comparators, as opposed to assuming clinical equivalence between all treatments.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Differences in the safety profile compared to comparators. However, the EAG notes that any QALY differences between comparators are extremely minimal and should be interpreted with caution.

Overall, the technology is modelled to affect costs by:

- Lower drug acquisition costs compared to available comparators,
- Lower adverse event management costs.

The modelling assumptions that have the greatest effect on the ICER are:

- Assumed equivalence in progression-free survival between all included PARPi treatments,
- Assumed equivalence in overall survival between all included PARPi treatments,
- Inclusion of a stopping rule for treatment discontinuation of niraparib,
- Data source used to inform adverse events.

1.3 EAG's key issues

Table 2. Issue 1: Positioning of niraparib

Report section	Section 2.3.3
Description of issue and why the EAG has identified it as important	In response to a clarification question, the company confirmed that a recommendation is sought in patients who are not eligible for a first-line therapy of a platinum-based chemotherapy with bevacizumab. When considering the UK treatment pathway, the company does not consider bevacizumab monotherapy or olaparib with bevacizumab to be relevant comparators.
What alternative approach has the EAG suggested?	The company chose to submit evidence for a population that is narrower than niraparib MHRA authorisation. Accordingly, the EAG suggests that the population definition (i.e. limiting niraparib to only to patients for whom bevacizumab is not an option) needs to be highlighted (consistent with the published guidance for TA1055 ¹).
What is the expected effect on the cost-effectiveness estimates?	None (unless committee considers bevacizumab, and bevacizumab plus olaparib, should be comparators).
What additional evidence or analyses might help to resolve this key issue?	No additional evidence or analyses are required, unless a recommendation is sought in patients who are eligible for bevacizumab.

Abbreviations: EAG, External Assessment Group; NICE, National Institute for Health and Care Excellence.

Table 3. Issue 2: Consideration of HRD status

Report section	Section 2.3.1, Section 4.2.2, Section 4.2.4
Description of issue and why the EAG has identified it as important	The key trial for rucaparib of ATHENA-MONO ² stratified patients by a combination of HRD and BRCA classifications (i.e., BRCAm, HRd/BRCAwt, HRp/BRCAwt and HRD unknown/BRCAwt), with outcome data available for these subgroups. In the recent appraisal for rucaparib (TA1055 ¹), comparisons for the BRCAwt population were presented based on HRD classification. In addition, the PRIMA ³ trial was stratified for HRD status and not BRCA status. Accordingly, any subgroup analyses of BRCA status would result in trial randomisation being broken. Therefore, the EAG considers that the most appropriate comparison with rucaparib in the current appraisal for the BRCAwt population, and therefore the EAG preference, would be to separately compare the HRD/BRCAwt and HRp/BRCAwt populations, as this is the most robust use of the data from both ATHENA-MONO ² and PRIMA. As this was not provided by the company during clarification, the EAG did not have all of the outcomes from the PRIMA trial for each subgroup to implement this in the economic model.
What alternative approach has the EAG suggested?	In order to provide a meaningful analysis for committee, the EAG has maintained the company's approach of using the BRCAwt population as a whole (and not split by HRD classification). The EAG was able to construct an overall BRCAwt population from ATHENA-MONO ² data to allow an ITC against PRIMA ³ for PFS. However, the equivalent data were not available for overall survival. Therefore, the EAG has instead applied separate HRs for OS in the HRd/BRCAwt and HRp/BRCAwt populations in order to provide a range for the ICER that would be expected for the combined BRCAwt population.
What is the expected effect on the cost-effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	The EAG considers that the most robust comparison of niraparib with rucaparib in the current appraisal for the BRCAwt population, and therefore the EAG preference, would use the same approach as that used in TA1055 ¹ ; i.e. compare ATHENA-MONO ² against the PRIMA ³ trial, with ITC and cost-effectiveness results presented separately for the HRD/BRCAwt and HRp/BRCAwt populations.
Abbreviations: BRCAm, Breast cancer gene mutation; BRCAwt, Breast cancer gene wild type; EAG, External Assessment Group; HRD, homologous recombination deficiency; HRd, homologous recombination deficient; HRp, homologous recombination proficient; ICER, Incremental Cost Effectiveness Ratio; ITC, indirect treatment comparison; PFS, progression-free survival; OS, overall survival.	

Table 4. Issue 3: Indirect treatment comparisons performed using disparate trials

Report section	Section 3.4
Description of issue and why the EAG has identified it as important	Within the CS, the company noted that they considered their presented indirect treatment comparisons (ITCs) to be 'fundamentally flawed' due to considerable differences in the baseline characteristics between the included trials. The EAG agrees with this assessment, noting that these limitations affect the ITCs presented by the company and those presented by the EAG. However, the EAG considers that the EAG's analyses using data from PRIMA ³ are more appropriate given the inherent limitations with the PRIME ⁴ trial that have been noted within the EAG's report for this appraisal and in previous appraisals (TA1055 ¹).
What alternative approach has the EAG suggested?	For comparisons of niraparib to rucaparib, the company performed ITCs using data from PRIME ⁴ , as the ATHENA-MONO ² trial did not report outcomes for high-risk patients, while the PRIMA ³ trial only comprised of high-risk patients. As such, the company deemed it inappropriate to compare data from the PRIMA ³ and ATHENA-MONO ² trials. In contrast, the EAG considers it preferable to compare use data from PRIMA ³ given issues with the PRIME ⁴ trial limiting its generalisability to the UK clinical population. Additionally, the EAG's clinical experts indicated that high-risk patients are likely to experience a greater relative treatment benefit compared to low-risk patients, with this supported by data from the ATHENA-MONO ² and SOLO-1 ⁵ trials. As such, the ITCs performed by the EAG are unlikely to be biased in favour of the comparator treatments. The EAG notes that the use of data from the PRIMA ³ trial allows for ITCs to be performed for a greater number of outcomes (e.g., PFS2 and TFST) compared to those performed by the company using data from the PRIME ⁴ trial.
What is the expected effect on the cost-effectiveness estimates?	The inclusion of ITC results, based on PRIMA ³ , in the economic model results in a large difference in cost-effectiveness results, observed in the comparison of the EAG and company base-case analyses.
What additional evidence or analyses might help to resolve this key issue?	Given the differences in baseline characteristics between trials, the EAG suggests that matching-adjusted indirect comparisons (MAICs) may be useful to compare data from the PRIMA ³ trial to that from the ATHENA-MONO ² and SOLO-1 ⁵ trials. The use of MAICs to match the baseline characteristics of the PRIMA ³ trial to that of comparator trials would align with the approach implemented in the recent NICE appraisal of rucaparib (TA1055 ¹). As the company does not have individual patient data (IPD) for the PRIME ⁴ trial, MAICs would only be able to be implemented for the PRIMA ³ trial. However, the EAG acknowledges that baseline characteristics may not be available for all necessary HRD and BRCA status subgroups from the ATHENA-MONO ² and SOLO-1 ⁵ trials.
Abbreviations: CS, company submission; EAG, External Assessment Group; HRD, homologous recombination deficiency; IPD, individual patient data; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; PFS2, progression-free survival on the second line of therapy; TFST, time to first subsequent treatment.	

Table 5. Issue 4: Insufficient evidence for assumptions of clinical equivalence

Report section	Sections 3.4.5, Section 4.2.4
Description of issue and why the EAG has identified it as important	Throughout the company's submission, the company has asserted that niraparib is equivalent to rucaparib and olaparib. However, in response to clarification question, the company confirmed that equivalency testing had not been performed to support the assumptions of equivalence. In response to the clarification questions, the company performed non-inferiority analyses to demonstrate the non-inferiority of niraparib relative to olaparib and rucaparib. However, the EAG has multiple concerns with regards to these analyses and suggests that are inappropriate for use in concluding that niraparib is non-inferior to the comparators. Accordingly, the EAG is concerned that equivalence, or non-inferiority, between niraparib and the comparator treatments has not been demonstrated in a statistically robust, or clinically meaningful, manner. The company's assumption of clinical equivalence (modelled through progression-free survival and overall survival) is implemented in the economic model and is the key driver of cost-effectiveness results, with any additional assumptions made in the model having a minimal impact on the cost-effectiveness analyses as a result. The EAG notes that based on this assumption, the company did not vary the relative treatment effectiveness against either olaparib or rucaparib in the probabilistic sensitivity analyses, i.e. applied a fixed hazard ratio of 1 for both OS and PFS.
What alternative approach has the EAG suggested?	The EAG was unable to replicate the analyses as the code to perform these analyses was not provided by the company. However, the EAG suggests that standard approaches for assessing non-inferiority may be used instead.
What is the expected effect on the cost-effectiveness estimates?	Large. When the assumption of clinical equivalence is removed, as in the EAG preferred analysis, this has a large impact on the cost-effectiveness results. See subsequent key issue's 4a and 4b for further details.
What additional evidence or analyses might help to resolve this key issue?	The EAG suggests that standard non-inferiority analyses could be performed, using widely implemented approaches using clinically validated non-inferiority margins derived from data sources that do not form a core component of the analyses. However, the EAG notes that for the comparisons of niraparib to olaparib and rucaparib (in the relevant HRD/BRCA subgroups) the [REDACTED], meaning that non-inferiority is unlikely to be statistically demonstrated using the EAG's preferred approach.
Abbreviations: EAG, External Assessment Group; HRD, homologous recombination deficiency; PFS, progression-free survival; OS, overall survival.	

Table 6. 4a: Data to inform treatment comparisons in the model for the BRCAm population

Report section	Section 3.4.3, Section 4.2.4
Description of issue and why the EAG has identified it as important	As noted in key issue 4, the EAG considers that clinical equivalence between niraparib and olaparib in the BRCAm population has not been demonstrated in a statistically robust, or clinically meaningful, manner. Therefore, implementing this assumption in the cost-effectiveness results in large uncertainty in the company's economic model results.
What alternative approach has the EAG suggested?	In the company's preferred analysis for the BRCAm population, a hazard ratio (HRs) of 1 was applied to both the PFS and OS niraparib survival curves, assuming clinical equivalence. The EAG performed ITCs of PRIMA ³ versus SOLO-1 ⁵ in the BRCAm population for both PFS and OS and considers these to be the best available estimates of relative effectiveness between niraparib and olaparib.
What is the expected effect on the cost-effectiveness estimates?	Large. When applying the EAG-derived HRs for PFS (■■■■) and OS (■■■■) the company ICER changes from a ■■■■ (driven by negligible differences in QALYs) to a ■■■■
What additional evidence or analyses might help to resolve this key issue?	The EAG notes the limitations of applying a constant hazard ratio to baseline survival curves that do not support the proportional hazards assumption. The EAG notes that the preferred option would have been to conduct ITCs using a fractional polynomial network meta-analysis (fpNMA) to capture the underlying complex hazard function. However, this was not feasible for the EAG to conduct due to time constraints. alternatively, the company could have undertaken a multi-level network meta-regression (ML-NMR) to inform the indirect comparisons; this was not possible for the EAG to undertake due to not having access to the individual patient data (IPD) for PRIMA ³ .
Abbreviations: BRCAm, Breast cancer gene mutation; EAG, External Assessment Group; HR, hazard ratio; ICER, Incremental Cost Effectiveness Ratio; fpNMA, fractional polynomial NMA; IPD, individual patient data; ITC, indirect treatment comparison; ML-NMR, multi-level network meta-regression; OS, overall survival; PFS, progression-free survival; QALY, Quality-Adjusted Life Year	

Table 7. Issue 4b: Data to inform treatment comparisons in the model for the BRCAwt population (HRd/BRCAwt and HRp/BRCAwt)

Report section	Section 3.4.4, Section 4.2.4
Description of issue and why the EAG has identified it as important	As noted in key issue 4, the EAG considers that clinical equivalence between niraparib and rucaparib in the BRCAwt population has not been demonstrated in a statistically robust, or clinically meaningful, manner. Therefore, implementing this assumption in the economic model results in large uncertainty in the company's cost-effectiveness results. In addition, as noted in key issue 2, the EAG does not consider the comparison presented by the company to appropriately use the available data in the BRCAwt population based on HRD classification. As the company did not provide the requested analyses for the HRd/BRCAwt and HRp/BRCAwt populations in the economic model, the EAG could not present its preferred analyses for the BRCAwt populations.
What alternative approach has the EAG suggested?	Based on the use of the combined BRCAwt population for the comparison against rucaparib used in the company's economic model, the EAG constructed an overall BRCAwt population from ATHENA-MONO² data to allow an ITC against PRIMA³ for PFS. However, the equivalent data were not available for overall survival. Therefore, the EAG has instead applied separate HRs for OS in the HRd/BRCAwt and HRp/BRCAwt populations in order to provide a range that is likely to contain the ICER for the combined BRCAwt population.
What is the expected effect on the cost-effectiveness estimates?	Large. The company's analysis resulted in a dominant ICER in the BRCAwt population; however, the EAG advises caution when interpreting the ICER, as the [REDACTED] The EAG's preferred analysis in the BRCAwt population indicates a probabilistic [REDACTED] between [REDACTED] and [REDACTED] with corresponding NHB between [REDACTED] and [REDACTED] at a £20,000 WTP threshold and [REDACTED] and [REDACTED] at a WTP threshold of £30,000.
What additional evidence or analyses might help to resolve this key issue?	As noted in key issue 2, the EAG considers the most appropriate use of the available trial data for niraparib and rucaparib would be to perform ITCs of PRIMA³ versus ATHENA-MONO² for the key model outcomes and implement these in the economic model separately for the HRd/BRCAwt and HRp/BRCAwt populations. The EAG notes that the company's model appears to have been developed to initially include these populations; however the corresponding data were not provided or implemented. As noted in key issue 4a, the EAG also considers that the preferred option would have been to conduct ITCs using a fractional polynomial network meta-analysis (fpNMA) to capture the underlying complex hazard function. or a multi-level network meta-regression (ML-NMR).
Abbreviations: BRCAwt, Breast cancer gene wild type; EAG, External Assessment Group; fpNMA, fractional polynomial network meta-analysis; HRD, homologous recombination deficiency; HRd, homologous recombination deficient; HRp, homologous recombination proficient; ICER, Incremental Cost Effectiveness Ratio; ITC, indirect treatment comparison; ML-NMR, multi-level network meta-regression; NHB, net health benefit; OS, overall survival; PFS, progression-free survival; QALY, quality adjusted life years; WTP, willingness to pay.	

Table 8. Issue 5: Time to treatment discontinuation and implementation of stopping rules

Report section	Section 4.2.5
Description of issue and why the EAG has identified it as important	The EAG notes that there is uncertainty in the proportion of patients who will remain on treatment with PARPis in clinical practice compared to trial data. While rucaparib has an explicit stopping rule of two years in the SmPC this is not the case for olaparib and niraparib, although stopping rules at 2 and 3 years, respectively, were implemented in the key clinical trials, unless investigators considered continued treatment appropriate. While trial data are available for niraparib, showing a proportion of patients remained on treatment beyond 3 years, the equivalent Kaplan-Meier (KM) data are not available for olaparib or rucaparib as these were redacted from previous NICE committee papers. Therefore, for the included comparators, the company estimated time to treatment discontinuation (TTD) based on PFS and adverse events observed in the key trials. The EAG notes that uncertainty in the proportion of patients remaining on treatment beyond the stopping rules will impact the estimated drug acquisition costs for each included treatment.
What alternative approach has the EAG suggested?	The company provided a range of scenarios to examine the impact of TTD assumptions on the cost-effectiveness results. For consistency with the approach taken in TA1055¹, the EAG assumed that all patients on niraparib discontinue at three years and all patients on olaparib or rucaparib discontinue at two years. The EAG also provided scenario analyses in which niraparib TTD is informed by the full mature KM curve, with no stopping rule applied. An additional scenario analysis is also explored on the EAG base-case, directly applying the KM curves from the SACT data for niraparib and olaparib in the BRCAm population.
What is the expected effect on the cost-effectiveness estimates?	When applying the no stopping rule for niraparib in the BRCAm population, the EAG ICER (deterministic) changed from [REDACTED] to [REDACTED]. Applying the available SACT TTD data for niraparib and olaparib had a smaller impact on the ICER [REDACTED]. In the BRCAwt population, applying no stopping rule for niraparib changed the EAG ICER range (deterministic) from [REDACTED] to [REDACTED].
What additional evidence or analyses might help to resolve this key issue?	The EAG acknowledges that the company is unable to provide any further analyses for TTD in light of a lack of direct trial evidence for the comparators in the appropriate populations. The EAG highlights the uncertainty related to the approach used to estimate TTD, in order for it to be considered by committee.
Abbreviations: BRCAm, Breast cancer gene mutation; BRCAwt, Breast cancer gene wild type; EAG, External Assessment Group; ICER, Incremental Cost Effectiveness Ratio; KM, Kaplan-Meier; PARPi, poly(ADP-ribose) polymerase inhibitor; PFS, progression-free survival; SACT, systemic anti-cancer therapy; SmPC, summary of product characteristics; TTD, time to treatment discontinuation.	

1.4 Secondary issues identified by the EAG

A number of additional issues were identified. These have a less significant impact on results than the key issues identified in Section 1.3, but they still represent areas of uncertainty and/or required the EAG to make changes to the economic model.

1. Modelled adverse events: The company informed niraparib adverse event rates used in the economic model from a real-world evidence (RWE) study (MONITOR-UK⁶). The EAG considers that adverse events should be informed from the same source as the treatment effectiveness and discontinuation data for niraparib, which both use the PRIMA³ study. Therefore, this was updated in the EAG's preferred analysis. If the company preferred to use RWE for AEs, the EAG consider that a more appropriate dataset should have been consistently identified for all treatments considered in the analysis and not preferentially for only one treatment, to ensure a "like-for-like" comparison.
2. Model structure: The company used a three-state partition survival model (PSM) structure, despite all recent appraisals in the same disease area using a four-state PSM to include PFS2. While the EAG considers that the inclusion of PFS2 would have been more appropriate, due to a lack of evidence for the specific populations requested by the EAG in order to compare PFS2 against comparators (HRd/HRd/BRCAwt and HRp/HRp/BRCAwt), the EAG has not included PFS2 in the updated model but notes this as a limitation.
3. Niraparib dosing used in the model: The company informed starting distribution of niraparib using SACT data. As the treatment effectiveness and discontinuation used in the model are informed by the PRIMA³ trial, in the EAG base case, the dose distribution of niraparib at baseline has been informed using PRIMA and each cycle is informed by the observed proportion of patients receiving each of the three niraparib doses (100 mg, 200 mg, 300 mg) for either the BRCAm or BRCAwt population. The EAG notes that this is also the approach accepted by committee in the company's original submission, prior to entry into the Cancer Drugs Fund (CDF).

1.5 Company's modelling errors identified by the EAG

No further modelling errors have been identified post-clarification. Therefore, the company's latest ICERs provided in Section 5.1 are considered correct.

1.6 Summary of EAG's preferred assumptions and resulting ICER

Table 9 presents the EAG's preferred assumptions and resulting ICER in the BRCAm population. As discussed in key issues 2 and 4b, the company did not provide the EAG's preferred analysis for the comparison against rucaparib in the BRCAwt population (split based on HRD classification and relative treatment effect derived from PRIMA³ versus ATHENA-MONO² ITCs). Therefore, the EAG has presented a range within which it considers the true ICER for the whole BRCAwt population lies, shown in the final two rows of the Table 11.

Table 9. Summary of the EAG's preferred assumptions and resulting ICER in the BRCAm population, deterministic

Preferred assumption	EAG report section	Cumulative incremental costs	Cumulative incremental QALYs	Cumulative NMB at £20,000 (£)	Cumulative NMB at £30,000 (£)	Cumulative ICER £/QALY
Company base case (post-clarification)	Not applicable	██████	██████	██████	██████	██████ ██████ ██████
Olaparib PFS informed by application of HR = █████	Section 4.2.4.4	██████	██████	██████	██████	██████ ██████
Olaparib OS informed by application of HR = █████	Section 4.2.4.6	██████	██████	██████	██████	██████ ██████
Treatment discontinuation: all patients discontinue at 3 years for niraparib and 2 years for olaparib.	Section 4.2.5	██████	██████	██████	██████	██████ ██████
Niraparib dosing informed by PRIMA ³ per cycle dosing	Section 4.2.8.7	██████	██████	██████	██████	██████ ██████
Adverse events for niraparib based on PRIMA ³	Section 4.2.6.1	██████	██████	██████	██████	██████ ██████
End of life care costs sourcedd from PSSRU	Section 4.2.8.7	██████	██████	██████	██████	██████ ██████

Preferred assumption	EAG report section	Cumulative incremental costs	Cumulative incremental QALYs	Cumulative NMB at £20,000 (£)	Cumulative NMB at £30,000 (£)	Cumulative ICER £/QALY
EAG preferred base case		██████	██████	██████	██████	██████ ██████
Abbreviations: EAG, External Assessment Group; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; NMB, Net monetary benefit; OS, overall survival; PFS, progression-free survival; PSSRU, Personal Social Services Research Unit; QALY, quality-adjusted life-year; t; SW, south-west; TTD, time to treatment discontinuation						

Table 10. EAG base case results for BRCAm population

Interventions	Total Costs (£)	Total LY*	Total QALYs	Incremental costs (£)	Incremental LYs*	Incremental QALYs	ICER (£/QALY)
Deterministic results							
Olaparib	123,144	15.94	8.27	-	-	-	-
Niraparib	██████	11.30	██████	██████	██████	██████	██████ ██████
Probabilistic results							
Olaparib	123,218	NR	8.32	-	-	-	-
Niraparib	██████	NR	██████	██████	██████	██████	██████ ██████
*Undiscounted							
Abbreviations: ICER, incremental cost-effectiveness ratio; LY, life year; NR, not reported; QALY, quality-adjusted life-year; SW, south-west							

Table 11. Summary of the EAG's preferred assumptions and resulting ICER in the BRCAwt population, deterministic

Preferred assumption	EAG report section	Cumulative incremental costs	Cumulative incremental QALYs	Cumulative NMB at £20,000 (£)	Cumulative NMB at £30,000 (£)	Cumulative ICER £/QALY
Company base case (post-clarification)	Not applicable					
Rucaparib PFS informed by application of HR =	Section 4.2.4.8					
Treatment discontinuation: all patients discontinue at 3 years for niraparib and 2 years for olaparib.	Section 4.2.5					
Niraparib dosing informed by PRIMA ³ per cycle dosing	Section 4.2.8.7					
Adverse events for niraparib based on PRIMA ³	Section 4.2.6.1					
End of life care costs sourced from PSSRU	Section 4.2.8.7					
OS HR = based on EAG derived HR in the HRd/BRCAwt population	Section 4.2.4.10					
OS HR = based on EAG derived HR in the HRp/BRCAwt population	Section 4.2.4.10					
EAG preferred base case	-					

Abbreviations: BRCAwt, Breast cancer gene wild type; EAG, External Assessment Group; HR, hazard ratio; HRd, homologous recombination deficient; HRp, homologous recombination proficient; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; OS, overall survival; PFS, progression-free survival; PSSRU, Personal Social Services Research Unit; QALY, quality-adjusted life-year; SW, south-west; TTD, time to treatment discontinuation

The following tables present the EAG preferred base case results separately for when alternative HRs are applied for OS (either based on HRd/BRCAwt or HRp/BRCAwt, respectively) in the BRCAwt population and as previously noted, the EAG considers that the preferred ICER lies within this range.

Table 12. EAG base case results, BRCAwt with HRd/BRCAwt HR for overall survival applied

Interventions	Total Costs (£)	Total LY*	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Deterministic results							
Rucaparib	██████	8.19	████	-	-	-	-
Niraparib	██████	5.71	████	██████	████	████	████ ██████
Probabilistic results							
Rucaparib	██████	NR	████	-	-	-	-
Niraparib	██████	NR	████	██████	████	██████	████ ██████
*Undiscounted							
Abbreviations: BRCAm, Breast cancer gene mutation; BRCAwt, Breast cancer gene wild type; EAG, External Assessment Group; HR, hazard ratio; HRd, homologous recombination deficient; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life-year; SW, south-west.							

Table 13. EAG base case results , BRCAwt with HRp/BRCAwt HR for overall survival applied

Interventions	Total Costs (£)	Total LY*	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Deterministic results							
Rucaparib	██████	7.12	████	-	-	-	-
Niraparib	██████	5.71	████	██████	████	██████	████ ██████
Probabilistic results							
Rucaparib	██████	NR	████	-	-	-	-
Niraparib	██████	NR	████	██████	████	██████	████ ██████
*Undiscounted							
Abbreviations: BRCAm, Breast cancer gene mutation; BRCAwt, Breast cancer gene wild type; EAG, External Assessment Group; HR, hazard ratio; HRd, homologous recombination deficient; ICER, incremental cost-effectiveness ratio; LY, life year; NR, not reported; QALY, quality-adjusted life-year; SW, south-west.							

For further details of the exploratory and sensitivity analyses done by the EAG, see Section 5.2.4.

1.7 Outline of confidential comparator or subsequent treatment prices

A confidential price is available for olaparib and rucaparib, and so the EAG has produced a confidential appendix to this report. Further details of the confidential appendix are presented in Section 5.4.

2 Background

2.1 Introduction

This report contains the External Assessment Group (EAG)'s critique of the clinical and cost-effectiveness evidence submitted for the Single Technology Appraisal (STA) of niraparib (Zejula®; GlaxoSmithKline) as a maintenance regimen to maintain the response to first-line platinum-based chemotherapy for adults with newly diagnosed advanced high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer (collectively referred to as ovarian cancer henceforth). This STA constitutes a review of a previous appraisal (TA673⁷). The Medicines and Healthcare products Regulatory Agency (MHRA) marketing authorisation for niraparib in this indication is, “as a monotherapy for the maintenance treatment of adult patients with advanced epithelial (International Federation of Gynaecology and Obstetrics [FIGO] Stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy”. As such, the MHRA marketing authorisation for niraparib is in patients regardless of their homologous recombination deficiency (HRD) or breast cancer gene (BRCA) status.

2.2 Background

The company submission (CS) provides an overview of ovarian cancer, including the causes, prevalence, diagnosis, pathology, and symptom burden. It also provides a description of niraparib, its mechanism of action, indication, and methods of administration and dosage. Included below is the EAG's summary of the key background information presented in the CS, supplemented by information provided by the EAG's clinical experts.

Ovarian cancer is a general term that is used to refer to ovarian, fallopian tube, and peritoneal cancer.⁸ Epithelial ovarian cancer accounts for approximately 90% of cases and may often be linked to BRCA mutations and HRD status, which result in an increased risk of ovarian cancer.⁸ Patients with ovarian cancer may be classified according to BRCA status and HRD status.⁸ Accordingly, the majority of patients may be categorized into the following groups:

- BRCA mutations (BRCA_m) and be homologous recombination deficient (HRd);
 - Hence referred to as BRCA_m;
- No BRCA mutations (BRCA_{wt}) and be HRd;
 - Hence referred to as HRd/BRCA_{wt};
- BRCA_{wt} and be homologous recombination proficient (HRp);

- Hence referred to as HRp/BRCAwt.

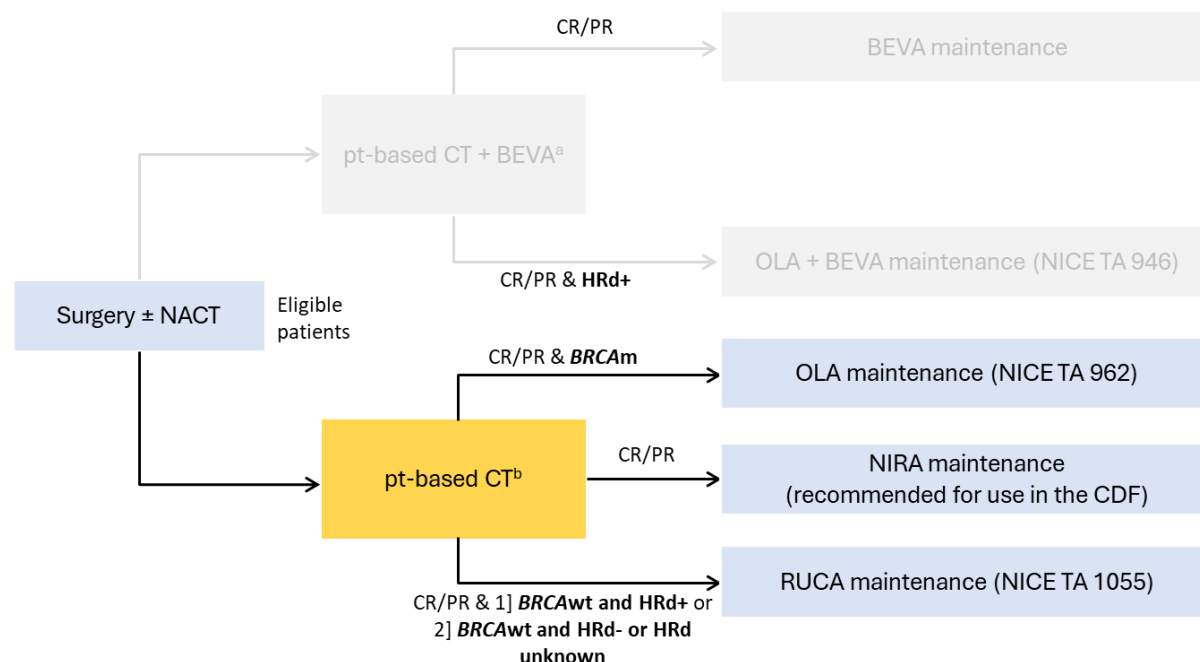
Throughout the report, the EAG uses the above notations to refer to the specific combinations of BRCA status and HRD status for each subgroup. The EAG notes that where HRd is referred to without a corresponding BRCA subgroup, this refers to a HRd population comprising all BRCA status subgroups. Likewise, where BRCAwt is referred to without a corresponding HRD subgroup, this refers to a BRCAwt population comprising all HRD status subgroups.

The majority (~60%) of patients are diagnosed at an advanced stage (namely FIGO stage III-IV), with ovarian cancer being the fifth most common cause of cancer-related mortality in women in the United Kingdom. Of those diagnosed with advanced stage ovarian cancer, one of the EAG's clinical experts noted that the five-year survival rates are 40% to 50% for FIGO stage III patients and 15 to 20% for FIGO stage IV patients. Approximately 80% of patients experience disease recurrence and progression following standard first-line treatment.

Within UK clinical practice, FIGO stage III and IV patients typically receive neoadjuvant chemotherapy with interval surgery. One of the EAG's clinical experts noted that this would be the expected course of action for approximately 60% to 65% of FIGO stage III patients and in excess of 80% of FIGO stage IV patients. First-line (1L) induction treatment is with a platinum-based chemotherapy, that may be administered with, or without, bevacizumab. If patients achieve a complete or partial response to platinum-based chemotherapy, patients typically receive a 1L maintenance treatment. Those patients who are eligible to receive a platinum-based chemotherapy with bevacizumab are able to receive either bevacizumab monotherapy or olaparib with bevacizumab (if patients are HRd). In contrast, those patients who received platinum-based chemotherapy without bevacizumab are able to receive either olaparib (if patients are BRCAm) or rucaparib (if patients are BRCAwt). Following NICE TA673⁷, niraparib was made available as a maintenance treatment through the Cancer Drugs Fund (CDF). Niraparib was made available to patients regardless of BRCA status and HRD status.

Within this NICE appraisal to review TA673⁷, niraparib is proposed as a maintenance treatment, in patients with advanced ovarian cancer, who have achieved partial or complete response following the completion of a first-line platinum-based chemotherapy in patients who are unable to receive bevacizumab. The company's proposed positioning of niraparib, alongside the current UK clinical pathway, is outlined in Figure 1. As shown in Figure 1, the company has proposed that niraparib is available to patients regardless of BRCA status or HRD status. In contrast, olaparib is only available to BRCAm patients, while rucaparib is only available to BRCAwt patients.

Figure 1. Proposed positioning of niraparib within UK clinical practice (reproduced from Figure 5 of the CS).



Abbreviations: BEVA = bevacizumab; BRCAm = breast cancer gene mutant; BRCAwt = breast cancer gene wildtype; CDF = cancer drug fund; CR/PR = complete response/partial response; CT = chemotherapy; HRd = homologous recombination deficient; NACT = neoadjuvant chemotherapy; NICE = National Institute for Health and Care Excellence; NIRA = Niraparib; OLA = olaparib; PARPi = poly(ADP-ribose) polymerase inhibitor; pt = platinum; RUCA = rucaparib; TA = Technology Appraisal

^a Patients who receive BEVA during induction chemotherapy can then receive BEVA or OLA + BEVA as maintenance therapy. Since PARPi monotherapy as maintenance therapy is recommended only for patients who did not receive or could not tolerate BEVA during induction chemotherapy, the bevacizumab treatment path is greyed out in the figure above.

^b PARPi monotherapy is usually given to patients who do not receive BEVA during induction.

Adapted from NICE TA946⁹; NICE TA962¹⁰; NICE TA1055¹.

2.3 Critique of the company's definition of the decision problem

The company provided a summary of the final scope issued by NICE, together with the rationale for any deviation from it, in Section 1.2 of the CS. This is summarised in Table 14 below and more detailed comments from the EAG are provided in the subsections that follow. Overall, the EAG considers the decision problem addressed, and the evidence used to address it, to be in line with the NICE final scope or any deviations to be reasonable given the rationale provided.

Table 14. Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope	EAG comment
Population	Adults with advanced epithelial (Federation of Gynaecology and Obstetrics [FIGO] stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of 1L platinum-based chemotherapy	Adults with advanced epithelial (Federation of Gynaecology and Obstetrics [FIGO] stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of 1L platinum-based chemotherapy	NA	The CS considers two trials that compared niraparib to placebo. The PRIMA ³ trial was conducted in Europe and North America, while the PRIME ⁴ trial was solely conducted in China. While the population of the PRIME trial aligned with the NICE final scope, the population considered in PRIMA was narrower. The PRIMA trial excluded stage III patients with a favourable prognosis due to being optimally debulked following upfront primary debulking surgery. Additionally, the PRIMA trial was not stratified for the core subgroup of BRCA status. As a result of this, subgroup analyses of BRCA status (required to facilitate comparisons to olaparib and rucaparib in the relevant population) resulted in trial randomisation being broken. Additionally, within the PRIME trial, HRD status was assessed using an unvalidated assay. The EAG notes that some baseline characteristics within the PRIME trial do not necessarily align with those expected in UK clinical practice.

Intervention	Niraparib (Zejula)	Niraparib (Zejula)	NA	The EAG considers the intervention in the company's submission to align with the NICE final scope. The EAG notes that for both the PRIMA³ and PRIME⁴ trials, comparing niraparib to placebo, the starting dose at the start of the trial was 300mg per day (referred to as a fixed starting dose). However, following protocol amendments in each trial, patients were assigned an individualised starting dose of either 200mg per day for patients with a body weight less than 77 kg and/or a platelet count lower than 150,000 per μL at baseline and otherwise, 300 mg per day if neither of the above conditions was met. Within the summary of product characteristics (SmPC), it is recommended that patients are assigned a starting dose based on the individual starting dose conditions (as opposed to the fixed starting dose). As such, the data for the PRIMA³ trial presented within the company's submission, comprises patients who received a fixed starting dose of 300mg whereas under an individualised starting dose, they would have received a 200mg starting dose. As such, the EAG notes that there were patients included in the PRIMA and who received niraparib starting doses that did not align with SmPC recommendations.
Comparator(s)	• Olaparib plus bevacizumab (if HRD-positive and after	• Olaparib (if BRCA mutation-positive)	Clinical experts confirmed that due to the approval of one or more PARPis	In response to a clarification question, the company confirmed that a recommendation is

	complete or partial response to 1L platinum-based chemotherapy with bevacizumab) • Olaparib (if BRCA mutation-positive) • Rucaparib (if HRd BRCAwt or non-HRD [HRp and HRunknown]) • Bevacizumab monotherapy at a dose of 7.5 mg/kg (after response to 1L platinum-based chemotherapy plus bevacizumab) • Routine surveillance	• Rucaparib (if BRCA mutation-negative, also referred to as BRCA wild-type ([BRCAwt])	across various biomarkers (e.g., HRd, HRp, BRCAm and BRCAwt), routine surveillance is not considered for patients who are eligible for PARPi in clinical practice. As such, GSK does not consider to be a relevant comparator for evaluating niraparib. Bevacizumab monotherapy is not considered a relevant comparator as availability of niraparib will not displace its usage from the treatment pathway. Bevacizumab is initiated alongside 1L platinum-based chemotherapy and continued until disease progression or for a maximum of 15 months or until unacceptable toxicity, whichever occurs earlier. In contrast, PARPi monotherapies such as niraparib are utilised as maintenance therapies following a response to 1L PBC alone or if bevacizumab could not be tolerated alongside PBC. Therefore, as stated by clinical advice, PARPi monotherapies do not displace bevacizumab from the treatment pathway. Similarly, the olaparib plus bevacizumab regimen is also not displaced with niraparib availability and therefore is not considered a	sought in patients who were not eligible for a first-line therapy of a platinum-based chemotherapy with bevacizumab. As such, based on the UK treatment pathway, the company does not consider bevacizumab monotherapy or olaparib with bevacizumab to be relevant comparators. In contrast, the current treatment pathway indicates that olaparib and rucaparib would be considered to be comparators in the population that the company is seeking a recommendation. The EAG's clinical experts did not consider routine surveillance to be a relevant comparator. Accordingly, the EAG accepts that the comparators listed by the company (namely olaparib and rucaparib) are the only relevant comparators for the population in which the company is seeking a recommendation.

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope	EAG comment
			suitable comparator. This regimen is indicated as an add-on of olaparib to a pre-existing bevacizumab component which is initiated alongside PBC. Clinical experts have confirmed that PARPi monotherapies, such as niraparib are used in patients who have not initiated bevacizumab alongside 1L platinum-based chemotherapy or had to discontinue due to intolerance.	
Outcomes	• Overall survival • Progression-free survival • Progression-free survival 2, that is progression-free survival on the next line of therapy • Response rate • Time to first subsequent therapy • Adverse effects of treatment • Health-related quality of life	• Overall survival • Progression-free survival • Progression-free survival 2, that is progression-free survival on the next line of therapy • Response rate • Time to first subsequent therapy • Adverse effects of treatment • Health-related quality of life	NA	The outcomes in the clinical submission broadly align with those stated in the NICE final scope. However, the EAG notes that response rate was not considered in the company's submission. The EAG is not aware of response rate being reported for the PRIMA ³ or PRIME ⁴ trials. However, the EAG notes that evidence for response rate was presented in the NICE appraisal of rucaparib (TA1055 ¹). Additionally, PFS2 was not reported for the PRIME trial.

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope	EAG comment
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability and cost of biosimilar and generic products should be taken into account.	Not explicitly stated within the decision problem section of the CS.	Not explicitly stated within the decision problem section of the CS.	The economic analysis adheres to the reference case.

Subgroups	If the evidence allows the following subgroups will be considered: • BRCA mutation status • HRD status	Not explicitly stated within the decision problem section of the CS.	Not explicitly stated within the decision problem section of the CS.	The NICE final scope states that subgroup analyses for BRCA status and HRD status should be presented, if evidence permits. As such, the CS comprised results of the following combinations of BRCA mutation status and HRD status: • HRd; • BRCAm; • HRd/BRCAwT; • HRp/BRCAwT; and • BRCAwT. Of the above populations, the EAG considers that the BRCAm, HRd/BRCAwT, HRp/BRCAwT, and BRCAwT populations are the most relevant subgroups to consider based upon previous NICE recommendations of olaparib (TA962¹⁰) and rucaparib (TA1055¹). The company provided subgroup analyses comparing niraparib to rucaparib using data from the PRIME⁴ trial. The EAG notes that the company has access to IPD for the PRIMA³ trial but not the PRIME trial. At the clarification stage the EAG requested that the company provided the results of subgroup analyses to compare niraparib to rucaparib using data from the PRIMA trial. However, the company did not provide the results of the requested subgroup analyses.

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope	EAG comment
Special considerations, including issues related to equity or equality	Not explicitly stated within the NICE final scope.	Not explicitly stated within the decision problem section of the CS.	Not explicitly stated within the decision problem section of the CS or NICE final scope.	NA

Abbreviations: 1L, first line; BRCAm, Breast cancer gene mutation; BRCAwt, Breast cancer gene wild type; CS, company submission; EAG, External Assessment Group; FIGO, International Federation of Gynaecology and Obstetrics; HRD, homologous recombination deficiency; HRd, homologous recombination deficient; HRp, homologous recombination proficient; IPD, individual patient data; NICE, National Institute for Health and Care Excellence; NHS, National Health Service; PARPi, poly(ADP-ribose) polymerase inhibitor; PBC, platinum-based chemotherapy; PFS2, progression-free survival on the second line of therapy; SmPC, summary of product characteristics.

2.3.1 Population

The population specified in the NICE final scope was adults with advanced epithelial (FIGO stages 3 and 4) high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy. The EAG notes that the population enrolled in the PRIMA³ trial, which informs the clinical effectiveness data for niraparib in the CS, comprised of patients with high-grade serous or endometrioid tumours, FIGO stage III (excluding stage III with no residual disease after primary debulking surgery) or IV and had received 6-9 cycles of 1L PBC, which had resulted in complete or partial response. As such, the PRIMA trial excluded stage III patients with a favourable prognosis due to being optimally debulked following upfront primary debulking surgery. As such, the PRIMA trial solely comprised a patient group termed 'high-risk' patients. This constitutes a narrower population than the NICE final scope and narrower populations than those considered in the NICE appraisals for the relevant comparator treatments of olaparib (TA962¹⁰) and rucaparib (TA1055¹). The EAG notes that while the PRIMA trial was stratified for HRD status, it was not stratified for the core subgroup of BRCA status. Accordingly, any subgroup analyses of BRCA status (which is necessary given that the relevant comparators of olaparib and rucaparib are approved in different populations based on BRCA status) would resolve in trial randomization being broken.

In contrast, the PRIME⁴ trial, comparing niraparib to placebo, was performed in an 'all-risk' population comprising both high-risk and low-risk patients. However, the PRIME trial has several limitations with regards to the population. The PRIME trial was performed solely in China and assessed HRD status using an unvalidated assay. Accordingly, these limitations may prevent the results of the PRIME trial from being directly relevant to UK clinical practice.

Within the CS, the company estimated that of patients with ovarian cancer, 25% were BRCAm, 25% were HRd/BRCAwt, and 50% were HRp/BRCAwt. In contrast, the EAG's clinical experts indicated that, of ovarian cancer patients seen in UK clinical practice, approximately 10% to 20% would be BRCAm, approximately 20% would be HRd/BRCAwt, and approximately 60% to 70% would be HRp/BRCAwt. As such, there is a considerable difference between the proportions of each BRCA and HRD subgroup presented by the company and those proposed by the EAG's clinical experts.

Within the CS, the company detailed 14 variables, identified through a review of HTA submissions, published ITCs, and clinical trials, that were considered to be prognostic factors or treatment effect modifiers as follows:

- Age;
- FIGO stage;
- Prior bevacizumab use;
- Eastern Cooperative Oncology Group performance status (ECOG PS);
- Response to first-line chemotherapy;
- Histology;
- BRCA status;
- CA-125 level;
- Tumour location;
- Receipt of neoadjuvant chemotherapy;
- Residual disease status;
- History of cytoreductive surgery;
- HRd status; and
- Timing of surgery.

Additionally, a recent study¹¹, which was funded in part by the company, identified several predictors of long-term (i.e., ≥ 2 years) progression-free survival (PFS) using data from the PRIMA³ trial (that compared niraparib to placebo). Each of these statistically significant predictors of long-term PFS are noted below:

- HRD status;
 - HRd was associated with a greater likelihood of long-term PFS compared to HRp or not determined tumours;
- FIGO stage;
 - FIGO stage III was associated with greater likelihood of long-term PFS compared to FIGO stage IV;
- Baseline non-target lesions;
 - 0 or 1 baseline non-target lesions were associated with a greater likelihood of long-term PFS compared to ≥ 2 baseline non-target lesions.

The EAG notes that considerable differences exist between trials, and between arms in a single trial, for the above prognostic variables and treatment effect modifiers (Section 3.4.1) listed above. As such, the EAG notes that differences in the prevalence of these variables between trial arms, and trials, may impact direct, and indirect, comparisons between treatments.

2.3.2 Intervention

The EAG considers the intervention in the company's submission to align with that in the NICE final scope. Niraparib (Zejula®; GlaxoSmithKline) received UK (MHRA) regulatory approval on 6 December 2022 as a monotherapy for the maintenance treatment of adult patients with advanced epithelial (FIGO Stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy.

Although the EAG considers the intervention in the CS to align with the NICE final scope, the EAG notes that for the PRIMA³ trial the starting dose of niraparib was adjusted following a protocol amendment. At the start of the PRIMA trial, the starting dose was 300mg per day (referred to as a fixed starting dose). However, following the implementation of the protocol amendment in both trials, patients were subsequently assigned an individualised starting dose of either 200mg per day or 300mg per day. Patients were assigned a starting dose of 200mg per day if, at baseline, they had a body weight of less than 77kg and/or a platelet count lower than 150,000 per µL. If patients did not meet one or more of these criteria, they were assigned a starting dose of 300mg per day.

Within the SmPC, it is recommended that patients are assigned a starting dose based on the individual starting dose conditions implemented in the PRIME⁴ trial and PRIMA³ (post-amendment). Accordingly, the clinical trial data presented within the CS, comprises patients who received a fixed starting dose of 300mg whereas under an individualised starting dose they would have received a 200mg starting dose. As such, the EAG notes that there were patients included in the PRIMA trial who received niraparib starting doses that did not align with SmPC recommendations.

2.3.3 Comparators

Within the NICE final scope, the following comparators were listed:

- Routine surveillance;
- Olaparib (BRCAm population);
- Rucaparib (BRCAwt population);
- Olaparib with bevacizumab (HRd population who have received first-line platinum-based chemotherapy with bevacizumab); and
- Bevacizumab monotherapy, at a dose of 7.5mg/kg (population who have achieved a response to first-line platinum-based chemotherapy with bevacizumab at a dose of 7.5mg/kg).

Olaparib was previously recommended for use by NICE (TA962¹⁰) in adults with a BRCA1 and/or BRCA2 mutation (BRCAm). Likewise, NICE has previously recommended rucaparib (TA1055¹) for use in adults without a BRCA1 and/or BRCA2 mutation (BRCAwt). As shown in the company's treatment pathway, the company considered both olaparib and rucaparib to be relevant comparators for niraparib. The EAG agrees that olaparib and rucaparib are relevant comparators for niraparib, with the EAG's clinical experts in agreement. Additionally, the EAG notes that direct evidence is not available for the comparisons of niraparib to either olaparib or rucaparib. Accordingly, indirect treatment comparisons (ITCs) are required to assess the relative efficacy of niraparib to both olaparib and rucaparib (Section 3.4).

Within the CS, the company stated that olaparib with bevacizumab, and bevacizumab monotherapy were not considered to be relevant comparators to niraparib. In response to a clarification question, the company clarified that bevacizumab monotherapy and olaparib with bevacizumab were not considered to be relevant comparators. The company stated that (in line with NICE TA946⁹) olaparib with bevacizumab is only recommended in HRd patients who have partially or completely responded to first-line platinum-based chemotherapy with bevacizumab. Likewise, the company stated that the use of bevacizumab as a maintenance therapy requires that patients have completed first-line induction chemotherapy in combination with bevacizumab. This contrasts with the NICE recommendation for rucaparib (TA1055¹) that stipulates that only patients who are ineligible for bevacizumab maintenance therapy are eligible for rucaparib maintenance therapy. Furthermore, in response to a clarification question, the company noted that PARPi monotherapies are considered for patients who did not receive, or are unable to tolerate, bevacizumab during induction chemotherapy. Accordingly, the EAG accepts the company's rationale for not considering either bevacizumab monotherapy or olaparib with bevacizumab within the CS. Accordingly, the EAG suggests that any NICE recommendation clearly stipulates that it applies where bevacizumab is not a treatment option (consistent with the wording for TA1055¹). However, the EAG notes that within the minutes of the advisory board meeting conducted by the company, the company stated that ITCs comparing niraparib to olaparib with bevacizumab were being performed, although these analyses were not provided by the company.

The EAG agrees with the company's suggestion that routine surveillance is not a relevant comparator for niraparib in patients who are eligible for a PARPi. Likewise, this viewpoint was supported by the EAG's clinical experts, who also indicated that routine surveillance was not considered to be a relevant comparator.

The EAG's clinical experts did not consider there to be any comparators missing from the CS or NICE final scope.

2.3.4 Outcomes

The outcomes presented by the company in the CS are broadly aligned with those specified in the NICE final scope. Within the NICE final scope, the following outcomes were listed:

- Overall survival (OS);
- Progression-free survival (PFS);
- Progression-free survival 2 (PFS2) (i.e., progression-free survival on next line of therapy);
- Response rate;
- Time to first subsequent therapy (TFST);
- Adverse effects of treatment (AEs); and
- Health-related quality of life (HRQoL).

Of the outcomes listed in the NICE final scope, OS, PFS, AEs, and HRQoL are used in the economic model provided by the company. Within both the PRIMA³ and PRIME⁴ trials, the primary outcome was PFS. For the PRIMA trial, investigator-assessed PFS (PFS-INV) and blinded independent central review-assessed PFS (PFS-BICR) was reported. For the PRIME trial, PFS-INV was only reported for the ITT population as a sensitivity analysis. As PFS-INV was used in the economic model, the EAG has predominantly focused on this outcome as opposed to PFS-BICR. PFS2 was assessed in the PRIMA trial but was not measured within the PRIME trial. As such, all discussions of PFS2 have used data from the PRIMA trial. This included ITCs of PFS2, performed by the EAG, to compare niraparib to olaparib and rucaparib. TFST was provided in both the PRIMA and PRIME trials.

Within the NICE final scope, response rate is listed as a key outcome of interest. However, while the CS states that response rate was considered, the EAG is not aware of data for this outcome (e.g., overall response rate or duration of response) being presented. Additionally, the EAG notes that within the NICE appraisal for rucaparib (TA1055¹), data for response rate is presented within the CS.

Overall, the EAG's clinical experts did not consider there to be any additional outcomes missing from the NICE final scope.

The EAG notes that for the key subgroups of BRCA status and HRD status (Section 2.3.5), data is available from the PRIMA³ trial for OS, PFS-INV, PFS-BICR, PFS2, and TFST. In contrast, for the PRIME⁴

trial, PFS-INV is not available for any of the subgroups of interest, though PFS-BICR is available of all subgroups. In contrast, OS is only available in the PRIME trial for the HRd subgroup. Likewise, PFS2 and TFST are not available for any subgroups of interest.

The EAG notes that there was a considerable difference in the maturity of outcome data between the PRIMA³ and PRIME⁴ trials. For the PRIMA trial, the EAG considers the data to be mature, with a median follow-up of 73.9 months and 73.8 months in the niraparib and placebo populations, respectively. In contrast, the EAG considers the data from PRIME to be immature, with a median follow-up of 27.5 months and 27.6 months in the niraparib and placebo populations, respectively.

2.3.5 Subgroups

2.3.5.1 BRCA mutation status and HRD status

Within the NICE final scope it was stated that, evidence permitting, the subgroup analyses of BRCA mutation status and HRD status should be considered. Accordingly, the company provided subgroup analyses, for the results of the PRIMA³ and PRIME⁴ trials and ITCs comparing niraparib to olaparib and rucaparib. To this end, the CS comprised results of the following combinations of BRCA mutation status and HRD status:

- ITT;
- HRd;
- BRCAm;
- HRd/BRCAwT;
- HRp/BRCAwT; and
- BRCAwT.

Of the above populations, the EAG considers that the BRCAm, HRd/BRCAwT, HRp/BRCAwT, and BRCAwT populations are the most relevant subgroups to consider. As previously noted (Section 2.3.3), olaparib (TA962¹⁰) and rucaparib (TA1055¹) have received recommendations from NICE in contrasting populations. Accordingly, olaparib is only a relevant comparator to niraparib for the BRCAm population, while rucaparib is only a relevant comparator to the HRd/BRCAwT, HRp/BRCAwT, and BRCAwT populations. While rucaparib has received a recommendation in the entire BRCAwT population, the EAG considers it appropriate to perform subgroup analyses for the smaller subgroups of HRd/BRCAwT and HRp/BRCAwT, given that testing for HRD status is now widely performed in UK clinical practice. The EAG notes that ITCs were not performed by the company for

the comparison of niraparib to rucaparib for the BRCAwt population. However, the EAG has subsequently performed an ITC to compare niraparib to rucaparib in the BRCAwt population for the outcome of PFS.

2.3.5.2 Additional subgroup analyses

Although ITCs were only performed for the subgroups of BRCA mutation status and/or HRD status, subgroup results were presented for the PRIMA³ trial for both PFS and OS, and for the PRIME⁴ trial for PFS. For these trials and outcomes, results were presented for the following subgroups:

- Age;
- Baseline CA-125 level;
- Best response to first platinum regimen at randomisation;
- Best response to first platinum regimen from electronic case report form;
- Cytoreductive surgery outcome;
- Eastern Cooperative Oncology Group (ECOG) Performance Score (PS);
- International Federation of Gynaecology and Obstetrics (FIGO) stage;
- Intraperitoneal chemotherapy;
- Neoadjuvant chemotherapy at randomisation;
- Primary tumour site;
- Race;
- Receipt of neoadjuvant chemotherapy (NACT);
- Region;
- Response to platinum-based chemotherapy;
- Stage of disease at initial diagnosis; and
- Starting dose cohort.

Of the subgroups listed above, not all subgroups were presented for all outcomes and trials. As these subgroups were not listed in the NICE final scope, the EAG has briefly summarised these results, unless the EAG considered it necessary to expand upon specific subgroup analyses.

3 Clinical effectiveness

This section presents a summary and critique of the clinical-effectiveness evidence included in the company's submission. Section 3.1 focuses on the company's review of clinical and safety evidence. Sections 3.2 to 3.3 provide a critique of the included studies and clinical-effectiveness analyses. Section 3.4 critique any indirect comparisons presented by the company and Section 3.5 presents the conclusions.

3.1 Critique of the methods review

The company undertook a systematic literature review (SLR) to identify existing efficacy, safety, and health-related quality-of-life (HRQoL) evidence of niraparib and relevant comparators in first-line maintenance therapy of ovarian cancer. The SLR sought to identify data from clinical trials and real-world evidence studies and was performed in March 2024, with an update subsequently undertaken in February 2025. The SLR included both peer-reviewed articles and evidence obtained from pre-defined grey literature sources. The EAG summarises the SLR methods in Table 15. The EAG considers the company SLR to be appropriate, and notes that the SLR was broader than would have been necessary given the final scope issued by the National Institute for Health and Care Excellence (NICE) and the decision problem addressed by the company in the company submission (CS). The latest update to the SLR was performed in February 2025, approximately five months prior to the submission, suggesting that most relevant evidence was likely to be captured in the CS.

Table 15. Summary of EAG’s critique of the methods implemented by the company to identify evidence relevant this appraisal

Systematic review step	Section of CS in which methods are reported	EAG’s assessment of robustness of methods
Data sources	Appendix B.1.1.1	Appropriate Searches were performed on the following dates: • Original search, March 2024; and • Update search, February 2025. The following electronic databases were searched: • MEDLINE; • MEDLINE In-process; • Embase; • Cochrane Central Register of Controlled Trials; • NHS EED; and • NHS HTA. Abstracts from the following conferences were searched from 2020 to present: • European Society of Gynaecological Oncology; • American Society of Clinical Oncology; • European Society for Medical Oncology; • Asian Society of Gynaecologic Oncology; • Society of Gynaecologic Oncology; • National Cancer Research Institute; • European Association for Cancer Research; • The Professional Society for Health Economics and Outcomes Research; • International Gynaecologic Cancer Society; and • British Gynaecological Cancer Society. Searches were performed for HTA submissions from the following organisations: • NICE; • Scottish Medicines Consortium; • National Centre for Pharmacoeconomics; • Canadian Agency for Drugs and Technologies in Health; • pan-Canadian Oncology Drug Review; and • Pharmaceutical Benefits Advisory Committee.
Search strategies	Appendix B.1.1.1	Appropriate Searches were broad, while limits were defined using both keywords and subject heading terms. The original SLR was performed in March 2024, with update searches subsequently performed in February 2025. Accordingly, the most recent update search was performed approximately five months prior to the company’s submission.

Systematic review step	Section of CS in which methods are reported	EAG's assessment of robustness of methods
Inclusion criteria	Appendix B.1.1.2	Appropriate The EAG considers the inclusion criteria to be broader than the final scope issued by NICE and the decision problem addressed by the company in the CS. Hence, the EAG considers it unlikely any studies relevant to the decision problem have been missed.
Screening	Appendix B.1.1.2	Appropriate Title/abstract review and full-text review were completed by two independent reviewers. Discrepancies were resolved through input from a third reviewer.
Data extraction	Appendix B.1.1.3	Appropriate Data extraction was performed by a single reviewer, while a quality assessment of all entries was performed by a second independent reviewer. Any discrepancies were resolved by consensus across both reviewers.
Tool for quality assessment of included study or studies	Appendix B.1.1.3	Appropriate Quality assessments for RCTs were performed using the Cochrane Risk of Bias Assessment Tool 2.0. In contrast, RWE studies and single-arm trials were assessed using the Risk of Bias in Non-Randomised Studies of Interventions tool. Quality assessments were not performed for conference abstracts.
Abbreviations: CS, company submission; EAG, External Assessment Group; EED, Economic Evaluation Database; HTA, health technology assessment; NICE, National Institute for Health and Care Excellence; RCT, randomized controlled trial; RWE, real world evidence; SLR, systematic literature review.		

In total, the SLR (combining the searches performed in March 2024 and February 2025) identified 507 unique records, which underwent title and abstract level screening. Of these 507 records, 149 records underwent full text screening, while 358 records were excluded. Following the full text screening a total of 33 records from the searches were deemed eligible for inclusion, while one further record was deemed eligible for inclusion following grey literature searches. Overall, a total of 34 records, representing 14 unique studies, were included in the SLR. Of the 14 unique studies, 8 clinical trials were identified, which are summarised below in Table 16.

Table 16. Trials identified through the systematic literature review.

Trial name (trial identifier)	Study design	Intervention(s)
ATHENA-MONO ² ATHENA-COMBO ¹² (NCT03522246) ^a	Phase 3, double-blind RCT	Rucaparib + placebo vs placebo (ATHENA-MONO) Rucaparib + nivolumab vs rucaparib + placebo (ATHENA-COMBO)
FLAMES ¹³ (NCT04169997)	Phase 3, double-blind RCT	Senaparib vs placebo
Oda et al. 2024 ¹⁴ (JRCT 2080223978)	Phase 2, single-arm trial ^b	Olaparib
OVARIO ¹⁵ (NCT03326193)	Phase 2, open-label, single-arm trial	Niraparib + bevacizumab
PAOLA-1 ¹⁶ (NCT02477644)	Phase 3, double-blind RCT	Olaparib + bevacizumab vs bevacizumab
PRIMA ³ (NCT02655016)	Phase 3, double-blind RCT	Niraparib vs placebo
PRIME ⁴ (NCT03709316)	Phase 3, double-blind RCT	Niraparib vs placebo
SOLO-1 ⁵ (NCT01844986)	Phase 3, double-blind RCT	Olaparib vs placebo
Abbreviations: RCT, randomised controlled trial		

^a The ATHENA-MONO and ATHENA-COMBO trials are registered under a single NCT identifier that corresponds to the ATHENA trial.

^b Patients (n=32) were initially randomly assigned, in a 2:1 ratio, to receive either olaparib or placebo. Following the approval of olaparib for BRCAm patients in 2019, the trial became a single-arm design with a further 26 patients enrolled for treatment with olaparib.

As shown in Table 16, the SLR identified two trials that considered niraparib monotherapy (PRIMA³ and PRIME⁴). Both the PRIMA and PRIME trials compared niraparib monotherapy to a placebo; accordingly, there are no trials that provide direct evidence comparing niraparib to relevant comparators. Consequently, to enable comparisons of niraparib to the comparators of olaparib and rucaparib, the company performed indirect treatment comparisons (ITCs) leveraging data from the PRIMA, PRIME, ATHENA-MONO², and SOLO-1⁵ trials, which are discussed in Section 3.4.

3.2 Critique of trials of the technology of interest

Two randomised controlled trials (RCTs) provided the clinical evidence base for niraparib as a first-line maintenance therapy in patients with advanced ovarian cancer in the CS. Both the PRIMA³ and PRIME⁴ trials are considered by the EAG to be pivotal trials for niraparib. For both of these trials, the EAG has summarised the trial design, conduct, and analysis below.

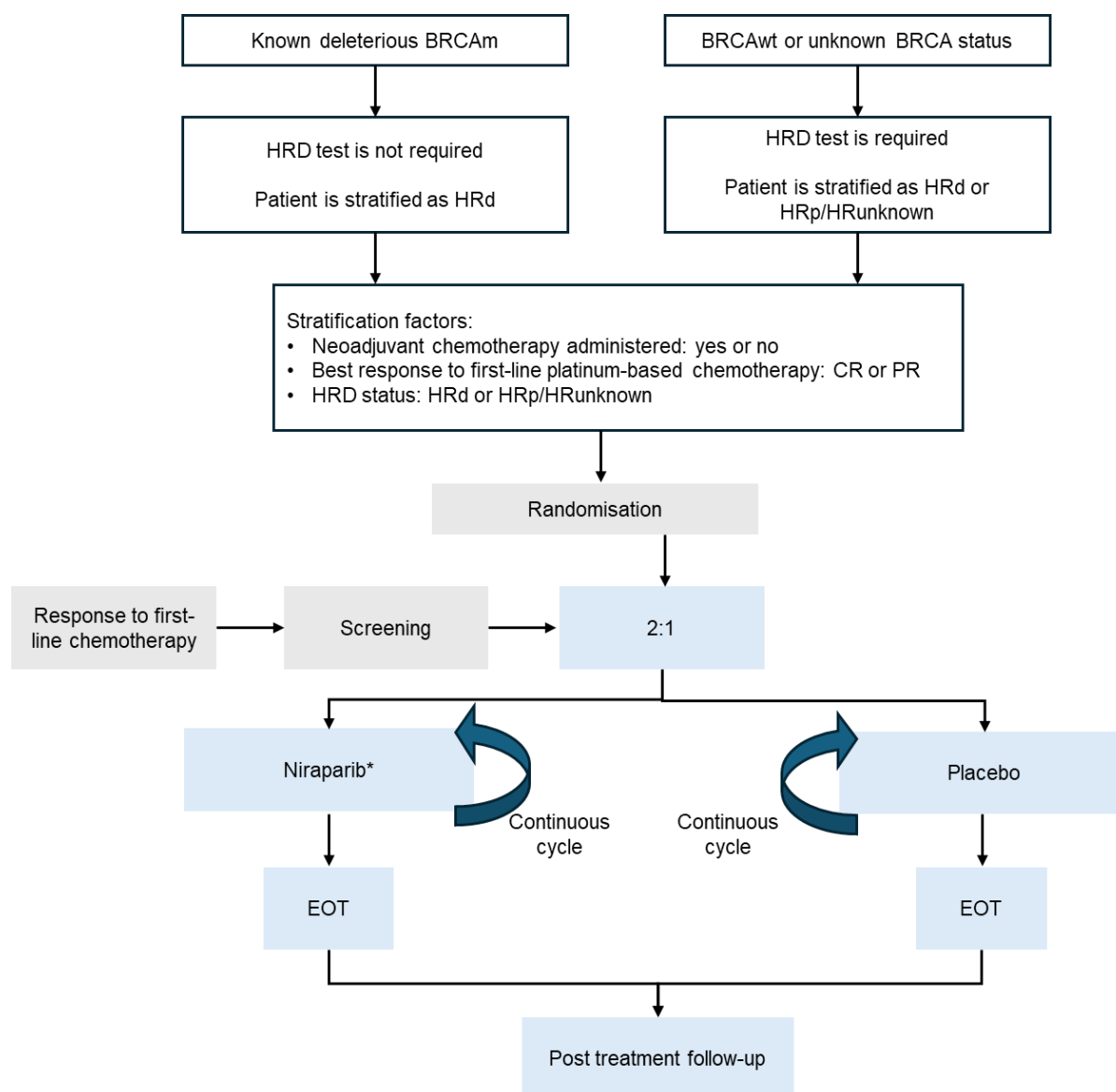
3.2.1 *PRIMA trial*

The PRIMA³ trial was a randomised, double-blind, placebo-controlled, multi-centre, phase III clinical trial to assess the efficacy and safety of niraparib as a maintenance treatment in patients with advanced ovarian cancer who have achieved an effective response after first-line platinum-containing chemotherapy. Within the PRIMA trial, patients were randomised 2:1 to receive either niraparib or placebo. At the start of the trial, all patients in the niraparib arm received a 300mg starting dose. However, a trial amendment occurred on 27 November 2017 to incorporate an individualised starting dose which was dependent on body weight and platelet count, although patients who experienced adverse events were subsequently able to undergo dose reduction. The exact criteria to determine a patient's dose were as follows:

- 300mg QD for patients with a body weight of ≥ 77 kg and a platelet count of $\geq 150,000$ per cubic millilitre; or
- 200mg QD for patients with a body weight of < 77 kg and/or a platelet count of $< 150,000$ per cubic millilitre.

Overall, 475 patients received the fixed starting dose of 300mg, while 258 patients received the individualised starting dose of 200mg. However, the PRIMA³ trial allowed for patients who experienced adverse events to undergo dose modifications regardless of the starting dose. Within the PRIMA trial, patients were treated until disease progression or up to a maximum of 36 months; however, patients who were benefitting from treatment per investigator assessment were eligible to continue receiving treatment beyond 36 months.¹⁷ The trial design for the PRIME⁴ trial is shown below in Figure 2.

Figure 2. Trial design for the PRIMA trial (reproduced from Figure 7 of the CS).



Within the PRIMA³ trial, patients received niraparib, or placebo, once daily in 28-day cycles for a 36-month period or until disease progression. A maximum treatment duration is not specified in the niraparib SmPC, though the company noted that a 36-month stopping rule is typically adhered to in UK clinical practice, though it is unclear as to whether this was assessed using data from the cancer drugs fund (CDF) or expert opinion.

The inclusion criteria for the PRIMA³ trial specified that only ‘high-risk’ patients with high-grade serous or endometrioid tumours, FIGO stage III (excluding stage III with no residual disease after primary debulking surgery) or IV and had received 6-9 cycles of 1L PBC, which had resulted in

complete or partial response were included in the trial. As such, the PRIMA trial excluded stage III patients with a favourable prognosis due to being optimally debulked following upfront primary debulking surgery, termed 'low-risk' patients. As such, the PRIMA trial comprises a narrower population than the NICE final scope. The EAG's clinical experts asserted that the relative treatment benefit of PARPi monotherapies, following a response to platinum-based chemotherapy, was likely to be greater in those high-risk patients included in the PRIMA trial compared to those low-risk patients excluded from the PRIMA trial. The EAG's clinical experts' opinion was supported by data from the ATHENA-MONO² and SOLO-1⁵ trials. Firstly, within the SOLO-1 trial comparing olaparib to placebo, the hazard ratio for progression-free survival reported for the high-risk subgroup was 0.34, which was nearly identical to the reported hazard ratio of 0.33 for the ITT population (i.e., an all-risk population).¹⁸ As such, the SOLO-1 trial suggests that there is a minimal difference in the relative treatment benefit of olaparib compared to placebo, in the high-risk and all-risk populations. Secondly, progression-free survival data from high-risk and low-risk populations from the ATHENA-MONO trial were presented at ESMO 2024.¹⁹ In the high-risk population, the median PFS was 14.8 months and 9.1 months in the rucaparib and placebo arms, respectively; furthermore, the hazard ratio comparing rucaparib to placebo in the high-risk population was 0.47 (95% CI: 0.35 to 0.63). In contrast, in the low-risk population, the median PFS was 31.4 months and 24.0 months in the rucaparib and placebo arms, respectively; furthermore, the hazard ratio comparing rucaparib to placebo in the low-risk population was 0.80 (95% CI: 0.49 to 1.31). Accordingly, data from the ATHENA-MONO trial clearly supports the EAG's clinical expert in demonstrating that the relative treatment benefit of PARPi monotherapies is greater in a high-risk population compared to a low-risk population. Additionally, the EAG notes that the ESMO presentation is not available online. As such, despite contacting multiple authors of the presentation, the EAG has not been able to obtain a copy of the presentation. Instead, the EAG has obtained median PFS and hazard ratio data from a published overview of the presentation.¹⁹ Overall, data from the SOLO-1 and ATHENA-MONO trials supports the views of the EAG's clinical experts with regards to the relative treatment benefit of PARPi monotherapies being the same or greater in a high-risk population compared to a low-risk population.

The EAG notes that while the PRIMA³ trial was stratified for HRD status, it was not stratified for the core subgroup of BRCA status. Accordingly, any subgroup analyses of BRCA status (which is necessary given that the relevant comparators of olaparib and rucaparib are approved in different populations based on BRCA status) would resolve in trial randomization being broken.

Additionally, in the final analysis, the median follow-up in the PRIMA³ trial was 73.9 months and 73.8 months in the niraparib and placebo populations, respectively. As such, the EAG considers the available data to be mature.

Table 17. EAG's summary of the design, conduct and analysis of the PRIMA trial.

Aspect of trial design or conduct	Section of CS in which information is reported	EAG's critique
Randomisation	Section 2.4.3 (Table 8)	Appropriate Randomisation was double-blinded and performed using an interactive web-response system, with stratification according to three factors. Accordingly, the EAG considers the randomisation process to be appropriate.
Concealment of treatment allocation	Section 2.4.3 (Table 8)	Appropriate Treatment identity was hidden using study treatments that had identical appearance, packaging, labelling, and administration schedules. Unblinding only occurred for important medical reasons, with patients who required unblinding discontinued from study treatment but were followed-up until progression or death, withdrawal of consent, or loss to follow-up. Accordingly, the EAG considers the concealment of treatments to be appropriate.
Eligibility criteria	Section 2.3 (Table 5)	Appropriate The EAG's clinical experts considered the inclusion and exclusion criteria for the PRIMA ³ trial to be appropriate.
Blinding	Section 2.4.3 (Table 8)	Appropriate Patients, investigators, and study staff were all blinded to the treatment from the time of randomisation until final database lock.
Baseline characteristics	Section 2.4.1 (Table 7)	Minor concerns There was broadly an alignment between the baseline characteristics of patients in the niraparib and placebo arms of the PRIMA ³ trial. However, the EAG's clinical experts noted that there were some differences in baseline characteristics in the PRIMA trial compared to what would be expected in UK clinical practice. For instance, the EAG's clinical experts noted that neoadjuvant chemotherapy would be expected to be in the range of 70% to 80% in UK clinical practice, compared to 63.2% to 66.3% in the PRIMA trial. Likewise, the EAG's clinical experts noted that in UK clinical practice, there would be a greater proportion of patients with an ECOG score of 1 (~60%) compared to the PRIMA trial. Overall, the EAG has some minor concerns regarding these differences between the baseline characteristics in the PRIMA trial and UK clinical practice.
Stratification factors	Section 2.3 (Table 5)	Moderate concerns The PRIMA ³ trial was stratified by three factors (given below). The EAG is concerned by the absence of BRCA status as a stratification factor given that this factor is used to determine treatment pathways

Aspect of trial design or conduct	Section of CS in which information is reported	EAG's critique
		in UK clinical practice and hence determine relevant comparators for this appraisal. Accordingly, subgroup analyses based on BRCA status would result in randomization being broken. • Clinical response after first-line platinum-based chemotherapy (complete or partial response); • Receipt of neoadjuvant chemotherapy (yes or no); • Homologous recombination status determined by Myriad myChoice HRD test (deficient vs proficient or not determined).
Pre-planned subgroups	Section 2.3 (Table 5)	Moderate concerns The EAG considers that the following pre-planned subgroup analyses are appropriate given that the trial arms were stratified for these factors: • Neoadjuvant chemotherapy (yes or no), according to randomisation; • Neoadjuvant chemotherapy (yes or no), according to eCRF; • Best response to platinum regimen (CR or PR), according to randomisation; • Best response to first platinum regimen (CR or PR), according to eCRF; and • HRD status (HRp, HRd, HRnd). The EAG has some minor concerns regarding these analyses, given that the trial arms were not stratified for these variables: • Age categories (<65 years or ≥65 years); • Region (North America or rest of world); • ECOG performance status (0 or 1); • Stage of disease at initial diagnosis (III or IV); • Primary tumour site (ovarian, primary peritoneal, fallopian tube); • Baseline CA-125 level (≤ULN or >ULN); • Starting dose subgroup (fixed starting dose or individualised starting dose); and • BRCA status (BRCAm, BRCAwt). The EAG notes that subgroup analyses, based on BRCA status, were necessary to compare niraparib to the comparators of olaparib and rucaparib. As such, the EAG notes that such comparisons would result in trial randomisation being broken.
Location	Section 2.3 (Table 5)	Appropriate The PRIMA³ study was conducted in 181 clinical sites in 20 countries in North America and Europe, including the United Kingdom.

Aspect of trial design or conduct	Section of CS in which information is reported	EAG's critique
Statistical analysis		
Sample size and power	Section 2.3 (Table 6)	Appropriate It was calculated that 620 patients (which included a total of 310 patients with HRd) would provide a power of over 90% to detect a significant difference in PFS between the niraparib and placebo groups at a one-sided type I error of 0.025 which would correspond to HRs of 0.65 for the overall population and 0.50 for the HRd population respectively. Accordingly, the EAG has no concerns regarding sample size or power.
Handling of missing data	Section B1.3 (Table 99)	No concerns When performing quality assessments for the RCTs identified through the SLR, it was noted that for the PRIMA³ trial five patients who did not receive either niraparib or placebo after randomisation were excluded from the safety analysis. The EAG notes that this corresponds to the All-Patients Treated definition of the ITT population.
Outcome assessment		Appropriate The PRIMA³ trial considers the following outcomes: • PFS; • OS; • PFS2; • TFST; • FOSI; • EQ-5D-5L; • EORTC-QLQ-C30; • EORTC-QLQ-OV28; and • AEs.
Abbreviations: AE, adverse event; BRCAm, Breast cancer gene mutation; BRCAwt, Breast cancer gene wild type; CA-125, cancer antigen 125; CR, complete response; EAG, External Assessment Group; ECOG, Eastern Cooperative Oncology Group; eCRF, electronic case report form; EORTC-QLQ-C30, European Organisation for the Research and Treatment of Cancer 30-item core quality of life questionnaire; EORTC-QLQ-OV28, European Organisation for the Research and Treatment of Cancer 28-item quality of life questionnaire for ovarian cancer; EQ-5D-5L, European Quality of Life 5 Dimensions 5 Level Version; FOSI, Functional Assessment of Cancer Therapy-Ovarian Symptom Index; HR, hazard ratio; HRd, homologous recombination deficiency; HRd, homologous recombination deficient; HRd, homologous recombination not determined; HRp, homologous recombination proficient; ITT, intention to treat; OS, overall survival; PFS, progression-free survival; PFS2, progression-free survival on the second line of therapy; PR, partial response; SLR, systematic literature review; TFST, time to first subsequent treatment; UK, United Kingdom; ULN, upper limit of normal.		

3.2.2 PRIME trial

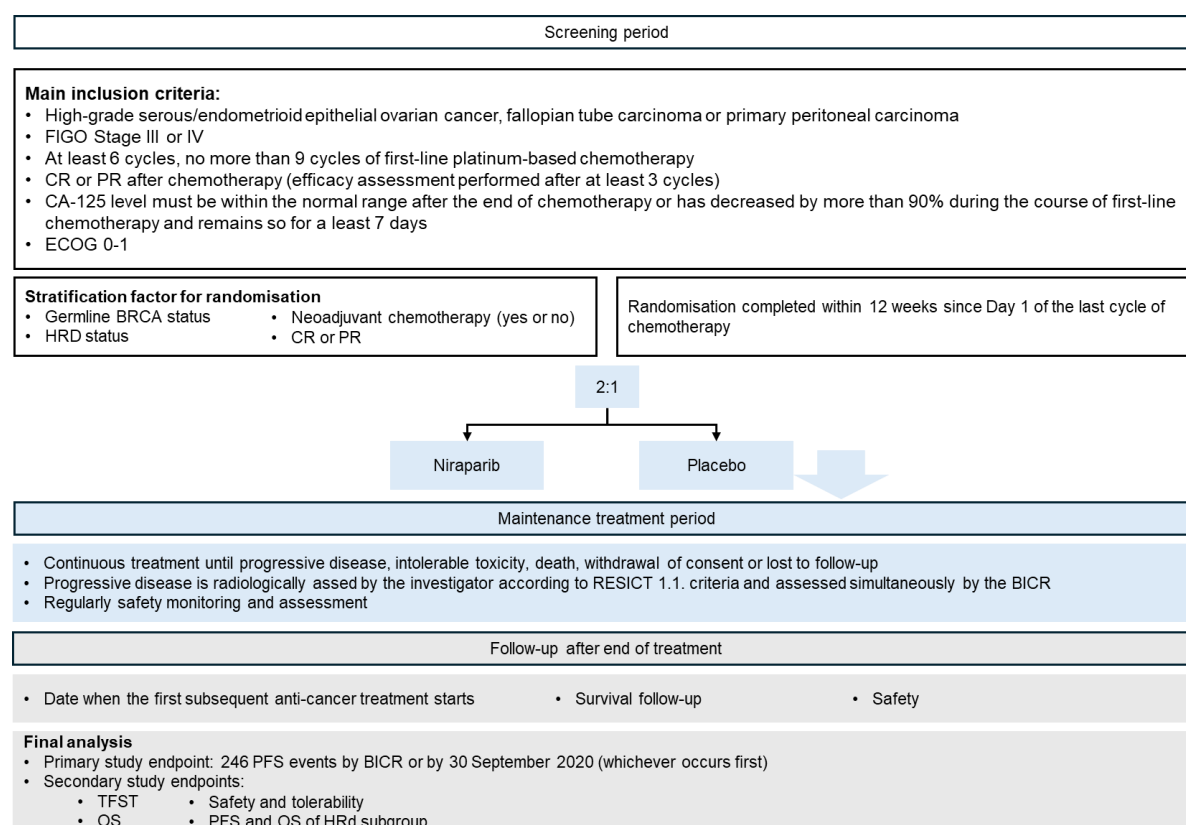
The PRIME⁴ trial was a randomised, double-blind, placebo-controlled, multi-centre, phase III clinical trial to assess the efficacy and safety of niraparib as a maintenance treatment in patients with advanced ovarian cancer who have achieved an effective response after first-line platinum-

containing chemotherapy. Within the PRIME trial, patients were randomised 2:1 to receive either niraparib or placebo. Patients who were randomised to the niraparib arm of the trial received an individualised dose that was dependent on body weight and platelet count. The exact criteria to determine a patient's dose were as follows:

- 300mg QD for patients with a body weight of ≥ 77 kg and a platelet count of $\geq 150,000$ per cubic millilitre; or
- 200mg QD for patients with a body weight of < 77 kg and/or a platelet count of $< 150,000$ per cubic millilitre.

Within the PRIME⁴ trial, patients who experienced adverse events (AEs) caused by the study treatments were able to undergo dose reduction. Patients who received a starting dose of 300mg QD were able to reduce to 200mg QD, and subsequently to 100mg QD. In contrast, patients who received a starting dose of 200mg were only able to have a treatment reduction to 100mg QD. Within the PRIME trial, patients were treated until disease progression, unacceptable toxicity, or up to a maximum of 36 months. The PRIME trial was performed by Zai Lab Co., Ltd. Accordingly, in response to a clarification question, the company stated that due to this trial being performed by an alternative sponsor, the company does not have access to data for this trial beyond that which is publicly available. The trial design for the PRIME trial is shown below in Figure 3.

Figure 3. Trial design for the PRIME trial (reproduced from Figure 15 of the CS).



The company provided an overview of the risk of bias for the PRIME⁴ trial in Table 99 (Appendix B1.3) of the CS. Overall, the company concluded that there was a low risk of bias for the PRIME trial across all attributes considered as part of the Cochrane Risk of Bias Tool.

The EAG contends that there are several issues associated with the PRIME⁴ trial. Firstly, the PRIME trial was conducted at 29 locations within China. Accordingly, the EAG is unclear whether the patient population considered within the PRIME trial is representative of UK clinical practice. Furthermore, within the PRIME trial, both BRCA and HRD status were assessed using an assay performed by the Beijing Genomics Institute (BGI). As noted in the company's advisory board meeting notes,²⁰ this assay is not used within UK clinical practice and is an unvalidated test. As such, the EAG is concerned that, given the unvalidated nature of this assay, it may result in patients being assigned different BRCA and/or HRD status compared to if a different, validated, assay was used. Additionally, the median follow-up in the PRIME trial, at the primary analysis clinical cut off, was 27.5 months (95% CI: 25.3 to 27.6) in the niraparib population and 27.6 months (95% CI: 24.9 to 30.3) in the placebo population. As such, the EAG has concerns regarding the maturity of OS and PFS data from the

PRIME trial. Accordingly, the EAG has concerns that the use of data from the PRIME trial may not be the most appropriate source of data when making comparisons to UK clinical practice.

Within the PRIME⁴ trial, patients received niraparib, or placebo, once daily in 28-day cycles for a 36-month period or until disease progression. A maximum treatment duration is not specified in the niraparib SmPC, though the company noted that a 36-month stopping rule is typically adhered to in UK clinical practice, though it is unclear as to whether this was assessed using data from the CDF or expert opinion.

With regards to baseline characteristics, the EAG's clinical experts noted that the age and ECOG performance status of patients in the PRIME⁴ trial more closely aligned to what would be expected in UK clinical practice compared to the PRIMA³ trial. However, the EAG's clinical experts noted that the proportion of patients receiving neoadjuvant chemotherapy in the PRIME trial was less than what would be expected in UK clinical practice. Furthermore, the EAG's clinical experts noted that the prevalence of patients achieving a complete response, and the proportion of BRCAm patients, was higher than would be expected in UK clinical practice. Overall, the EAG's clinical experts indicated that they considered the population in the PRIMA trial to be more consistent with UK clinical practice than the population of the PRIME trial.

The EAG notes that 32 patients dropped out of the PRIME⁴ trial (27 patients in the niraparib arm and 5 patients in the placebo arm). Censoring rules are provided for the PRIME trial for each outcome, and are considered to be appropriate by the EAG. Additionally, the EAG notes that the proportion of patients who dropped out was far greater in the niraparib arm compared to the placebo arm. Furthermore, within the NICE final scope, two of the key outcomes are PFS2 and response rate; however, these outcomes were not measured within the PRIME trial.

Table 18. EAG's summary of the design, conduct and analysis of the PRIME trial.

Aspect of trial design or conduct	Section of CS in which information is reported	EAG's critique
Randomisation	Section 2.5.3 (Table 19)	Appropriate Randomisation was double-blinded and performed using an interactive web-response system, with stratification according to four factors. Accordingly, the EAG considers the randomisation process to be appropriate.

Aspect of trial design or conduct	Section of CS in which information is reported	EAG's critique
Concealment of treatment allocation	Section 2.5.3 (Table 19)	Appropriate Treatment identity was hidden using study treatments that had identical appearance, packaging, labelling, and administration schedules. Unblinding only occurred for important medical reasons, with patients who required unblinding permanently discontinued from the trial. Accordingly, the EAG considers the concealment of treatments to be appropriate.
Eligibility criteria	2.3 (Table 5)	Appropriate The EAG's clinical experts considered the inclusion and exclusion criteria for the PRIME⁴ trial to be appropriate.
Blinding	Section 2.5.3 (Table 19)	Appropriate Patients, investigators, and study staff were all blinded to the treatment from the time of randomisation until final database lock.
Baseline characteristics	Section 2.5.1 (Table 18)	Minor concerns There was broadly an alignment between the baseline characteristics of patients in the niraparib and placebo arms of the PRIME⁴ trial. However, the EAG's clinical experts noted that there were some differences in baseline characteristics in the PRIME trial compared to what would be expected in UK clinical practice. For instance, the EAG's clinical experts noted that neoadjuvant chemotherapy would be expected to be in the range of 70% to 80% in UK clinical practice, compared to 45.7% to 47.5% in the PRIME trial. Likewise, the EAG's clinical experts noted that the complete response rate was higher than expected in the PRIME trial (with the expectation that complete response rate would be approximately 70%). Finally, the EAG's clinical experts noted that 10% to 15% of patients in UK clinical practice would be expected to be BCRAM, compared to the 31.0% to 33.3% of patients in the PRIME trial. Overall, the EAG has some minor concerns regarding these differences between the baseline characteristics in the PRIME trial and UK clinical practice.
Stratification factors	2.3 (Table 5)	Appropriate The PRIME⁴ trial was stratified by four factors (given below). The EAG considers that these subgroups were appropriate for stratification. • Germline BRCA status; • Clinical response after first-line platinum-based chemotherapy (complete or partial response); • Receipt of neoadjuvant chemotherapy (yes or no); • Homologous recombination status determined by BGI HRD test (deficient vs proficient or not determined).
Pre-planned subgroups	2.3 (Table 5)	Minor concerns The EAG considers that the following pre-planned subgroup analyses are appropriate, given that the trial arms were stratified for these factors:

Aspect of trial design or conduct	Section of CS in which information is reported	EAG's critique
		• HRD status (positive or negative); • Administration of neoadjuvant chemotherapy from CRF (yes or no); • Best overall response following the first-line platinum-based chemotherapy from CRF (CR or PR); • BRCA mutation status from central laboratory (yes or no). The EAG has some minor concerns regarding the following analyses, given that the trial arms were not stratified for these variables: • Age (18-64 years or ≥65 years); • History of intraperitoneal chemotherapy (yes or no); • Satisfactory surgical cytoreduction for ovarian cancer (yes or no); • Tumour staging (III or IV).
Location	2.3 (Table 5)	Significant concerns The PRIME⁴ study considered patients at 29 locations in China. Accordingly, it is unclear whether this patient population is representative of the population in the UK who would be expected to receive niraparib.
Statistical analysis		
Sample size and power	2.3 (Table 6)	Appropriate It was calculated that 246 PFS events would provide a power of 90% to detect a significant difference in PFS between the niraparib and placebo groups at a two-sided significance level of 0.05, assuming a 0.65 HR for PFS in the ITT population. A sample size of 381 patients (254 receiving niraparib and 127 receiving placebo) was determined to be appropriate. Accordingly, the EAG has no concerns regarding sample size or power.
Handling of missing data	Section B1.3 (Table 99)	Appropriate In the PRIME⁴ trial 27 patients in the niraparib arm and 5 in the placebo arm withdrew from treatment. Censoring rules are provided for each outcome, which the EAG considers to be appropriate.
Outcome assessment	Section 2.5.2	Minor concerns The PRIME⁴ trial considers the following outcomes: • PFS; • OS; • TFST; and • AEs. The EAG notes that the NICE final scope list PFS2 and response rate a key outcomes to consider. As such, the EAG has minor concerns that PFS2 and response rate are not reported for the PRIME⁴ trial.

Aspect of trial design or conduct	Section of CS in which information is reported	EAG's critique
Abbreviations: AE, adverse event; BRCAm, Breast cancer gene mutation; CR, complete response; CRF, case report form; EAG, External Assessment Group; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; HRD, homologous recombination deficiency; ITT, intention to treat; OS, overall survival; PFS, progression-free survival; PFS2, progression-free survival on the second line of therapy; PR, partial response; TFST, time to first subsequent treatment; UK, United Kingdom.		

3.3 Critique of the clinical effectiveness analysis and interpretation

Each of the core outcomes considered in the PRIMA¹⁷ and PRIME⁴ trials are discussed in the sections below. When drawing comparisons between the PRIMA and PRIME trials, there are a number of differences between the trials that are important to consider. Firstly, the PRIMA trial solely comprises high-risk patients, while the PRIME trial comprises an all-risk patient population. The EAG's clinical experts have asserted that high-risk patients would be expected to have a greater relative treatment benefit compared to low-risk patients. Likewise, the EAG has identified evidence from clinical trials to support this assertion (Section 3.4.1). Accordingly, the EAG anticipates that this difference would result in greater relative efficacy estimates for niraparib in the PRIMA trial compared to the PRIME trial. Additionally, the PRIME trial was solely conducted in China while the PRIMA trial was conducted in multiple countries across the globe; however, it is unclear how this difference would be expected to impact comparisons between the PRIMA and PRIME trials. Furthermore, the PRIME study used an unvalidated assay to assess HRD status; however, it is unclear how this difference would be expected to impact comparisons between the PRIMA and PRIME trials.

3.3.1 Primary outcome

3.3.1.1 Investigator assessed progression-free survival

Investigator-assessed progression-free survival (PFS-INV) was the primary outcome in both the PRIMA¹⁷ and PRIME⁴ trials and was used in the company's economic model. For the PRIMA trial, PFS was reported for the ITT population and multiple subgroups based on HRD status and BRCA status. The statistical analysis plan for the PRIME trial indicated that PFS-INV was measured, although the EAG is only aware of data for this endpoint being available for the ITT population.⁴ In response to a clarification question, the company confirmed that as the PRIME trial was performed by a different company (Zai Ltd), the company does not have access to IPD and subsequently is unable to provide any further information on the PRIME trial that is not published. Hazard ratios for PFS for all available subgroups, from the PRIMA and PRIME trials, are shown in Table 19.

Table 19. Hazard ratios reported for investigator-assessed progression-free survival from the PRIMA and PRIME trials.

Population	PRIMA hazard ratio (95% CI)	PRIME hazard ratio (95% CI)
ITT		0.47 (0.36 to 0.62)
HRd		Not reported
BRCAm		Not reported
HRd/BRCAwT		Not reported
BRCAwT		Not reported
HRp/BRCAwT		Not reported

Abbreviations: BRCAm, Breast cancer gene mutation; BRCAwT, Breast cancer gene wild type; CI, confidence interval; HRd, homologous recombination deficient; HRp, homologous recombination proficient; ITT, intention to treat.

^a As reported at the final data cut-off at 8th April 2024.

For all subgroups from the PRIMA¹⁷ trial, the reported hazard ratios indicated a statistically significant improvement in PFS-INV for niraparib compared to placebo. However, the EAG notes that for the HRd/BRCAwT subgroup, the 95% CI was reported as 1.00; as such it is unclear whether this hazard ratio is statistically significant. The EAG notes that there was considerable variation in the magnitude of the reported hazard ratios across subgroups. The BRCAm population [REDACTED] had the largest improvement in PFS-INV for niraparib, compared to placebo. In contrast, the BRCAwT population [REDACTED] had the smallest improvement in PFS-INV for niraparib compared to placebo.

For the PRIME⁴ trial, PFS-INV was only reported for the ITT population. However, when comparing hazard ratios for the ITT population across the trials, the PRIME trial reported a substantially greater improvement in PFS-INV (0.47; 95% CI: 0.36 to 0.62) compared to the PRIMA¹⁷ trial. The EAG notes that there was a substantially greater proportion of patients who were HRd in the PRIME ITT population compared to the PRIMA ITT population. As HRd status has been shown to be a key treatment effect modifier¹¹, the EAG notes that this difference in the prevalence of HRd patients between trials may explain the difference in the relative improvement in PFS-INV for niraparib, compared to placebo, between the trials. However, the EAG notes that the HRD assay implemented in the PRIME trial has not been validated. Given these differences in baseline characteristics, the EAG cautions against making direct naïve comparisons between the results of PRIMA and PRIME trials due to concerns that they may not be directly comparable. Such caution also applies to the subgroup analyses and secondary outcomes considered below.

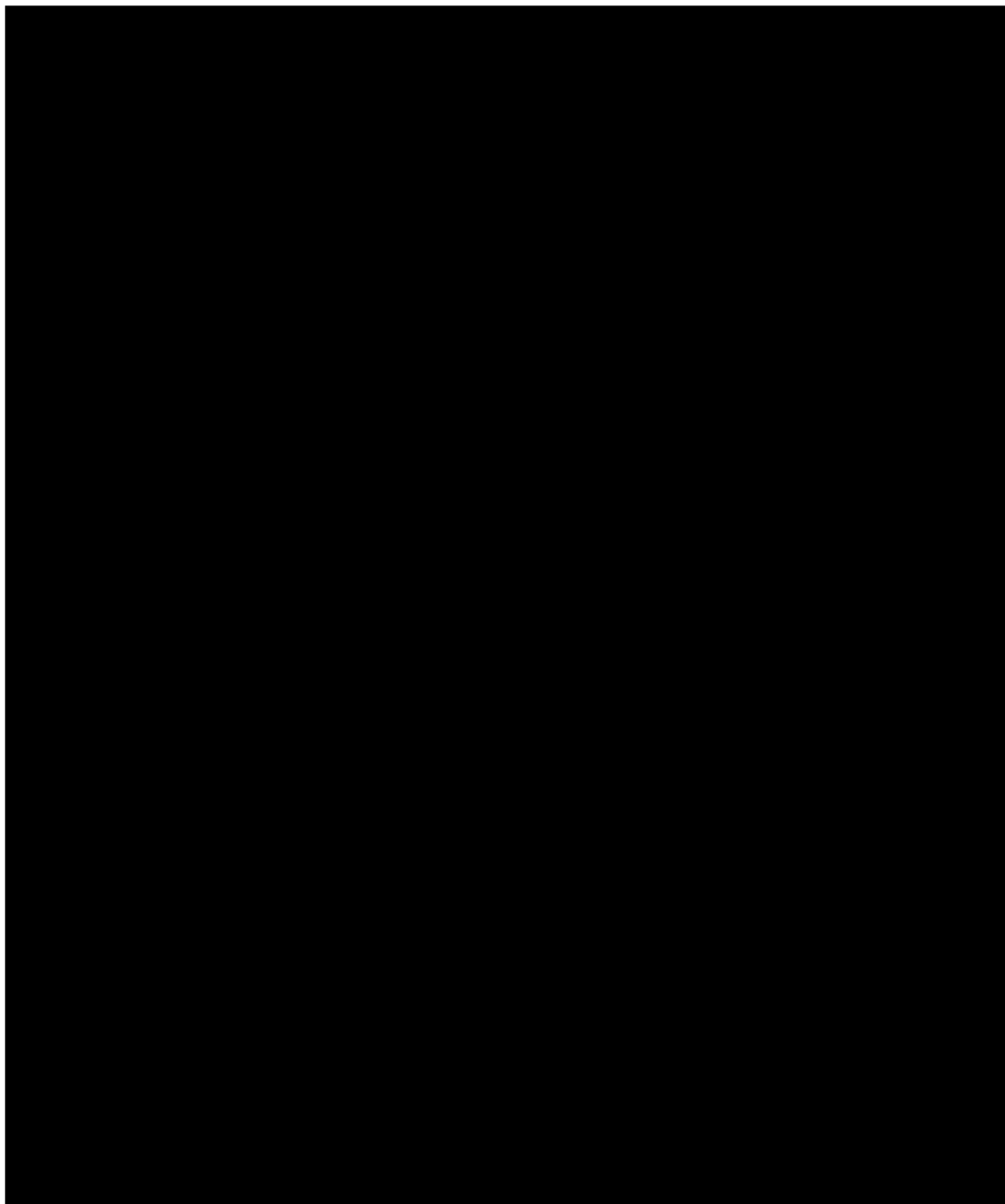
3.3.1.1.1 Additional subgroups

Alongside subgroups based on HRD and BRCA status, the company also provided additional subgroup analyses for PFS-INV, for the PRIMA trial, for the following variables:

- Age;
- Race;
- Eastern Cooperative Oncology Group (ECOG) Performance Score (PS);
- Stage of disease at initial diagnosis;
- Primary tumour site;
- Neoadjuvant chemotherapy at randomisation;
- Best response to first platinum regimen at randomisation;
- Neoadjuvant chemotherapy from electronic case report form;
- Best response to first platinum regimen from electronic case report form;
- Baseline CA-125 level;
- Region; and
- Starting dose cohort.

The results of these additional subgroup analyses are provided in Figure 4. The EAG notes that the hazard ratios for all subgroups were in favour of niraparib, compared to placebo. While the majority of hazard ratios were statistically significant, there were several hazard ratios with 95% confidence intervals that overlapped 1, although these hazard ratios typically corresponded to analyses with smaller sample sizes.

Figure 4. Forest plot of investigator-assessed progression-free survival by subgroup, using data from the final analysis of the PRIMA trial with a cut-off 8 April 2024 (reproduced from Figure 14 of CS).



3.3.1.2 *Blinded independent central review progression-free survival*

Although PFS-BICR was not considered within the economic model, it is presented here. Available hazard ratios for PFS-BICR are provided in Table 20.

Table 20. Hazard ratios reported for blinded independent central review progression-free survival from the PRIMA and PRIME trials.

Population	PRIMA hazard ratio (95% CI)	PRIME hazard ratio (95% CI)
ITT		0.45 (0.34 to 0.6)
HRd		0.48 (0.34 to 0.68)
BRCAm	0.40 (0.27 to 0.62)	0.40 (0.23 to 0.68)
HRd/BRCAwT	0.50 (0.31 to 0.83)	0.58 (0.36 to 0.93)
BRCAwT	Not reported	0.48 (0.34 to 0.67)
HRp/BRCAwT	0.68 (0.51 to 1.43)	0.41 (0.22 to 0.75)

Abbreviations: BRCAm, Breast cancer gene mutation; BRCAwT, Breast cancer gene wild type; CI, confidence interval; HRd, homologous recombination deficient; HRp, homologous recombination proficient; ITT, intention to treat.

^a As reported at the data cut-off 17 May 2019.

For all subgroups from the PRIME⁴ trial, the reported hazard ratios indicated a statistically significant improvement in PFS-BICR for niraparib compared to placebo. The EAG notes that there was some variation in the magnitude of the reported hazard ratios across subgroups. The BRCAm population (0.40; 95% CI: 0.23 to 0.68) had the largest improvement in PFS-BICR for niraparib, compared to placebo. In contrast, the HRd/BRCAwT population (0.58; 95% CI: 0.36 to 0.93) had the smallest improvement in PFS-BICR for niraparib compared to placebo.

For the PRIMA¹⁷ trial, a statistically significant improvement in PFS-BICR was reported for the ITT, HRd, BRCAm, and HRd/BRCAwT populations. However, a statistically non-significant improvement in PFS-BICR was reported for HRp/BRCAwT population.

3.3.1.2.1 Of the two populations for which it is possible to compare across the PRIMA¹⁷ and PRIME⁴ trials, a substantially greater improvement in PFS-BICR was reported in the PRIME trial, compared to the PRIMA trial, for the ITT population. In contrast, for the HRd population, a similar improvement in PFS-BICR was reported in both the PRIMA and PRIME trials. The EAG notes that the PRIME trial comprised a greater proportion of HRd patients than the PRIMA trial. As HRd status has been shown to be a key treatment effect modifier, this difference in the prevalence of HRd patients between the trials may partially explain the difference in results between the PRIMA and PRIME trials for the ITT population.

Additional subgroups

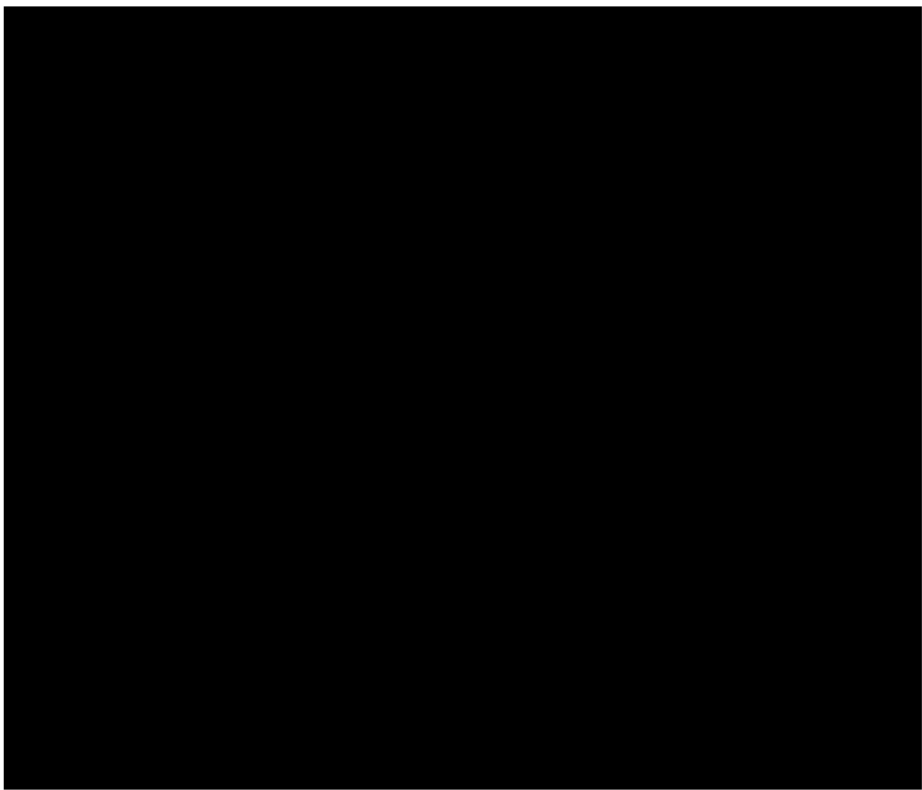
Alongside subgroups based on HRD and BRCA status, the company also provided additional subgroup analyses for PFS-BICR for the PRIME⁴ trial, for the following variables:

- Age;
- Intraperitoneal chemotherapy;
- Cytoreductive surgery outcome;

- Stage of disease at diagnosis;
- Neoadjuvant chemotherapy; and
- Response to platinum-based chemotherapy.

The results of these additional subgroup analyses are provided in Figure 5. The EAG notes that the hazard ratios for all subgroups were statistically significant and in favour of niraparib, compared to placebo. The single exception to this was patients with a missing cytoreductive surgery outcome, though this likely due, in part, to the minimal sample sizes for this analysis.

Figure 5. Forest plot of blinded independent central review progression-free survival, from the PRIME trial, by subgroup (reproduced from Figure 19 of CS).



3.3.2 Secondary outcomes

3.3.2.1 Overall survival

Overall survival (OS) was measured in both the PRIMA¹⁷ and PRIME⁴ studies. For both studies, OS was reported for the ITT population and multiple subgroups based on HRD status and BRCA status, as shown in Table 21.

Table 21. Hazard ratios reported for overall survival from the PRIMA and PRIME trials.

Population	PRIMA hazard ratio (95% CI)	PRIME hazard ratio (95% CI)
ITT		0.63 (0.38 to 1.03)
HRd		0.88 (0.43 to 1.78)
BRCAm		Not reported
HRd/BRCAwT		Not reported
BRCAwT		Not reported
HRp/BRCAwT		Not reported

Abbreviations: BRCAm, Breast cancer gene mutation; BRCAwT, Breast cancer gene wild type; CI, confidence interval; HRd, homologous recombination deficient; HRp, homologous recombination proficient; ITT, intention to treat.

^a As reported at the final data cut-off 8 April 2024.

For all available hazard ratios, the associated 95% CIs overlapped 1, indicating that there was no statistically significant difference in OS between the niraparib and placebo arms for any subgroup in either trial. All considered populations were reported as having a hazard ratio that favoured niraparib, with the notable exceptions of the ITT and BRCAwt populations in the PRIMA¹⁷ trial. For the PRIME⁴ trial, the EAG was unable to identify hazard ratios for the BRCAm, HRd/BRCAwt, BRCAwt, and HRp/BRCAwt populations. Hazard ratios for the ITT population were reported for both the PRIMA and PRIME trials, with the hazard ratio for the PRIMA trial exceeding 1 [REDACTED] while the hazard ratio for the ITT population in the PRIME trial was substantially lower [REDACTED]. Likewise, hazard ratios were reported for the HRd population for both the PRIMA and PRIME trials, with the hazard ratio for the PRIMA trial close to 1 [REDACTED] while the hazard ratio for the ITT population in the PRIME trial was lower [REDACTED]. As such, for both the ITT and HRd populations, the hazard ratios reported by the PRIME trial indicate a greater OS benefit of niraparib than that reported for the PRIMA trial.

3.3.2.1.1 Additional subgroups

Alongside subgroups based on HRD and BRCA status, the company also provided additional subgroup analyses for OS, the PRIMA¹⁷ trial, for the following variables:

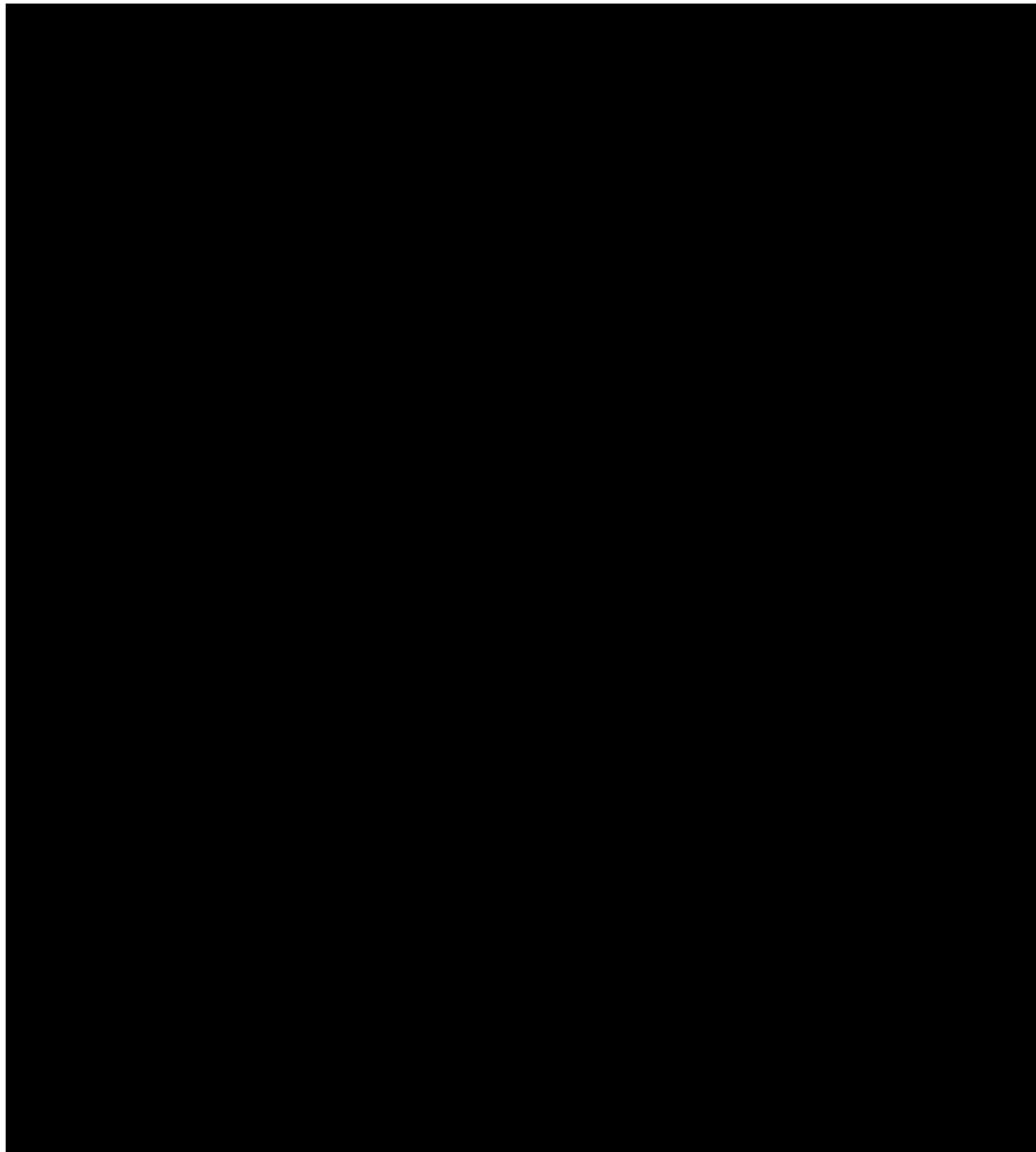
- Dose regime;
- Age;
- Region;
- Eastern Cooperative Oncology Group (ECOG) Performance Score (PS);
- International Federation of Gynaecology and Obstetrics (FIGO) stage;
- Receipt of neoadjuvant chemotherapy (NACT); and
- Response to first line platinum-based chemotherapy.

The results of these additional subgroup analyses are provided in Figure 6. For all but one of the performed subgroup analyses, the reported hazard ratios were statistically non-significant. The single exception was the hazard ratio for patients with FIGO stage IV [REDACTED]

[REDACTED]. With regards to this subgroup analysis, the EAG is concerned that the reported hazard ratio indicates that FIGO stage IV patients receiving niraparib have substantially worse OS compared to those patients who received placebo. In response to a clarification question, the company noted that this analysis was subject to small sample sizes. Furthermore, the company noted that there were small imbalances in some baseline characteristics between the FIGO stage IV

niraparib and placebo arms but noted that these were unlikely to account for the reported difference in OS in this population. Overall, the EAG does not consider that the better OS in FIGO stage IV patients who received placebo, compared to niraparib, has been fully explained.

Figure 6. Forest plot of overall survival by subgroup, using data from the final analysis of the PRIMA trial with a cut-off 8 April 2024 (reproduced from Figure 50 of CS).



The EAG notes that equivalent subgroup analyses were not reported for the PRIME⁴ trial.

3.3.2.2 Progression-free survival on the second line of therapy

Progression-free survival on the second line of therapy was not measured in the PRIME⁴ trial. However, PFS2 was measured in the PRIMA³ trial for all subgroups. The available data for PFS2 are shown in Table 22.

Table 22. Hazard ratios reported for progression-free survival on the second line of therapy from the PRIMA and PRIME trials.

Population	PRIMA hazard ratio (95% CI)	PRIME hazard ratio (95% CI)
ITT		Not reported
HRd		Not reported
BRCAm		Not reported
HRd/BRCAwT		Not reported
BRCAwT		Not reported
HRp/BRCAwT		Not reported

Abbreviations: BRCAm, Breast cancer gene mutation; BRCAwT, Breast cancer gene wild type; CI, confidence interval; HRd, homologous recombination deficient; HRp, homologous recombination proficient; ITT, intention to treat.

^a As reported at the final data cut-off 8 April 2024.

For all subgroups from the PRIMA¹⁷ trial, the reported hazard ratios indicated a statistically nonsignificant improvement in PFS2 for niraparib compared to placebo. The EAG notes that there was some variation in the magnitude of the reported hazard ratios across subgroups. The HRd population (0.87; 95% CI: 0.656 to 1.165) had the largest improvement in PFS2 for niraparib, compared to placebo. In contrast, the ITT population (0.96; 95% CI: 0.794 to 1.167) had the smallest, statistically nonsignificant, improvement in PFS2 for niraparib compared to placebo.

3.3.2.3 Time to first subsequent treatment

Table 23. Hazard ratios reported for time to first subsequent treatment from the PRIMA and PRIME trials.

Population	PRIMA hazard ratio (95% CI)	PRIME hazard ratio (95% CI)
ITT		0.45 (0.34 to 0.59)
HRd		Not reported
BRCAm		Not reported
HRd/BRCAwT		Not reported
BRCAwT		Not reported
HRp/BRCAwT		Not reported

Abbreviations: BRCAm, Breast cancer gene mutation; BRCAwT, Breast cancer gene wild type; CI, confidence interval; HRd, homologous recombination deficient; HRp, homologous recombination proficient; ITT, intention to treat.

^a As reported at the final data cut-off 8 April 2024.

For all subgroups from the PRIMA¹⁷ trial, the reported hazard ratios indicated an improvement in TFST for niraparib compared to placebo. However, these hazard ratios were only statistically

significant for the ITT, HRd, and BRCAm populations. The EAG notes that there was considerable variation in the magnitude of the reported hazard ratios across subgroups. The BRCAm population (0.45; 95% CI: 0.319 to 0.621) had the largest improvement in TFST for niraparib, compared to placebo. In contrast, the BRCAwt population (0.90; 95% CI: 0.724 to 1.123) had the smallest, statistically nonsignificant, improvement in TFST for niraparib compared to placebo.

For the PRIME⁴ trial, TFST was only reported for the ITT population. However, when comparing hazard ratios for the ITT population across the trials, the PRIME trial reported a substantially greater improvement in TFST (0.45; 95% CI: 0.34 to 0.59) compared to the PRIMA¹⁷ trial (0.74; 95% CI: 0.622 to 0.887). The EAG notes that there was a substantially greater proportion of patients who were HRd in the PRIME ITT population compared to the PRIMA ITT population. As HRd status has been shown to be a key treatment effect modifier, the EAG notes that this difference in the prevalence of HRd patients between trials may explain the difference in the relative improvement in TFST for niraparib, compared to placebo, between the trials. However, the EAG notes that the HRD assay implemented in the PRIME trial has not been validated.

3.3.2.4 *Response rate*

Within the NICE final scope, response rate is listed as key outcome. Likewise, in the decision problem section of the CS, the company has stated that response rate was an outcome considered by the company. However, the EAG is not aware of response rate being presented in the company's submission or being available in publications associated with the PRIMA¹⁷ and PRIME⁴ trials. In contrast, the EAG is aware that the NICE appraisal of rucaparib (TA1055¹) included data for response rate (namely overall response rate and duration of response).

3.3.3 *Safety*

Within the economic model, the company used data from the observational MONITOR-UK⁶ study. However, within the EAG's base case, the EAG has incorporated data from the PRIMA¹⁷ trial as this is in line with the effectiveness data informing the model (see Section 4.2.6 for further detail). Within the CS, the company presented the incidence of grade 3+ adverse events for the both the MONITOR-UK study and PRIMA trial, alongside data from the ATHENA-MONO² trial (which compared rucaparib to placebo), and SOLO-1⁵ trial (which compared olaparib to placebo). The incidence of grade 3+ events across these studies are shown in Table 24.

Table 24. Grade 3+ adverse event incidence (reproduced from Table 42 of company's submission).

	MONITOR-UK Niraparib (N = 165)	PRIMA Niraparib (N = 484)	ATHENA-MONO Rucaparib (N = 425)	SOLO-1 Olaparib (N=260)
Anaemia	9.8%		28.7%	21.9%
Hypertension	15.2%		0.0%	0.0%
Increased ALT/AST	0.0%		10.6%	0.0%
Neutropenia	0.0%		14.6%	8.5%
Neutrophil count decreased	7.7%		0.0%	0.0%
Platelet count decreased	11.0%		0.0%	0.0%
Thrombocytopenia	0.0%		7.1%	0.8%

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

There were considerable differences in the incidence rates of grade 3+ adverse events between the MONITOR-UK⁶ and PRIMA¹⁷ studies for patients receiving niraparib. [REDACTED]

[REDACTED]

Comparing grade 3+ adverse event incidence from the ATHENA-MONO² trial to those from MONITOR-UK⁶ and PRIMA¹⁷, there are considerable differences between the trials. Firstly, the ATHENA-MONO trial was the only trial in which patients (10.6%) experienced increased ALT/AST. However, in contrast to the MONITOR-UK and PRIMA trials, no patients in the ATHENA-MONO trial experienced hypertension, decreased neutrophil count, or decreased platelet count. While the incidence of anaemia and neutropenia in the ATHENA-MONO trial was similar to that in the PRIMA trial, it was considerably greater than that reported in the MONITOR-UK trial. Finally, the incidence of thrombocytopenia in the ATHENA-MONO trial was considerably lower than that in the PRIMA trial, but greater than that reported in the MONITOR-UK trial.

Comparing grade 3+ adverse event incidence from the SOLO-1⁵ trial to those from MONITOR-UK⁶ and PRIMA¹⁷, there are considerable differences between the trials. In contrast to the MONITOR-UK and PRIMA trials, no patients in the SOLO-1 trial experienced hypertension, decreased neutrophil count, or decreased platelet count. The incidence of anaemia (21.9%) and neutropenia (8.5%) in the SOLO-1 trial was considerably lower than that in the PRIMA trial, it was considerably greater than

that reported in the MONITOR-UK trial. [REDACTED]

[REDACTED]

[REDACTED]

Based on the results provided by the company in the CS, the EAG notes that niraparib may be associated with increased incidence of anaemia, hypertension, decreased neutrophil count, decreased platelet count, and thrombocytopenia compared to both rucaparib and olaparib. This is in line with the EAG's clinical experts opinion, who noted patients experienced greater AEs with niraparib than olaparib, in their clinical experience. However, niraparib is likely associated with a reduced incidence of increased ALT/AST compared to rucaparib and an approximately similar incidence of neutropenia compared to both rucaparib and olaparib.

3.3.4 *Health-related quality of life*

Health-related quality of life (HRQoL) data were collected during PRIMA³ using the EuroQol five-dimension, five-level (EQ-5D-5L) questionnaire. EQ-5D(-5L) data were collected every 8 weeks for 56 weeks, then every 12 weeks while on study treatment. During the follow-up period, assessments occurred at 4, 8, 12, and 24 weeks. The resulting mean EQ-5D values used in the company's economic model have been discussed further in (Section 4.2.7).

3.4 Critique of indirect treatment comparisons

3.4.1 *Trials informing the indirect treatment comparison*

Following the completion of the systematic literature review (SLR), the company identified eight studies relevant for first line maintenance in advanced ovarian cancer. Of the eight trials, four were considered appropriate for the ITCs. Of these trials, two (PRIMA³ and PRIME⁴) compared niraparib to placebo, one (SOLO-1⁵) compared olaparib to placebo, and one (ATHENA-MONO²) compared rucaparib to placebo. Of the four trials considered inappropriate for inclusion for the ITCs, one was excluded due to being a single-arm Phase 2 trial with a limited sample size (Oda et al. 2024¹⁴). The other three trials were excluded due to the irrelevant comparators of seneparib (FLAMES¹³), niraparib plus bevacizumab (OVARIO¹⁵), and olaparib plus bevacizumab (PAOLA-1¹⁶). Of the excluded studies, the EAG notes that olaparib plus bevacizumab was considered a relevant comparator for the NICE appraisal of rucaparib (TA1055¹) with ITCs performed using data from the ATHENA-MONO and PAOLA-1 trials. Furthermore, the EAG notes that within the company's advisory board meeting

minutes, the company stated that ITCs for PFS comparing niraparib to olaparib plus bevacizumab, using data from PAOLA-1, were being performed, although these ITCs were not presented in the CS.

Of the included trials, all four trials had a common comparator of placebo. As such, it was possible to perform indirect treatment comparisons to compare niraparib to both olaparib and rucaparib. However, olaparib and rucaparib have received NICE recommendations in distinct populations. Olaparib has been approved in patients with BRCAm, while rucaparib has received a recommendation in patients with BRCAwt. Accordingly, given the differences in recommended populations, it is not possible to perform a single analysis (e.g., network meta-analysis) that compares niraparib to both olaparib and rucaparib. Accordingly, the company performed individual Bucher analyses for comparisons of niraparib to olaparib and niraparib to rucaparib, with separate Bucher analyses performed for each subgroup. The EAG considers the use of Bucher analyses in this context to be appropriate.

When performing Bucher analyses, the company compared niraparib to olaparib using data from the BRCAm population from the PRIMA³ trial and the high-risk BRCAm population from the SOLO-1⁵ trial. In contrast, the company compared niraparib to rucaparib using data from the PRIME⁴ and ATHENA-MONO² trials. Accordingly, comparisons of the baseline characteristics for the BRCAm population from the PRIMA trial and the high-risk BRCAm population from the SOLO-1 trial and the ITT populations from PRIME and ATHENA-MONO trials are shown in Table 25 and Table 26, respectively.

Table 25. Baseline characteristics BRCAm population from the PRIMA trial and the high-risk BRCAm population from the SOLO-1 trial.

	PRIMA		SOLO-1	
	Niraparib	Placebo	Olaparib (n=146)	Placebo (n=73)
Age (years), median (range)			54 (29–82)	54 (35–84)
Race, n (%)				
White			NR	NR
Black			NR	NR
Asian			NR	NR
Other			NR	NR
FIGO stage, n (%)				
Stage III			106 (72.6)	47 (64.3)
Stage IV			40 (27.4)	26 (35.6)
ECOG PS, n (%)				
0			107 (73.3)	54 (74.0)
1			39 (26.7)	19 (26.0)

Primary tumour location, n (%)				
Ovary			NR	NR
Fallopian tube			NR	NR
Primary peritoneal			NR	NR
Histology, n (%)				
Serous	NR	NR	NR	NR
Endometrioid	NR	NR	NR	NR
Clear cell	NR	NR	NR	NR
Mixed	NR	NR	NR	NR
Other	NR	NR	NR	NR
BRCA mutation, n (%)				
Yes			260 (100.0)	131 (100.0)
No			0 (0.0)	0 (0.0)
HRD status, n (%)				
HRd			260 (100.0)	131 (100.0)
HRp			0 (0.0)	0 (0.0)
Prior bevacizumab use, n (%)				
Yes	NR	NR	NR	NR
No	NR	NR	NR	NR
Response to 1L chemotherapy, n (%)				
Complete response			107 (73.3)	54 (74.0)
Partial response			39 (26.7)	19 (26.0)
No evidence of disease			0 (0.0)	0 (0.0)
CA-125 level, n (%)				
≤ULN			133 (91.1)	66 (90.4)
>ULN			13 (8.9)	7 (9.6)
Receipt of NACT, n (%)				
Yes			94 (64.4)	43 (58.9)
No			NR	NR
Timing of surgery, n (%)				
PCS/PDS or upfront	NR	NR	NR	NR
ICS/IDS	NR	NR	94 (64.4)	43 (58.9)

Abbreviations: 1L, first-line; CA-125, cancer antigen 125; ECOG-PS, Eastern Cooperative Oncology Group-performance status; FIGO, International Federation of Gynaecology and Obstetrics; HRD, homologous recombination deficiency; HRd, homologous recombination deficient; HRp, homologous recombination proficient; ICS, interval cytoreductive surgery; IDS, interval debulking surgery; ITT, intent-to-treat; NACT, neoadjuvant chemotherapy; PCS, primary cytoreductive surgery; PDS, primary debulking surgery; NR, not reported; ULN, upper limit of normal.

Table 26. Baseline characteristics for the PRIME and ATHENA-MONO trials for the ITT population.

	PRIME		ATHENA-MONO	
	Niraparib (n=255)	Placebo (n=129)	Rucaparib (n=427)	Placebo (n=111)
Age (years), median (range)	53 (32-77)	54 (33-77)	61 (30-83)	61 (31-80)
Race, n (%)				
White	NR	NR	328 (76.8)	87 (78.4)
Black	NR	NR	NR	NR
Asian	255 (100.0)	129 (100.0)	80 (18.7)	16 (14.4)
Other	NR	NR	11 (2.6)	6 (5.4)
FIGO stage, n (%)				
Stage III	182 (71.4)	94 (72.9)	323 (75.6)	78 (70.3)
Stage IV	73 (28.6)	35 (27.1)	104 (24.4)	33 (29.7)
ECOG PS, n (%)				
0	98 (38.4)	52 (40.3)	295 (69.1)	76 (68.5)
1	157 (61.6)	77 (58.7)	131 (30.7)	35 (31.5)
Primary tumour location, n (%)				
Ovary	229 (89.8)	117 (90.7)	336 (78.7)	85 (76.6)
Fallopian tube	19 (7.5)	9 (7)	50 (11.7)	18 (16.2)
Primary peritoneal	7 (2.7)	3 (2.3)	41 (9.6)	8 (7.2)
Histology, n (%)				
Serous	253 (99.2)	128 (99.2)	384 (89.9)	106 (95.5)
Endometrioid	2 (0.8)	0 (0.0)	13 (3.0)	1 (0.9)
Clear cell	NR	NR	13 (3.0)	2 (1.8)
Mixed	NR	NR	10 (2.3)	1 (0.9)
Other	0 (0.0)	1 (0.8)	7 (1.6)	1 (0.9)
BRCA mutation, n (%)				
Yes	85 (33.3)	40 (31.0)	91 (21.3)	24 (21.6)
No	NR	NR	336 (78.8)	87 (78.4)
HRD status, n (%)				
HRd	170 (66.7)	87 (67.4)	185 (43.3)	49 (44.1)
HRp	60 (23.5)	25 (19.4)	189 (44.3)	49 (44.1)
Prior bevacizumab use, n (%)				
Yes	NR	NR	84 (19.7)	12 (10.8)
No	NR	NR	NR	NR
Response to 1L chemotherapy, n (%)				
Complete response	212 (83.1)	103 (79.8)	73 (17.1)	11 (9.9)
Partial response	43 (16.9)	26 (20.2)	76 (17.8)	22 (19.8)
No evidence of disease	NR	NR	224 (52.5)	64 (57.7)
CA-125 level, n (%)				
≤ULN	252 (98.8)	128 (99.2)	371 (86.9)	100 (90.1)

>ULN	3 (1.2)	1 (0.8)	56 (13.1)	11 (9.9)
Receipt of NACT, n (%)				
Yes	NR	NR	218 (51.1)	57 (51.4)
No	NR	NR	NR	NR
Timing of surgery, n (%)				
PCS/PDS or upfront	NR	NR	209 (48.9)	54 (48.6)
ICS/IDS	NR	NR	218 (51.1)	57 (51.4)

Abbreviations: 1L, first-line; CA-125, cancer antigen 125; ECOG-PS, Eastern Cooperative Oncology Group-performance status; FIGO, International Federation of Gynaecology and Obstetrics; HRD, homologous recombination deficiency; HRd, homologous recombination deficient; HRp, homologous recombination proficient; ICS, interval cytoreductive surgery; IDS, interval debulking surgery; ITT, intent-to-treat; NACT, neoadjuvant chemotherapy; PCS, primary cytoreductive surgery; PDS, primary debulking surgery; NR, not reported; ULN, upper limit of normal.

As shown in Table 25, there was considerable alignment between the baseline characteristics of the BRCAm population from the PRIMA³ trial and the high-risk BRCAm population from the SOLO-1⁵ trial. However, there were some differences in FIGO stage and ECOG PS between the studies. For the PRIMA study, [REDACTED] of patients in the niraparib arm were FIGO stage III compared to [REDACTED] in the placebo arm, a difference of [REDACTED] which also applied to the prevalence of FIGO stage IV patients. As previously noted, subgroup analyses from the PRIMA trial indicated that FIGO stage IV patients who received niraparib had substantially worse OS compared to patients received placebo [REDACTED] [REDACTED]. Likewise, a recent publication noted that FIGO stage III patients were associated with a greater likelihood of long-term PFS compared to FIGO stage IV patients.¹¹ Accordingly, the EAG is concerned that this imbalance in FIGO stage III and IV patients between the arms of the PRIMA study may bias estimates from the PRIMA study in favour of niraparib.

Additionally, there was a 8.3% difference in the prevalence of FIGO stage III patients in the SOLO-1⁵ trial. Additionally, when comparing data between the PRIMA³ and SOLO-1 trials, the prevalence of FIGO stage III patients considerably varied from [REDACTED] a range of [REDACTED]. Furthermore, for the PRIMA study, [REDACTED] of patients in the niraparib arm had an ECOG PS of 0 compared to [REDACTED] in the placebo arm, a difference of [REDACTED] which also applied to the prevalence of patients with an ECOG score of 1. Additionally, when comparing data between the PRIMA and SOLO-1 trials, the prevalence of patients with an ECOG PS of 0 considerably varied from [REDACTED] a range of [REDACTED].

As shown in Table 26, there were considerable differences in the baseline characteristics of the ITT populations of the PRIME⁴ and ATHENA-MONO² trials. Firstly, there was an approximately 8-year difference in the median age reported in the PRIME (niraparib arm: 53 years; placebo arm: 54 years) and ATHENA-MONO trials (rucaparib arm: 61 years; placebo arm: 61 years). Likewise, the PRIME trial solely comprised Asian patients, while the ATHENA-MONO trial mainly comprised white patients

(rucaparib arm: 76.8%; placebo arm: 78.4%). There were considerable differences in the prevalence of patients with an ECOG PS of 0 between the PRIME (niraparib arm: 38.4%; placebo arm: 40.3%) and ATHENA-MONO trials (rucaparib arm: 69.1%; placebo arm: 68.5%). Additionally, there was considerable variation in the proportion of patients with ovaries as the primary tumour location between the PRIME (niraparib arm: 89.8%; placebo arm: 90.7%) and ATHENA-MONO trials (rucaparib arm: 78.7%; placebo arm: 76.6%). Such differences were also present for proportion of patients with fallopian tubes as the primary tumour location between the PRIME (niraparib arm: 7.5%; placebo arm: 7.0%) and ATHENA-MONO trials (rucaparib arm: 11.7%; placebo arm: 16.2%). Differences were also present for proportion of patients with a primary peritoneal primary tumour location between the PRIME (niraparib arm: 2.7%; placebo arm: 2.3%) and ATHENA-MONO trials (rucaparib arm: 9.6%; placebo arm: 7.2%). Additionally, there were differences in the proportion of patients with serous histology between the PRIME (niraparib arm: 99.2%; placebo arm: 99.2%) and ATHENA-MONO trials (rucaparib arm: 89.9%; placebo arm: 95.5%). The proportion of BRCAm patients varied between the PRIME (niraparib arm: 33.3%; placebo arm: 31.0%) and ATHENA-MONO trials (rucaparib arm: 21.3%; placebo arm: 21.6%). Furthermore, there were considerable differences in the proportion of patients who achieved a complete response to first line chemotherapy between the PRIME (niraparib arm: 83.1%; placebo arm: 79.8%) and ATHENA-MONO trials (rucaparib arm: 17.1%; placebo arm: 9.9%). However, in the PRIME trial, complete response at baseline included all patients with either no evidence of disease or who had achieved a complete response. In contrast, in the ATHENA-MONO trial, complete response at baseline did not include patients with no evidence of disease. Within the ATHENA-MONO trial, 52.5% and 57.7% of patients had no evidence of disease at baseline in the rucaparib and placebo arms, respectively. As such, in the ATHENA-MONO trial, 69.6% and 67.6% of patients had no evidence of disease or a complete response at baseline in the rucaparib and placebo arms, respectively. Accordingly, there is a considerable difference between the proportion of patients, at baseline, with no evidence of disease or complete response between the PRIME and ATHENA-MONO trials. Finally, there was a difference in the proportion of patients with a CA-125 level that was $\leq$ ULN between the PRIME (niraparib arm: 98.8%; placebo arm: 99.2%) and ATHENA-MONO trials (rucaparib arm: 86.9%; placebo arm: 90.1%). Additionally, there were differences between the prevalence of HRd patients across the PRIME (niraparib arm: 66.7%; placebo arm: 67.4%) and ATHENA-MONO trials (rucaparib arm: 43.3%; placebo arm: 44.1%). Such differences were also reported for the prevalence of HRp patients across the PRIME (niraparib arm: 23.5%; placebo arm: 19.4%) and ATHENA-MONO trials (rucaparib arm: 44.3%; placebo arm: 44.1%). As HRd status has been shown to be a key treatment effect modifier, the EAG is concerned that this

imbalance in the prevalence of HRd and HRp patients between trials may bias relative efficacy estimates in favour of niraparib.

Within the PRIMA³ trial, only those patients with a high risk of progression were enrolled. As such, this inclusion criteria results in a narrower patient population compared to other similar trials who included patients regardless of risk of disease progression. As such, the PRIMA trial comprised patients who were considered to be 'high-risk', as opposed to the 'all-risk' populations within the PRIME⁴ trial (Section 3.2.2) and other trials considered for the ITCs (Section 3.4). As the PRIMA trial solely comprised high-risk patients, the company asserted that it was only appropriate to undertake ITCs that compared the PRIMA trial to high-risk subgroups from other trials. Specifically, in response to a clarification question, the company stated that comparisons of the high-risk population from PRIMA to all-risk populations from other trials were inappropriate as "restricting ITCs based on PRIMA to a high-risk population is essential for valid statistical inference". However, within the CS, the company noted that the split of 'high-risk' and 'low-risk' patients within the PRIME trial (and ATHENA-MONO² trial to which PRIME was compared in ITCs) was unknown. As such, the EAG considers that the company's concerns regarding the statistical validity of ITCs involving PRIMA may also apply to the company's preferred ITCs involving PRIME. Additionally, the EAG's clinical experts asserted that the relative treatment benefit of PARPis was likely to be greater in those high-risk patients included in the PRIMA trial compared to those low-risk patients excluded from the PRIMA trial, with this supported by evidence from the ATHENA-MONO and SOLO-1⁵ trials (Section 3.2.1).

The EAG has concerns regarding the relevance of the PRIME⁴ trial to UK clinical practice. For instance, the PRIME trial solely comprised Chinese patients, and HRD status was assessed using an unvalidated assay (as noted in the company's advisory board meeting minutes).²⁰ However, the company has stated, within the CS and response to clarification questions, that it was not appropriate to perform ITCs using data from the PRIMA³ trial, as this trial only comprised patients considered to be high-risk, while the ATHENA-MONO² and SOLO-1⁵ trials comprised a mix of high-risk and low-risk patients (for which subgroup data were not available). The single exception was that the company performed a Bucher analysis comparing high-risk patients from SOLO-1 to the PRIMA trial for the single outcome of investigator-assessed PFS. Additionally, the EAG notes that in the NICE appraisal of rucaparib (TA1055¹), the company excluded the PRIME study from any ITCs due the PRIME trial using an unvalidated assay to determine HRD status, solely comprising patients from China, and comprising a higher proportion of patients with germline BRCA mutation compared to all

other studies identified through an SLR. It was also noted that the EAG for TA1055¹ considered the exclusion of the PRIME trial from any ITCs to be appropriate.

Based upon the available evidence, the EAG considers that ITCs that are most reflective of clinical practice would comprise a comparison of ATHENA-MONO² and SOLO-1⁵ to data from the PRIMA³ trial. The EAG acknowledges that this results in differences between the proportion of high-risk patients in the included trials. However, as shown by the evidence presented above, these differences are either likely to result in relative efficacy estimates that are biased in favour of niraparib (i.e., EAG's clinical experts' views, and data from ATHENA-MONO) or result in no bias between niraparib and the comparator treatments (i.e., data from the SOLO-1 trial). Although the EAG agrees with the company that the Bucher analyses are 'fundamentally flawed', it is the opinion of the EAG that the use of the PRIMA trial within ITCs represents the best approach to obtain estimates of the relative efficacy of niraparib to olaparib and rucaparib in a population that is relevant to UK clinical practice.

Given the EAG's concerns regarding the appropriateness of performing ITCs using data from the PRIME⁴ trial, a comparison of the baseline characteristics for the ITT populations from the PRIMA³ and ATHENA-MONO² trials is shown in Table 27.

Table 27. Baseline characteristics for the PRIMA and ATHENA-MONO trials for the ITT populations.

	PRIMA		ATHENA-MONO	
	Niraparib (n=487)	Placebo (n=246)	Rucaparib (n=427)	Placebo (n=111)
Age (years), median (range)	62 (32-85)	62 (33-88)	61 (30-83)	61 (31-80)
Race, n (%)				
White	436 (89.5)	219 (89.0)	328 (76.8)	87 (78.4)
Black	10 (2.1)	2 (0.8)	NR	NR
Asian	14 (2.9)	11 (4.5)	80 (18.7)	16 (14.4)
Other	Not reported	Not reported	11 (2.6)	6 (5.4)
FIGO stage, n (%)				
Stage III	318 (65.3)	158 (64.2)	323 (75.6)	78 (70.3)
Stage IV	169 (34.7)	88 (35.8)	104 (24.4)	33 (29.7)
ECOG PS, n (%)				
0	337 (69.2)	174 (70.7)	295 (69.1)	76 (68.5)
1	150 (30.8)	72 (29.3)	131 (30.7)	35 (31.5)
Primary tumour location, n (%)				
Ovary	388 (79.7)	201 (81.7)	336 (78.7)	85 (76.6)
Fallopian tube	65 (13.3)	32 (13.0)	50 (11.7)	18 (16.2)

Primary peritoneal	34 (7.0)	13 (5.3)	41 (9.6)	8 (7.2)
Histology, n (%)				
Serous	465 (95.5)	230 (93.5)	384 (89.9)	106 (95.5)
Endometrioid	11 (2.3)	9 (3.7)	13 (3.0)	1 (0.9)
Clear cell	NR	NR	13 (3.0)	2 (1.8)
Mixed	NR	NR	10 (2.3)	1 (0.9)
Other	11 (2.3)	6 (2.4)	7 (1.6)	1 (0.9)
BRCA mutation, n (%)				
Yes	152 (31.2)	71 (28.9)	91 (21.3)	24 (21.6)
No	335 (68.8)	175 (71.1)	336 (78.8)	87 (78.4)
HRD status, n (%)				
HRd			185 (43.3)	49 (44.1)
HRp			189 (44.3)	49 (44.1)
Prior bevacizumab use, n (%)				
Yes	NR	NR	84 (19.7)	12 (10.8)
No	NR	NR	NR	NR
Response to 1L chemotherapy, n (%)				
Complete response	337 (69.2)	172 (70.0)	73 (17.1)	11 (9.9)
Partial response	150 (30.8)	74 (30.0)	76 (17.8)	22 (19.8)
No evidence of disease	NR	NR	224 (52.5)	64 (57.7)
CA-125 level, n (%)				
≤ULN	450 (92.4)	226 (91.9)	371 (86.9)	100 (90.1)
>ULN	34 (7.0)	18 (7.3)	56 (13.1)	11 (9.9)
Receipt of NACT, n (%)				
Yes	322 (66.1)	167 (67.9)	218 (51.1)	57 (51.4)
No	165 (33.9)	79 (32.1)	NR	NR
Timing of surgery, n (%)				
PCS/PDS or upfront	NR	NR	209 (48.9)	54 (48.6)
ICS/IDS	NR	NR	218 (51.1)	57 (51.4)

Abbreviations: 1L, first-line; CA-125, cancer antigen 125; ECOG-PS, Eastern Cooperative Oncology Group-performance status; FIGO, International Federation of Gynaecology and Obstetrics; HRD, homologous recombination deficiency; HRd, homologous recombination deficient; HRp, homologous recombination proficient; ICS, interval cytoreductive surgery; IDS, interval debulking surgery; ITT, intent-to-treat; NACT, neoadjuvant chemotherapy; PCS, primary cytoreductive surgery; PDS, primary debulking surgery; NR, not reported; ULN, upper limit of normal.

As shown in Table 27, there were some differences in the baseline characteristics of the ITT populations of the PRIMA³ and ATHENA-MONO² trials. Firstly, there was a considerable difference in the proportion of white patients between the PRIMA (niraparib arm: 89.5%; placebo arm: 89.0%) and ATHENA-MONO trials (rucaparib arm: 76.8%; placebo arm: 78.4%). Likewise, there was a considerable difference in the proportion of Asian patients between the PRIMA (niraparib arm: 2.9%; placebo arm: 4.5%) and ATHENA-MONO trials (rucaparib arm: 18.7%; placebo arm: 14.4%). There were differences in the prevalence of FIGO stage III patients between the PRIMA (niraparib arm:

65.3%; placebo arm: 64.2%) and ATHENA-MONO trials (rucaparib arm: 75.6%; placebo arm: 70.3%). The proportion of BRCAm patients varied between the PRIMA (niraparib arm: 31.2%; placebo arm: 28.9%) and ATHENA-MONO trials (rucaparib arm: 21.3%; placebo arm: 21.6%). Furthermore, there were considerable differences in the proportion of patients who achieved a complete response to first line chemotherapy between the PRIMA (niraparib arm: 69.2%; placebo arm: 70.0%) and ATHENA-MONO trials (rucaparib arm: 17.1%; placebo arm: 9.9%). Likewise, such differences were also observed for the proportion of patients who achieved a partial response to first line chemotherapy between the PRIMA (niraparib arm: 30.8%; placebo arm: 30.0%) and ATHENA-MONO trials (rucaparib arm: 17.8%; placebo arm: 19.8%). Additionally, there were differences between the prevalence of HRd patients across the PRIMA [REDACTED] and ATHENA-MONO trials [REDACTED]. Such differences were also reported for the prevalence of HRp patients across the PRIMA ([REDACTED]) and ATHENA-MONO trials ([REDACTED]). As HRd status has been shown to be a key treatment effect modifier, the EAG is concerned that this imbalance in the prevalence of HRd and HRp patients between trials may bias relative efficacy estimates in favour of niraparib. Finally, there were differences between the proportion of patients receiving neoadjuvant chemotherapy across the PRIMA ([REDACTED]) and ATHENA-MONO trials ([REDACTED]). The EAG's clinical experts indicated that, with respect to the prevalence of neoadjuvant chemotherapy, the PRIMA more closely aligned with the expectation that 70% to 80% of patients would receive neoadjuvant chemotherapy.

3.4.2 Statistical methods and performed indirect treatment comparisons

When performing indirect treatment comparisons (ITCs), the company identified four studies that they considered to be relevant and able to be included within Bucher analyses. These four studies were the PRIMA³ study (comparing niraparib to placebo in high-risk patients), the PRIME⁴ study (comparing niraparib to placebo), the SOLO-1⁵ study (comparing olaparib to placebo), and the ATHENA-MONO² study (comparing rucaparib to placebo). A full list of ITCs presented by the company in the CS are shown in Table 28. However, the EAG notes that within the CS, the company has described their analyses as being 'fundamentally flawed' due to between-trial differences in the timing and type of HRD testing, and inclusion criteria regarding visible residual disease status.

Table 28. Bucher analyses performed by the company and provided in the company's submission.

Comparisons	Data Sources	ITT	HRd	HRd/BRCawt	BRCAm	HRp/BRCawt
Niraparib vs Rucaparib	ATHENA-MONO ² and PRIME ⁴	PFS-BICR OS	PFS-BICR OS	PFS-BICR ^a	PFS-BICR ^a	PFS-BICR
Niraparib vs Olaparib	PRIMA ³ and SOLO-1 ^{5b}	NA	NA	NA	PFS-INV	NA

Abbreviations: BRCAm, Breast cancer gene mutation; BRCawt, Breast cancer gene wild type; HRd, homologous recombination deficient; HRp, homologous recombination proficient; ITT, intention to treat; NA, not applicable; OS, overall survival; PFS-BICR, blinded independent central review-assessed progression-free survival; PFS-INV, investigator-assessed progression-free survival.

^a PRIME reported subgroup results for patients with i) germline BRCAm and ii) non-germline BRCAm and HRd, which were used as proxies for Bucher ITCs vs the BRCAm and HRd / BRCawt subgroups in ATHENA-MONO.

^b Only those patients considered to be high-risk were used from the SOLO-1 trial to align with the PRIMA trial.

For the ITC comparing niraparib to olaparib, using data from the PRIMA³ and SOLO-1⁵ trials, the company initially considered implementing a simulated treatment comparison (STC). However, following initial investigations, the company reported that counter-intuitive associations were observed in the PRIMA trial between PFS and the two key prognostic factors and effect modifiers of ECOG and age. Additionally, matching on several potential effect modifiers (e.g., type of surgery) was not possible. Given this, the company presented the results of Bucher analyses for the comparison of PFS between the PRIMA and SOLO-1 trials. Given the limitations with the STC, the EAG agrees with the use of Bucher analyses for this comparison.

As previously discussed, the EAG has concerns regarding the relevance of the PRIME⁴ trial to UK clinical practice. Given the difference in opinions between the EAG and company, regarding the appropriateness of performing ITCs using data from the PRIMA³ study, the EAG requested, at the clarification stage, that the company provide the results of new Bucher analyses that compared PRIMA to ATHENA-MONO² and SOLO-1⁵, for a variety of subgroups and endpoints. However, the company declined provide such analyses stating that such analyses were inappropriate. A full list of analyses requested by the EAG and those provided by the company, at the clarification stage, are provided in Table 29.

Table 29. Bucher analyses requested by the EAG at the clarification stage.

Niraparib trial	Comparator	Requested subgroups	Requested outcomes	Provided analyses
PRIMA ³	Rucaparib	- HRd;^a and - HRp or HRp/HRnd	- OS; - PFS-INV; - PFS-BICR; - PFS2; and - TFST	No additional ITCs were provided by the company.
PRIME ⁴	Rucaparib	- HRd;^a and - HRp or HRp/HRnd	- OS; - PFS-INV; - PFS-BICR;	The company provided additional Bucher analyses for the ITT

			• PFS2; and • TFST	population for the endpoints of PFS-INV and TFST.
PRIMA ³	Olaparib	• BRCAm	• OS; • PFS-INV; • PFS-BICR; • PFS2; and • TFST	No additional ITCs were provided by the company.
PRIME ⁴	Olaparib	• BRCAm	• OS; • PFS-INV; • PFS-BICR; • PFS2; and • TFST	The company provided an additional Bucher analysis for the BRCAm population for PFS-BICR.

Abbreviations: BRCAm, Breast cancer gene mutation; EAG, external assessment group; HRd, homologous recombination deficient; HRnd, homologous recombination not determined; HRp, homologous recombination proficient; ITC, indirect treatment comparison; ITT, intention to treat; NA, not applicable; OS, overall survival; PFS-BICR, blinded independent central review-assessed progression-free survival; PFS-INV, investigator-assessed progression-free survival; PFS2, progression-free survival on the second line of therapy; TFST, time to first subsequent treatment.

^a The EAG noted that there is an imbalance between the PRIMA and ATHENA-MONO trials regarding BRCA status. The EAG therefore recommended that the company rebalanced the PRIMA population using, for example, Method of Moments. The EAG also noted that the company could break randomisation in PRIMA and perform a subgroup analysis using the HRd/BRCawt subgroup from both trials.

As shown by Table 29, none of the requested Bucher analyses, using the PRIMA³ trial, were performed by the company. However, the company provided three additional Bucher analyses using data from the PRIME⁴ trial. On receiving the company's submission, the EAG requested that the company provide the R code that was used to perform the ITCs (amongst other analyses) for validation. As such, the company provided R code for the Bucher analyses that were performed for the comparison of PRIME to ATHENA-MONO² for the endpoints of OS and PFS (though not for the comparison of PRIMA to SOLO-1⁵). Accordingly, the EAG has subsequently used this R code to perform Bucher analyses comparing data from the PRIMA trial to the ATHENA-MONO and SOLO-1 trials. By using the company's R code, the EAG has attempted to ensure that methods are consistent across the analyses performed by the company and those performed by the EAG. Prior to performing any analyses, the EAG undertook a comprehensive review of the R code to perform Bucher analyses provided by the company. In doing so, the EAG did not identify any major concerns and considers the code appropriate to perform Bucher analyses.

A full list of the Bucher analyses performed by the EAG and by the company for the comparisons of niraparib to rucaparib and olaparib are provided in Table 30 and For the ATHENA-MONO trial, the corresponding reference from which data was extracted by the EAG for each outcome is provided.

Table 31, respectively. When performing ITCs, the EAG has focused on conducting analyses for those outcomes that were used in the economic model, namely OS, PFS-INV, PFS2, and TFST.

Table 30. Bucher analyses performed by the EAG and company comparing niraparib to rucaparib.

Comparator (trial)	Population	Outcomes analysed, by company, using PRIME	Outcomes analysed, by EAG, using PRIMA
Rucaparib (ATHENA-MONO)	ITT	- OS; - PFS-INV; - PFS-BICR; and - TSFT	- OS;¹ - PFS-INV;²¹ - PFS2;²² and - TFST²²
Rucaparib (ATHENA-MONO)	HRd	- OS; and - PFS-BICR	- OS;¹ - PFS-INV;²¹ - PFS2;²² and - TFST²²
Rucaparib (ATHENA-MONO)	BRCAm	PFS-BICR	PFS-INV²¹
Rucaparib (ATHENA-MONO)	BRCAm (high-risk)	No Bucher analyses performed for this population.	No Bucher analyses performed for this population.
Rucaparib (ATHENA-MONO)	HRd/BRCAwT	PFS-BICR	- OS;¹ - PFS-INV;²¹ - PFS2;¹ and - TFST¹
Rucaparib (ATHENA-MONO)	BRCAwT	No Bucher analyses performed for this population.	PFS-INV²¹
Rucaparib (ATHENA-MONO)	HRp/BRCAwT	PFS-BICR	- OS;¹ - PFS-INV;²¹ - PFS2;¹ and - TFST¹
Rucaparib (ATHENA-MONO)	HRnd	No Bucher analyses performed for this population.	No Bucher analyses performed for this population.

Abbreviations: BRCAm, Breast cancer gene mutation; BRCAwT, Breast cancer gene wild type; HRd, homologous recombination deficient; HRnd, homologous recombination not determined; HRp, homologous recombination proficient; ITC, indirect treatment comparison; ITT, intention to treat; NA, not applicable; OS, overall survival; PFS-BICR, blinded independent central review-assessed progression-free survival; PFS-INV, investigator-assessed progression-free survival; PFS2, progression-free survival on the second line of therapy; TFST, time to first subsequent treatment.

For the ATHENA-MONO trial, the corresponding reference from which data was extracted by the EAG for each outcome is provided.

Table 31. Bucher analyses performed by the EAG and company comparing niraparib to olaparib.

Comparator (trial)	Population	Outcomes analysed, by company, using PRIMA	Outcomes analysed, by EAG, using PRIMA
Olaparib (SOLO-1)	ITT	No Bucher analyses performed for this population.	No Bucher analyses performed for this population.
Olaparib (SOLO-1)	HRd	No Bucher analyses performed for this population.	No Bucher analyses performed for this population.
Olaparib (SOLO-1)	BRCAm	No Bucher analyses performed for this population.	- OS;⁵ - PFS-INV;¹⁸ - PFS2;²³ and - TFST⁵
Olaparib	BRCAm	PFS-INV; and	PFS-INV¹⁸

(SOLO-1)	(high-risk)	• PFS-BICR	
Olaparib (SOLO-1)	HRd/BRCAwt	No Bucher analyses performed for this population.	No Bucher analyses performed for this population.
Olaparib (SOLO-1)	BRCAwt	No Bucher analyses performed for this population.	No Bucher analyses performed for this population.
Olaparib (SOLO-1)	HRp/BRCAwt	No Bucher analyses performed for this population.	No Bucher analyses performed for this population.
Olaparib (SOLO-1)	HRnd	No Bucher analyses performed for this population.	No Bucher analyses performed for this population.

Abbreviations: BRCAm, Breast cancer gene mutation; BRCAwt, Breast cancer gene wild type; HRd, homologous recombination deficient; HRnd, homologous recombination not determined; HRp, homologous recombination proficient; ITC, indirect treatment comparison; ITT, intention to treat; NA, not applicable; OS, overall survival; PFS-BICR, blinded independent central review-assessed progression-free survival; PFS-INV, investigator-assessed progression-free survival; PFS2, progression-free survival on the second line of therapy; TFST, time to first subsequent treatment.

For the SOLO-1 trial, the corresponding reference from which data was extracted by the EAG for each outcome is provided.

For each of the above analyses, the EAG has identified and extracted data, with references given for the corresponding sources of data in Table 30 and Table 31. Where data from multiple timepoints is available, the EAG has prioritised the use of data from the most recent (i.e., latest) timepoint.

Additionally, in the ATHENA-MONO² trial, subgroup data were presented, for some outcomes, for the following subgroups:

- Overall population;
- HRD population;
- BRCA population;
- non-BRCA LOH^{high};
- non-BRCA LOH^{low}; and
- non-BRCA^{unknown}.

Within the CS, the data the company has collated for PFS-BICR for the HRd/BRCAwt and HRp/BRCAwt populations (Table 24) aligns with data presented for the ATHENA-MONO² trial for the non-BRCA LOH^{high} and non-BRCA LOH^{low} populations, respectively.²¹ Accordingly, where presented, the EAG has continued the company's approach for the equating the HRd/BRCAwt and HRp/BRCAwt populations to the non-BRCA LOH^{high} and non-BRCA LOH^{low} populations, respectively.

Within the NICE submission for rucaparib (TA1055¹), Kaplan-Meier curves were presented for the subgroups of HRd/BRCAwt and HRp/BRCAwt for the outcome of PFS-INV. As PFS-INV data for BRCAwt subgroup was not available from ATHENA-MONO² trial, the EAG generated this subgroup by combining data from the HRd/BRCAwt and HRp/BRCAwt subgroups. To this end, the EAG digitized the corresponding Kaplan-Meier curves and generated pseudo-IPD for PFS-INV using the Guyot

method.²⁴ The pseudo-IPD for the HRd/BRCawt and HRp/BRCawt subgroups were then pooled, resulting in pseudo-IPD for the BRCawt population for the ATHENA-MONO trial, this is subsequently referred to as the *pooled BRCawt* population for the ATHENA-MONO trial. The pooled BRCawt data were then used to calculate a hazard ratio comparing PFS-INV between the rucaparib and placebo arms in the ATHENA-MONO trial. Furthermore, the pooled BRCawt data for the ATHENA-MONO trial for PFS-INV allowed an indirect comparison of rucaparib to niraparib, for the BRCawt subgroup, to be performed.

As a validity check of the method for generating pseudo-IPD, the EAG calculated hazard ratios for the comparison of rucaparib to placebo, for PFS-INV, for the HRd/BRCawt and HRp/BRCawt subgroups from the ATHENA-MONO² trial using the pseudo-IPD. As shown in Table 32, there was good alignment between the hazard ratios reported in TA1055¹ and those calculated by the EAG using pseudo-IPD. Furthermore, the hazard ratio for the comparison of rucaparib to placebo, in the BRCawt subgroup, that was calculated by the EAG using pseudo-IPD is also provided in Table 32. It should be noted that the hazard ratios derived from pseudo-IPD slightly underestimated the relative effect of rucaparib compared to placebo. Accordingly, it is likely that the relative ITC of niraparib to rucaparib, for the pooled BRCawt population, may be slightly biased in favour of niraparib.

Table 32. Results of Bucher analyses for investigator-assessed progression-free survival and blind independent central review progression-free survival performed by the company and the EAG for the comparison of rucaparib to placebo.

Subgroup	Hazard ratio reported in TA1055 ¹ (95% confidence intervals)	Hazard ratio calculated using pseudo-IPD (95% confidence intervals)
HRd/BRCawt	0.58 (0.33 to 1.01)	0.595 (0.343 to 1.03)
HRp/BRCawt	0.65 (0.45 to 0.95)	0.665 (0.456 to 0.970)
BRCawt	Not reported	0.637 (0.466 to 0.869)

Abbreviations: BRCawt, Breast cancer gene wild type; HRd, homologous recombination deficient; HRp, homologous recombination proficient; IPD, individual patient data.

The results of the indirect treatment comparisons performed by the company, and by the EAG, are provided in Sections 3.4.3 and 3.4.4 for the comparisons of niraparib to olaparib and niraparib to rucaparib, respectively. As previously noted, within the CS the company has stated that the performed ITCs are ‘fundamentally flawed’. The EAG agrees that there are limitations with the analyses performed by both the company and the EAG. However, these ITCs represent the only available measures of the relative efficacy of niraparib compared to both olaparib and rucaparib.

3.4.3 Indirect treatment comparison results: niraparib and olaparib

3.4.3.1 Progression-free survival

The results of ITCs performed by the EAG and by the company for the comparison of niraparib to olaparib for PFS-INV and PFS-BICR are provided in Table 33. [REDACTED]

[REDACTED]. The EAG notes that there was a small difference in the hazard ratio, and associated 95% confidence intervals, for the BRCaM high-risk population, for PFS-INV, between the ITCs performed by the company and EAG. The EAG anticipates that these differences may be due to the input data being considered to a different number of decimal places between the EAG and company's analysis. To note, the EAG requested that the company provided all code used to perform all ITCs. However, the company did not provide any R code for the ITCs comparing niraparib to olaparib, as such it is not possible for the EAG to confirm the cause of the difference in reported hazard ratios for this subgroup. Additionally, the EAG performed an ITC for the BRCaM population which comprised both low-risk and high-risk patients in the SOLO-1 trial.⁵ [REDACTED]

Table 33. Results of Bucher analyses for investigator assessed progression free survival performed by the company and the EAG for the comparison of niraparib to olaparib.

Comparator (trial)	Population	PFS-INV Hazard ratio (95% CI) Company's PRIMA analysis	PFS-INV Hazard ratio (95% CI) EAG's PRIMA analysis	PFS-BICR Hazard ratio (95% CI) Company's PRIMA analysis	PFS-BICR Hazard ratio (95% CI) EAG's PRIMA analysis
Olaparib (SOLO-1)	ITT	Not performed.	Not performed.	Not performed.	Not performed.
Olaparib (SOLO-1)	HRd	Not performed.	Not performed.	Not performed.	Not performed.
Olaparib (SOLO-1)	BRCaM	Not performed.	[REDACTED]	Not performed.	Not performed.
Olaparib (SOLO-1)	BRCaM (high-risk)	[REDACTED]	[REDACTED]	[REDACTED]	Not performed.
Olaparib	HRd/BRCaM	Not performed.	Not performed.	Not performed.	Not performed.

(SOLO-1)					
Olaparib (SOLO-1)	BRCAwt	Not performed.	Not performed.	Not performed.	Not performed.
Olaparib (SOLO-1)	HRp/BRCAwt	Not performed.	Not performed.	Not performed.	Not performed.
Olaparib (SOLO-1)	HRnd	Not performed.	Not performed.	Not performed.	Not performed.

Abbreviations: BRCAm, Breast cancer gene mutation; BRCAwt, Breast cancer gene wild type; CI, confidence interval; HRd, homologous recombination deficient; HRnd, homologous recombination not determined; HRp, homologous recombination proficient; ITT, intention to treat; PFS-BICR, blinded independent central review-assessed progression-free survival; PFS-INV, investigator-assessed progression-free survival.

Relevant comparisons, based on the NICE final guidance for olaparib (TA962¹⁰), are shown in grey cells.

3.4.3.2 Overall survival

The results of the ITC performed by the EAG for the comparison of niraparib to olaparib for OS are provided in Table 34. The company did not perform any ITCS for OS. The EAG's analysis, using data from the PRIMA³ trial, indicated that there was a statistically significant hazard ratio [REDACTED] that indicated a relative benefit of olaparib compared to niraparib in the BRCAm population.

Table 34. Results of Bucher analyses for overall survival performed by the company and the EAG for the comparison of niraparib to olaparib.

Comparator (trial)	Population	Hazard ratio (95% CI) Company's PRIMA analysis	Hazard ratio (95% CI) EAG's PRIMA analysis
Olaparib (SOLO-1)	ITT	Not performed.	Not performed.
Olaparib (SOLO-1)	HRd	Not performed.	Not performed.
Olaparib (SOLO-1)	BRCAm	Not performed.	[REDACTED]
Olaparib (SOLO-1)	BRCAm (high-risk)	Not performed.	Not performed.
Olaparib (SOLO-1)	HRd/BRCAwt	Not performed.	Not performed.
Olaparib (SOLO-1)	BRCAwt	Not performed.	Not performed.
Olaparib (SOLO-1)	HRp/BRCAwt	Not performed.	Not performed.
Olaparib (SOLO-1)	HRnd	Not performed.	Not performed.

Abbreviations: BRCAm, Breast cancer gene mutation; BRCAwt, Breast cancer gene wild type; CI, confidence interval; HRd, homologous recombination deficient; HRnd, homologous recombination not determined; HRp, homologous recombination proficient; ITT, intention to treat.

Relevant comparisons, based on the NICE final guidance for olaparib (TA962¹⁰), are shown in grey cells.

3.4.3.3 Second progression free survival

The results of the ITC performed by the EAG for the comparison of niraparib to olaparib for PFS2 are provided in Table 35. The company did not perform any ITCs for PFS2. The EAG's analysis, using data from the PRIMA³ trial, indicated that there was a statistically significant hazard ratio, [REDACTED] that indicated a relative benefit of olaparib compared to niraparib in the BRCAm population.

Table 35. Results of Bucher analyses for second progression free survival performed by the company and the EAG for the comparison of niraparib to olaparib.

Comparator (trial)	Population	Hazard ratio (95% CI) Company's PRIMA analysis	Hazard ratio (95% CI) EAG's PRIMA analysis
Olaparib (SOLO-1)	ITT	Not performed.	Not performed.
Olaparib (SOLO-1)	HRd	Not performed.	Not performed.
Olaparib (SOLO-1)	BRCAm	Not performed.	[REDACTED]
Olaparib (SOLO-1)	BRCAm (high-risk)	Not performed.	Not performed.
Olaparib (SOLO-1)	HRd/BRCAwt	Not performed.	Not performed.
Olaparib (SOLO-1)	BRCAwt	Not performed.	Not performed.
Olaparib (SOLO-1)	HRp/BRCAwt	Not performed.	Not performed.
Olaparib (SOLO-1)	HRnd	Not performed.	Not performed.

Abbreviations: BRCAm, Breast cancer gene mutation; BRCAwt, Breast cancer gene wild type; CI, confidence interval; HRd, homologous recombination deficient; HRnd, homologous recombination not determined; HRp, homologous recombination proficient; ITT, intention to treat.

Relevant comparisons, based on the NICE final guidance for olaparib (TA962¹⁰), are shown in grey cells.

3.4.3.4 Time to first subsequent treatment

The results of the ITC performed by the EAG for the comparison of niraparib to olaparib for TFST are provided in Table 26. The company did not perform any ITCs for TFST. The EAG's analysis, using data from the PRIMA³ trial, indicated that there was a non-statistically significant hazard ratio, [REDACTED] that indicated a relative benefit of olaparib compared to niraparib in the BRCAm population.

Table 36. Results of Bucher analyses for time to first subsequent treatment performed by the company and the EAG for the comparison of niraparib to olaparib.

Comparator (trial)	Population	Hazard ratio (95% CI) Company's PRIMA analysis	Hazard ratio (95% CI) EAG's PRIMA analysis
Olaparib (SOLO-1)	ITT	Not performed.	Not performed.
Olaparib (SOLO-1)	HRd	Not performed.	Not performed.
Olaparib (SOLO-1)	BRCAm	Not performed.	
Olaparib (SOLO-1)	BRCAm (high-risk)	Not performed.	Not performed.
Olaparib (SOLO-1)	HRd/BRCAwT	Not performed.	Not performed.
Olaparib (SOLO-1)	BRCAwT	Not performed.	Not performed.
Olaparib (SOLO-1)	HRp/BRCAwT	Not performed.	Not performed.
Olaparib (SOLO-1)	HRnd	Not performed.	Not performed.

Abbreviations: BRCAm, Breast cancer gene mutation; BRCAwT, Breast cancer gene wild type; CI, confidence interval; HRd, homologous recombination deficient; HRnd, homologous recombination not determined; HRp, homologous recombination proficient; ITT, intention to treat.

Relevant comparisons, based on the NICE final guidance for olaparib (TA962¹⁰), are shown in grey cells.

3.4.3.5 EAG conclusions

As previously noted, olaparib has received a recommendation from NICE (TA962¹⁰) for use in the BRCAm population. As such, the EAG considers olaparib to be the relevant comparator to niraparib in the BRCAm population. Based upon the EAG's preferred ITCs, performed using the PRIMA³ trial and the all-risk population from the SOLO-1⁵ trial, the EAG notes that there is no evidence of a clinical benefit of niraparib, relative to olaparib, in the BRCAm population. The EAG notes that there is a statistically non-significant benefit of olaparib, relative to niraparib, for the outcomes of PFS and TFST. Furthermore, the EAG notes that there is a statistically significant benefit of olaparib, relative to niraparib, for the outcomes of OS and PFS2.

3.4.4 Indirect treatment comparison results: niraparib and rucaparib

3.4.4.1 Progression-free survival

The results of ITCs performed by the EAG and by the company for the comparison of niraparib to rucaparib for PFS-INV and PFS-BICR are provided in Table 37. For PFS-INV, there was a clear difference in hazard ratios reported depending upon whether comparison of niraparib to rucaparib is based on data from the PRIMA³ or PRIME⁴ trials. Using the PRIME trial, the company reported that

there was a statistically non-significant hazard ratio ([REDACTED]) that indicated a relative benefit of niraparib compared to rucaparib in the ITT population. In contrast, the EAG's analysis, using data from the PRIMA trial, indicated that there was a statistically non-significant hazard ratio ([REDACTED]) that indicated a relative benefit of rucaparib compared to niraparib in the ITT population. Furthermore, the EAG's analyses indicated that for all subgroups considered, there were statistically non-significant hazard ratios that indicated a relative benefit for rucaparib compared to niraparib. However, the single exception to this was the BRCAm subgroup, where the statistically non-significant hazard ratio indicated a relative benefit of niraparib compared to rucaparib, although it should be noted that rucaparib is not considered to be a relevant comparator to niraparib in the BRCAm subgroup.

For the outcome of PFS-BICR, the company's analyses, using data from the PRIME⁴ study, indicated that there were non-statistically significant hazard ratios that indicated a relative benefit of niraparib compared to rucaparib for the ITT, BRCAm, and HRp/BRCAwt populations. In contrast, the company reported that there were non-statistically significant hazard ratios that indicated a relative benefit of rucaparib compared to niraparib for the HRd and HRd/BRCAwt populations.

Table 37. Results of Bucher analyses for investigator-assessed progression-free survival and blind independent central review progression-free survival performed by the company and the EAG for the comparison of niraparib to rucaparib.

Comparator (trial)	Population	PFS-INV Hazard ratio (95% CI) Company's PRIME analysis	PFS-INV Hazard ratio (95% CI) EAG's PRIMA analysis	PFS-BICR Hazard ratio (95% CI) Company's PRIME analysis	PFS-BICR Hazard ratio (95% CI) EAG's PRIMA analysis
Rucaparib (ATHENA-MONO)	ITT	[REDACTED]	[REDACTED]	[REDACTED]	Not performed.
Rucaparib (ATHENA-MONO)	HRd	Not performed.	[REDACTED]	[REDACTED]	Not performed.
Rucaparib (ATHENA-MONO)	BRCAm	Not performed.	[REDACTED]	[REDACTED]	Not performed.
Rucaparib (ATHENA-MONO)	BRCAm (high-risk)	Not performed.	Not performed.	Not performed.	Not performed.
Rucaparib (ATHENA-MONO)	HRd/BRCAwt	Not performed.	[REDACTED]	[REDACTED]	Not performed.

Rucaparib (ATHENA-MONO)	BRCAwt	Not performed.		Not performed.	Not performed.
Rucaparib (ATHENA-MONO)	HRp/BRCAwt	Not performed.			Not performed.
Rucaparib (ATHENA-MONO)	HRnd	Not performed.	Not performed.	Not performed.	Not performed.

Abbreviations: BRCAm, Breast cancer gene mutation; BRCAwt, Breast cancer gene wild type; CI, confidence interval; HRd, homologous recombination deficient; HRnd, homologous recombination not determined; HRp, homologous recombination proficient; ITT, intention to treat; PFS-BICR, blinded independent central review-assessed progression-free survival; PFS-INV, investigator-assessed progression-free survival.

Relevant comparisons, based on the NICE final guidance for rucaparib (TA1055¹), are shown in grey cells. The HRd population is not considered a relevant comparison as patients within this population will be treated according to BRCA status.

^a Analyses for the BRCAwt population was performed by using a hazard ratio reported for the PRIMA trial in the company's submission and a hazard ratio calculated using pseudo-IPD from a combination of the HRp/BRCAwt and HRd/BRCAwt populations.

The EAG notes that within the rucaparib NICE appraisal (TA1055¹), the results of an anchored matching adjusted indirect comparison (MAIC), for PFS-INV, were presented where the population of the ATHENA-MONO² trial was matched to that of the PRIMA³ trial to facilitate a comparison of rucaparib to niraparib for a high-risk population. Within the company submission for TA1055¹, it was stated that a statistically significant advantage for rucaparib compared to niraparib was reported, although hazard ratios for this comparison were redacted. However, this MAIC was not assessed by the EAG for TA1055¹, as niraparib was not considered by the EAG for TA1055¹ to be a relevant comparator for rucaparib. As such, the EAG is not able to assess the validity of the results presented for the comparison of rucaparib to niraparib for PFS-INV, for the high-risk population, in the CS for TA1055¹.

3.4.4.2 Overall survival

The results of ITCs performed by the EAG and by the company for the comparison of niraparib to rucaparib for OS are provided in Table 38. There was a clear difference in hazard ratios reported depending upon whether the comparison of niraparib to rucaparib is based on data from the PRIMA³ or PRIME⁴ trials. Using the PRIME trial, the company reported that there was a statistically non-significant hazard ratio () that indicated a relative benefit of niraparib compared to rucaparib in the ITT population. In contrast, the EAG's analysis, using data from the PRIMA trial, indicated that there was a statistically non-significant hazard ratio () that indicated a relative benefit of rucaparib compared to niraparib in the ITT population. However, both the company's and EAG's analyses reported statistically non-significant

hazard ratios that indicated a relative benefit of rucaparib compared to niraparib in the HRd population. In contrast to the company, the EAG performed ITCs for the HRd/BRCawt and BRCawt populations. For both populations, the EAG's analyses reported statistically non-significant hazard ratios that indicated a relative benefit of rucaparib compared to niraparib.

Table 38. Results of Bucher analyses for overall survival performed by the company and the EAG for the comparison of niraparib to rucaparib.

Comparator (trial)	Population	Hazard ratio (95% CI) Company's PRIME analysis	Hazard ratio (95% CI) EAG's PRIMA analysis
Rucaparib (ATHENA-MONO)	ITT		
Rucaparib (ATHENA-MONO)	HRd		
Rucaparib (ATHENA-MONO)	BRCAm	Not performed.	Not performed.
Rucaparib (ATHENA-MONO)	BRCAm (high-risk)	Not performed.	Not performed.
Rucaparib (ATHENA-MONO)	HRd/BRCawt	Not performed.	
Rucaparib (ATHENA-MONO)	BRCawt	Not performed.	Not performed.
Rucaparib (ATHENA-MONO)	HRp/BRCawt	Not performed.	
Rucaparib (ATHENA-MONO)	HRnd	Not performed.	Not performed.

Abbreviations: BRCAm, Breast cancer gene mutation; BRCawt, Breast cancer gene wild type; CI, confidence interval; HRd, homologous recombination deficient; HRnd, homologous recombination not determined; HRp, homologous recombination proficient; ITT, intention to treat.

Relevant comparisons, based on the NICE final guidance for rucaparib (TA1055¹), are shown in grey cells. The HRd population is not considered a relevant comparison as patients within this population will be treated according to BRCA status.

3.4.4.3 Progression-free survival on the second line of therapy

The results of ITCs performed by the EAG for the comparison of niraparib to rucaparib for PFS2 are provided in Table 39. The company did not perform any ITCs for PFS2. The EAG's analysis, using data from the PRIMA³ trial, indicated that there was a statistically non-significant hazard ratio () that indicated a relative benefit of rucaparib compared to niraparib in the ITT population.

Table 39. Results of Bucher analyses for second progression free survival performed by the company and the EAG for the comparison of niraparib to rucaparib.

Comparator (trial)	Population	Hazard ratio (95% CI) Company's PRIME analysis	Hazard ratio (95% CI) EAG's PRIMA analysis
Rucaparib (ATHENA-MONO)	ITT	Not performed.	

Rucaparib (ATHENA-MONO)	HRd	Not performed.	
Rucaparib (ATHENA-MONO)	BRCAm	Not performed.	Not performed.
Rucaparib (ATHENA-MONO)	BRCAm (high-risk)	Not performed.	Not performed.
Rucaparib (ATHENA-MONO)	HRd/BRCAwt	Not performed.	
Rucaparib (ATHENA-MONO)	BRCAwt	Not performed.	Not performed.
Rucaparib (ATHENA-MONO)	HRp/BRCAwt	Not performed.	
Rucaparib (ATHENA-MONO)	HRnd	Not performed.	Not performed.

Abbreviations: BRCAm, Breast cancer gene mutation; BRCAwt, Breast cancer gene wild type; CI, confidence interval; HRd, homologous recombination deficient; HRnd, homologous recombination not determined; HRp, homologous recombination proficient; ITT, intention to treat.

Relevant comparisons, based on the NICE final guidance for rucaparib (TA1055¹), are shown in grey cells. The HRd population is not considered a relevant comparison as patients within this population will be treated according to BRCA status.

3.4.4.4 Time to first subsequent treatment

The results of ITCs performed by the EAG and by the company for the comparison of niraparib to rucaparib for TFST are provided in Table 40. There was a clear difference in hazard ratios reported depending upon whether the comparison of niraparib to rucaparib is based on data from the PRIMA³ or PRIME⁴ trials. Using the PRIME trial, the company reported that there was a statistically non-significant hazard ratio () that indicated a relative benefit of niraparib compared to rucaparib in the ITT population. In contrast, the EAG's analysis, using data from the PRIMA trial, indicated that there was a statistically significant hazard ratio () that indicated a relative benefit of rucaparib compared to niraparib in the ITT population. However, both the company's and EAG's analyses reported statistically non-significant hazard ratios that indicated a relative benefit of rucaparib compared to niraparib in the HRd population. In contrast to the company, the EAG performed ITCs for the HRd/BRCAwt and BRCAwt populations. For both populations, the EAG's analyses reported statistically non-significant hazard ratios that indicated a relative benefit of rucaparib compared to niraparib. Furthermore, the EAG's analyses indicated that for the HRd/BRCAwt and HRp/BRCAwt populations there were statistically non-significant hazard ratios that indicated a relative benefit for rucaparib compared to niraparib. However, for the HRd population the reported hazard ratio was () due to the comparisons of niraparib to placebo and rucaparib to placebo reporting identical hazard ratios.

Table 40. Results of Bucher analyses for time to first subsequent treatment performed by the company and the EAG for the comparison of niraparib to rucaparib.

Comparator (trial)	Population	Hazard ratio (95% CI) Company's PRIME analysis	Hazard ratio (95% CI) EAG's PRIMA analysis
Rucaparib (ATHENA-MONO)	ITT		
Rucaparib (ATHENA-MONO)	HRd	Not performed.	
Rucaparib (ATHENA-MONO)	BRCAm	Not performed.	Not performed.
Rucaparib (ATHENA-MONO)	BRCAm (high-risk)	Not performed.	Not performed.
Rucaparib (ATHENA-MONO)	HRd/BRCAwT	Not performed.	
Rucaparib (ATHENA-MONO)	BRCAwT	Not performed.	Not performed.
Rucaparib (ATHENA-MONO)	HRp/BRCAwT	Not performed.	
Rucaparib (ATHENA-MONO)	HRnd	Not performed.	Not performed.

Abbreviations: BRCAm, Breast cancer gene mutation; BRCAwT, Breast cancer gene wild type; CI, confidence interval; HRd, homologous recombination deficient; HRnd, homologous recombination not determined; HRp, homologous recombination proficient; ITT, intention to treat.

Relevant comparisons, based on the NICE final guidance for rucaparib (TA1055¹), are shown in grey cells. The HRd population is not considered a relevant comparison as patients within this population will be treated according to BRCA status.

^a The lower 95% confidence interval for the hazard ratio for the ITT population Bucher analysis, performed by the EAG, was 1.0041.

^b The hazard ratio for the HRd population Bucher analysis, performed by the EAG, was 1.000.

^c The lower 95% confidence interval for the hazard ratio for the HRp/BRCAwT population Bucher analysis, performed by the EAG, was 0.9968.

3.4.4.5 EAG conclusions

As previously noted, rucaparib has received a recommendation from NICE (TA1055¹) for use in the BRCAwT population. As such, the EAG considers rucaparib to be the relevant comparator to niraparib in the BRCAwT, HRd/BRCAwT, and HRp/BRCAwT populations.

The EAG notes that the company did not perform ITCs for the BRCAwT, HRd/BRCAwT, and HRp/BRCAwT populations for the outcomes of OS, PFS2, and TFST. However, the company performed ITCs for PFS-BICR, using data from the PRIME⁴ trial, for the HRd/BRCAwT and HRp/BRCAwT populations, but not the BRCAwT population. The results of the PFS-BICR analysis for the HRd/BRCAwT population aligned with the results of the EAG's ITC for PFS-INV, with both analyses reporting a statistically non-significant benefit of rucaparib, relative to niraparib. However, the results of the PFS-BICR analysis for the HRp/BRCAwT population did not align with the results of the EAG's ITC for PFS-INV. While the EAG's ITC for PFS-INV for the HRp/BRCAwT population indicated

that there was a statistically non-significant benefit of rucaparib, relative to niraparib, the company's ITC for PFS-BICR indicated that there was statistically non-significant benefit of niraparib, relative to rucaparib. Additionally, the results of the Bucher analyses performed by the EAG for PFS-INV align with the results of a MAIC presented by the company in the NICE appraisal of rucaparib (TA1055¹). Within the CS for TA1055¹, the company reported that results from an anchored MAIC (comparing data from ATHENA-MONO² to PRIMA³) showed a statistically significant advantage for rucaparib compared to niraparib, though the hazard for this comparison was redacted. However, the EAG notes that the MAIC presented in TA1055¹ was not assessed by the corresponding EAG, therefore the statistical validity of this analysis has not been sufficiently validated.

Based upon the EAG's preferred ITCs, performed using data from the PRIMA³ and ATHENA-MONO² trials, the EAG notes that there is no evidence of a clinical benefit of niraparib, relative to rucaparib, for any outcome across the BRCAwt, HRd/BRCAwt, and HRp/BRCAwt populations.

3.4.5 Indirect treatment comparison results: assumptions of equivalence

Within the CS, the company makes multiple references to the assumption of equivalence between the efficacy of niraparib, olaparib, and rucaparib, with such an assumption implemented within the economic model (Section 4.2.4). However, in response to clarification question, the company confirmed that equivalency testing had not been performed to support the assumptions of equivalence. However, in response to a clarification question, the company performed additional *post-hoc* analyses to determine whether niraparib is non-inferior compared to both olaparib and rucaparib. The results of the ITCs performed by the company form a core component of the non-inferiority analyses. However, the company did not provide the EAG with the code used to perform the non-inferiority analyses; as such, the EAG was unable to replicate these results or perform corresponding non-inferiority analyses for the ITCs performed by the EAG.

When assessing non-inferiority, the company performed two separate forms of analyses, namely 'fixed margin analysis' (Section 3.4.5.1) and Monte-Carlo simulations (Section 3.4.5.2), each of which is assessed below.

3.4.5.1 Fixed margin analysis

The company performed 'fixed margin analysis' to assess non-inferiority, in line with the method described in Kaul and Diamond (2007).²⁵ However, the EAG is not aware of the method for fixed

margin analysis, as described in Kaul and Diamond (2007),²⁵ being used in any previous NICE appraisals. As noted by the company in the clarification question response, fixed margin analyses may be used to determine whether a new treatment is non-inferior to a comparator treatment up to, but not exceeding, a pre-defined margin (termed a non-inferiority margin). Likewise, the company noted that such fixed margin analyses are only appropriate when a trial has demonstrated that the comparator treatment is superior to placebo. The EAG notes that in the clarification response, the company refers to 'mixed margin analysis', although no reference is provided for this analysis, nor is it referred to in Kaul and Diamond (2007).²⁵ As such, the EAG assumes that this is a typo and refers to the 'fixed margin analysis'.

For the 'fixed margin analysis', the company stated that the maximum non-inferiority margin was derived as the lower 95% confidence interval for the hazard ratio of the comparison of placebo versus the comparator treatment. Within Kaul and Diamond (2007),²⁵ it is suggested that the non-inferiority margin is taken from the lower 95% confidence interval of the point estimate derived from a meta-analysis of relevant studies. However, as there is only one relevant trial (i.e., ATHENA-MONO² or SOLO-1⁵) for each comparison a meta-analysis was not possible to perform. Under the fixed margin analysis, non-inferiority of the treatment, relative to a comparator, is determined when 95% confidence intervals for the Bucher comparison do not overlap, and are entirely below, the non-inferiority margin.

The results of the non-inferiority analyses performed by the company, using the method of Kaul and Diamond (2007)²⁵ are shown in Table 41. As such, the company considers that non-inferiority was demonstrated for two of the eight ITCs (25%) performed by the company. The comparisons for which non-inferiority was demonstrated were the for the comparison of PFS-BICR between PRIME⁴ and ATHENA-MONO² in the ITT population and the comparison of PFS-INV between PRIMA³ and SOLO-1⁵ in the BRCAm (high-risk) population.

Table 41. Results of non-inferiority analyses using the method of Kaul and Diamond (2007) for the ITCs performed by the company.

Population	Outcome	Niraparib trial	Comparator trial	Non-inferiority assessment
ITT	PFS-BICR	PRIME	ATHENA-MONO	Established
ITT	OS	PRIME	ATHENA-MONO	Not performed
HRd	PFS-BICR	PRIME	ATHENA-MONO	Not established
HRd	OS	PRIME	ATHENA-MONO	Not performed
HRd/BRCawt	PFS-BICR	PRIME	ATHENA-MONO	Not established
BRCAm	PFS-BICR	PRIME	ATHENA-MONO	Not established
BRCAm (high risk)	PFS-INV	PRIMA	SOLO-1	Established

HRp/BRCawt	PFS-BICR	PRIME	ATHENA-MONO	Not established
Abbreviations: BRCAm, Breast cancer gene mutation; BRCawt, Breast cancer gene wild type; HRd, homologous recombination deficient; HRp, homologous recombination proficient; ITT, intention to treat; OS, overall survival; PFS-BICR, blinded independent central review-assessed progression-free survival; PFS-INV, investigator-assessed progression-free survival.				

The EAG has several concerns regarding the implementation of the fixed margin analysis to assess the non-inferiority of niraparib relative to comparator treatments. Firstly, the company stated that it was not possible to perform fixed margin analyses for the ITCs of OS due to data from ATHENA-MONO² not demonstrating the superiority of rucaparib over placebo in either the ITT or HRd populations for this endpoint. Secondly, the EAG notes that for the non-inferiority analyses of PFS-BICR, five different non-inferiority margins (ranging from 1.0 to 1.587) were used for the assessments of non-inferiority. The EAG notes that different values have been derived based on the lower 95% confidence intervals for different population subgroups. However, the EAG is concerned that this disparity indicates that these non-inferiority margins are not necessarily clinically meaningful. Accordingly, while the studies may be assessed as being non-inferior based on the performed statistical analyses, there is no evidence that this would translate into niraparib being considered to be non-inferior to olaparib and rucaparib from a clinical perspective. Finally, the EAG has concerns about the potential conflation of data from the ATHENA-MONO and SOLO-1⁵ trials within the non-inferiority analyses. For example, the ATHENA-MONO trial was used to derive the non-inferiority margin, which was then subsequently used to assess non-inferiority for the indirect treatment comparison of niraparib to rucaparib (again using data from ATHENA-MONO). The EAG is concerned that this 'dual-use' of data from the ATHENA-MONO and SOLO-1 trials may have unintentionally biased the assessments of non-inferiority. Furthermore, it is unclear to the EAG which direction such bias would apply (i.e., increasing or decreasing the likelihood of niraparib being considered to be non-inferior to olaparib or rucaparib).

3.4.5.2 Monte-Carlo simulations

In addition to the fixed margin analysis, the company also performed a Monte-Carlo simulation to estimate the probability that the hazard ratio for niraparib compared to placebo was lower than the hazard ratio for the comparator compared to placebo. This simulation was performed by drawing 1,000,000 values from two independent normal distributions that were parameterized to align with the reported hazard ratios used within each of the ITCs performed by the company. As such, the company asserted that the results of this analysis may be categorized as follows:

- A probability that the hazard ratio for niraparib compared to placebo is less than the hazard ratio for a comparator compared to placebo that is close to 50%, supports the hypothesis of non-inferiority as it reflects that the distributions of the reported hazard ratios are indistinguishable.
- A probability that the hazard ratio for niraparib compared to placebo is less than the hazard ratio for a comparator compared to placebo that greater 50%, may indicate that the assumption of non-inferiority is conservative.
- The probability of the hazard ratio for niraparib compared to placebo is less than the hazard ratio for a comparator compared to placebo will typically be lower than 50% when the reported hazard ratio in PRIMA³/PRIME is higher than the reported hazard ratio in the comparator study. However, niraparib could still be non-inferior to the comparator treatment if both treatments are highly efficacious compared to placebo and the fixed margin analysis supports non-inferiority.

As with the fixed margin analyses, the company has not provided code for these analyses to the EAG, preventing a thorough review of the analyses from taking place. However, the EAG notes that the company used normal distributions, which were parameterised to the reported hazard ratios used within each of the ITCs performed by the company. The EAG notes that hazard ratios are not normally distributed; as such, if normal distributions were to be used then they would need to be applied to the logarithm of the hazard ratios.

The results of the non-inferiority analyses performed by the company, using Monte-Carlo simulations are shown in Table 42. The EAG is concerned that the levels provided by the categorisations provided by the company may be open to interpretation and do not provide definitive assessments of non-inferiority. For instance, there is no indication of what 'close to 50%' entails (e.g., 40% to 60%, or 45% to 55%, etc). As such, the EAG considers that the results of this analysis should be viewed as an 'add-on' to the fixed margin analyses rather than being considered in isolation.

[Table 42. Results of non-inferiority analyses using the Monte-Carlo simulations for the ITCs performed by the company.](#)

Population	Outcome	Niraparib trial	Comparator trial	Non-inferiority probability
ITT	PFS-BICR	PRIME	ATHENA-MONO	58.41%
ITT	OS	PRIME	ATHENA-MONO	81.15%
HRd	PFS-BICR	PRIME	ATHENA-MONO	38.34%
HRd	OS	PRIME	ATHENA-MONO	46.18%
HRd/BRCAt	PFS-BICR	PRIME	ATHENA-MONO	26.97%
BRCAt	PFS-BICR	PRIME	ATHENA-MONO	65.18%
BRCAt (high risk)	PFS-INV	PRIMA	SOLO-1	16.87%
HRp/BRCAt	PFS-BICR	PRIME	ATHENA-MONO	84.54%

Abbreviations: BRCAt, Breast cancer gene mutation; BRCAt, Breast cancer gene wild type; HRd, homologous recombination deficient; HRp, homologous recombination proficient; ITT, intention to treat; OS, overall survival; PFS-BICR, blinded independent central review-assessed progression-free survival; PFS-INV, investigator-assessed progression-free survival.

3.4.5.3 EAG preference

All but one of the non-inferiority analyses presented by the company use data from the PRIME⁴ trial. However, the EAG considers that ITCs using data from PRIME are likely to be flawed (Section 3.4.1). As the EAG was not provided with the code to run the non-inferiority analyses presented by the company, the EAG has been unable to run equivalent analyses for the ITCs that were newly performed by the EAG using data from PRIMA³.

Given the issues with the non-inferiority analyses presented by the company, the EAG's preference would have been for standard non-inferiority analyses to have been performed using widely implemented approaches²⁶ using clinically validated non-inferiority margins derived from data sources that do not form a core component of the analyses. Accordingly, the EAG is concerned that equivalence, or non-inferiority, between niraparib and the comparator treatments has not been demonstrated in a statistically robust, or clinically meaningful, manner.

3.5 Conclusions of the clinical effectiveness section

The EAG considers that any differences between the NICE final scope and the CS are justified (Section 2.3). Likewise, the EAG considers that the SLR was performed using appropriate methods and is likely to have identified the most relevant and current evidence (Section 3.1). However, the EAG considers that the analyses provided by the company were insufficient to address the decision problem. To this end, the EAG performed multiple new ITCs to allow comparisons of niraparib to olaparib and rucaparib, for multiple different outcomes, to be obtained.

Within the CS, the company only included olaparib and rucaparib as relevant comparators despite the NICE final scope listing other comparators such as bevacizumab and olaparib with bevacizumab.

The EAG accepts the company's assertion that olaparib and rucaparib are the only relevant comparators, following the company clarifying the population in which they are seeking a recommendation. As such, the EAG suggests that in the interests of clarity that any NICE recommendation clearly stipulates that it only applies to where bevacizumab is not a treatment option (consistent with TA1055¹). Additionally, the EAG notes within the advisory board meeting conducted by the company, it was stated that ITCs comparing niraparib to olaparib with bevacizumab were being performed. However, these analyses were not provided by the company.

The company presented evidence from two distinct trials (PRIMA³ and PRIME⁴) that compared niraparib to placebo. The population of the PRIMA trial was narrower than the NICE final scope as it excluded stage III patients with a favourable prognosis due to being optimally debulked following upfront primary debulking surgery. The EAG's clinical experts indicated that high-risk patients are likely to experience a greater relative treatment benefit from PARPis compared to low-risk patients, with this assertion supported by data from both the ATHENA-MONO² and SOLO-1⁵ trials. The EAG has concerns regarding the PRIME trial and its relevance to UK clinical practice. For instance, the PRIME trial was solely conducted in China, implemented an unvalidated assay to assess HRD status, with the data from the trial being relatively immature. Overall, the EAG considers the PRIMA trial to be more relevant for UK clinical practice than the PRIME trial.

When considering the results of the PRIMA³ and PRIME⁴ trials, the EAG noted that the PRIMA trial was not stratified for BRCA status. As such, any subgroup analyses regarding BRCA status (e.g., BRCAm or HRd/BRCAwt populations) required trial randomisation to be broken. However, the EAG also notes that the HRD status was a stratification factor in the PRIMA trial. As such, the PRIMA trial has been designed to be analysed by HRp and HRd status rather than BRCAm or BRCAwt status. In contrast, the PRIME trial was stratified for both HRD status and BRCA status. When considering the relevant BRCA and HRD status subgroups (i.e., HRd/BRCAwt, BRCAm, BRCAwt, and HRp/BRCAwt) from the PRIMA trial, the reported hazard ratios indicated a statistically significant improvement in PFS-INV for niraparib compared to placebo for all subgroups. [REDACTED]

[REDACTED]. In contrast, the PRIME trial did not report PFS-INV for the relevant BRCA and HRD status subgroups. However, the PRIME trial reported statistically significant improvement in PFS-BICR for all relevant BRCA and HRD status subgroups. However, the PRIMA trial did not report PFS-INV for the relevant BRCA and HRD status subgroups. The PRIMA trial reported that, for the relevant BRCA and HRD status subgroups, all subgroup analyses for OS, PFS2, and TFST indicated a statistically

nonsignificant improvement for niraparib compared to placebo. The single exception to this was for the BRCAm subgroup for the BRCAm population which indicated a statistically significant benefit of niraparib relative to placebo. In contrast, the PRIME trial did not report data for OS, PFS2, or TFST for the relevant BRCA and HRD status subgroups. Additionally, the EAG is concerned that the hazard ratio for OS from the PRIMA trial for patients with FIGO stage IV indicated that patients who received niraparib have worse OS than patients who received placebo [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Within the CS, the company presented ITCs comparing to niraparib to olaparib using the PRIMA³ trial, and ITCs comparing niraparib to rucaparib using the PRIME⁴ trial. However, the EAG's preference was for ITCs to use data from PRIMA as opposed to PRIME. As such, the EAG requested that the company provide the results of new ITCs, using PRIMA, to compare niraparib to olaparib and rucaparib for a wider range of endpoints that initially provided. However, the company declined to do so. As such, the EAG performed multiple new ITCs, using code provided by the company. Considering the EAG's preferred ITCs, there is no evidence of a clinical benefit of niraparib, relative to olaparib, in the BRCAm population. The EAG notes that there is a statistically non-significant benefit of olaparib, relative to niraparib, for the outcomes of PFS and TFST. Furthermore, the EAG notes that there is a statistically significant benefit of olaparib, relative to niraparib, for the outcomes of OS and PFS2. Likewise, considering the EAG's preferred ITCs, there is no evidence of a clinical benefit of niraparib, relative to rucaparib, for any outcome across the BRCAwt, HRd/BRCAwt, and HRp/BRCAwt populations.

As previously noted, there are some substantial differences between the baseline characteristics of the PRIMA³ trial and the ATHENA-MONO² and SOLO-1⁵ trials. Accordingly, these differences in baseline characteristics (e.g., prevalence of HRd and HRp patients) may unduly bias the results of the ITCs used to determine the relative effectiveness of niraparib compared to olaparib and rucaparib. Accordingly, the EAG suggests that the use of matching-adjusted indirect comparisons (MAICs) may be appropriate, as this would result in the baseline characteristics of the PRIMA trial aligning with those from the ATHENA-MONO and SOLO-1 trials. The EAG notes that MAICs would only be able to be applied to the PRIMA trial as, in response to a clarification question, the company noted that individual patient data is not available for the PRIME trial. Furthermore, this would align with the MAICs implemented in the recent NICE appraisal of rucaparib (TA1055¹), although the EAG notes

that the MAICs presented in TA1055¹ were not assessed by the corresponding EAG. Additionally, the EAG notes that the use of MAICs to determine estimates of relative treatment effectiveness may not be possible for all HRD and BRCA status subgroups, if baseline characteristics for these subgroups were not reported in the ATHENA-MONO and SOLO-1 trials.

Within the economic modelling, the company made the assumption that PARPis are equivalent in their effectiveness. The EAG does not consider the company to have provided sufficient evidence to support this assertion within the CS.. However, in response to a clarification question, the company performed two separate non-inferiority analyses. However, the EAG considers there to be substantial limitations with these analyses and suggested an alternative, standard, non-inferiority analysis that the company could have performed. Furthermore, the results of the ITCs performed by the EAG indicate that there is a statistically significant benefit of olaparib, compared to niraparib, for the outcomes of OS and PFS2. Accordingly, the EAG does not consider there to be sufficient evidence that niraparib is non-inferior to either olaparib or rucaparib.

Overall, the EAG considers that there is limited evidence that niraparib is either equivalent to, or statistically significantly better than, either rucaparib or olaparib, in the relevant comparator populations and outcomes of interest.

Overall, a summary of the ITC results used within the model are shown within Table 43.

Table 43. EAG-derived hazard ratios from Bucher ITCs that are used within the economic model (a HR<1 favours niraparib, and a HR>1 favours the comparator).

	EAG-derived hazard ratio (95% CI)	
	Progression free survival	Overall survival
Niraparib vs olaparib		
BRCAm		
Niraparib vs rucaparib		
BRCAwt (all)		N/A
HRd/BRCAwt	Not used in EAG preferred	
HRp/BRCAwt	Not used in EAG preferred	

* Analyses for the BRCAwt population was performed by using a hazard ratio reported for the PRIMA trial in the company's submission and a hazard ratio calculated using pseudo-IPD from a combination of the HRp/BRCAwt and HRd/BRCAwt populations, as discussed in Section 3.4

Abbreviations: BRCAm, Breast cancer gene mutation; BRCAwt, Breast cancer gene wild type; CI, confidence interval; EAG, External Assessment Group; HR, hazard ratio; HRd, homologous recombination deficient; HRp, homologous recombination proficient; ITC, indirect treatment comparison.

3.5.1 Summary of EAG's core findings

By considering information available in the CS, the company's advisory board meeting, consultations with EAG's clinical experts, and additional EAG performed analyses, the EAG has performed a comprehensive review of the clinical effectiveness of niraparib, including relative comparisons to both olaparib and rucaparib. The core findings of the EAG are summarised in brief below.

- The EAG notes that the evidence provided by the company is only for patients for whom have not completed first-line induction chemotherapy in combination with bevacizumab.
 - The EAG notes that the advisory board meeting notes stated that the company was performing ITCs comparing niraparib to olaparib with bevacizumab (using data from the PAOLA-1¹⁶ trial).
 - Within the evidence presented in the CS, and company's response to clarification questions, the company did not provide any ITCs comparing niraparib to olaparib with bevacizumab or bevacizumab monotherapy.
 - In response to a clarification question, the company stated that it is not seeking a recommendation in patients who have completed first-line induction chemotherapy with bevacizumab.

The company chose to submit evidence for a population that is narrower than niraparib MHRA authorisation. The population definition (i.e. limiting niraparib to only to patients for whom bevacizumab is not an option) needs to be highlighted. EAG notes this is consistent with the recommendation for rucaparib in TA1055¹.

- The EAG considers it appropriate to compare data from high-risk patients (i.e., PRIMA³) to all-risk patients (i.e., ATHENA-MONO² and SOLO-1⁵).
 - The EAG's clinical experts indicated that the relative treatment benefit of PARPis in high-risk patients is likely to be greater than that seen in low-risk patients.
 - Evidence from the SOLO-1⁵ trial comparing olaparib to placebo supports this assertion, as the hazard ratio for PFS reported for the high-risk subgroup was 0.34, which was nearly identical to the reported hazard ratio of 0.33 for the ITT population (i.e., an all-risk population).¹⁸
 - Evidence from the ATHENA-MONO² trial comparing rucaparib to placebo supports this assertion, as the hazard ratio for PFS reported for the high-risk subgroup was 0.47 (95% CI: 0.35 to 0.63), which indicated a greater treatment effect of rucaparib

in this population compared to an all-risk population which reported a hazard ratio of 0.80 (95% CI: 0.49 to 1.31).

- The EAG considers that the most appropriate ITCs are of PRIMA³ (niraparib) to ATHENA-MONO² (rucaparib) and SOLO-1⁵ (olaparib).
 - With regards to PRIME⁴, the EAG has concerns about its applicability to UK clinical care, given that the trial was solely performed in China, and implemented a unvalidated assay to assess patients for HRD status.
 - The EAG considers PRIMA³ to be more appropriate given the trial locations, the greater maturity of survival data, and use of a validated assay to assess HRD status.
 - However, the EAG acknowledges that are limitations associated with the PRIMA³ trial, including the need to break randomization to perform BRCA-based subgroup analyses.
- The EAG considers there to be substantial issues with the ITCs performed by both the company and EAG.
 - There was considerable variation in the baseline characteristics between trials, and between trial arms, including for some variables known to impact efficacy outcomes (e.g., HRD status, BRCA status, and FIGO score). As such, these differences in baseline characteristics may bias estimates of relative treatment efficacy.
 - The EAG agrees with the company's assessment that the presented ITCs are 'fundamentally flawed'. However, the EAG suggests that the analyses presented by the EAG represent the most appropriate analyses, under the considerable limitations, to calculate estimates of relative efficacy between niraparib and relevant comparators.
 - The EAG notes that by using data from the PRIMA³ trial, ITCs were able to be performed for the outcomes of OS, PFS-INV, PFS2 and TFST. In contrast, using data from the PRIME⁴ trial, ITCs were only able to be performed for the outcomes of OS and PFS-BICR.
- The EAG considers there to be four distinct populations, based on BRCA and HRD status, in which the efficacy of niraparib, relative to relevant comparators for each subgroup, should be assessed:

- BRCAm, for which the relevant comparator is olaparib.
 - Based on the EAG analyses comparing PRIMA³ and SOLO-1⁵, there is evidence of a statistically significant benefit of olaparib, compared to niraparib, for the outcomes of OS [REDACTED] and PFS2 [REDACTED]. There is also evidence of a statistically nonsignificant benefit of olaparib, compared to niraparib, for the outcomes of PFS [REDACTED] and TFST [REDACTED].
- BRCAwt, for which the relevant comparator is rucaparib.
 - Based on the EAG analyses comparing PRIMA³ and ATHENA-MONO², there is evidence of a statistically nonsignificant benefit of rucaparib, compared to niraparib, for the outcome of PFS [REDACTED].
 - Although analyses were performed for the BRCAwt subgroup, the EAG's preference is to consider the BRCAwt population as split by HRD, in line with data available from ATHENA-MONO² and the approach used in the recent NICE appraisal of rucaparib (TA1055¹).
- HRd/BRCAwt, for which the relevant comparator is rucaparib.
 - Based on the EAG analyses comparing PRIMA³ and ATHENA-MONO², there is evidence of a statistically nonsignificant benefit of rucaparib, compared to niraparib, for the outcomes of OS [REDACTED], PFS [REDACTED], PFS2 [REDACTED], and TFST [REDACTED].
- HRp/BRCAwt, for which the relevant comparator is rucaparib.
 - Based on the EAG analyses comparing PRIMA³ and ATHENA-MONO², there is evidence of a statistically nonsignificant benefit of rucaparib, compared to niraparib, for the outcomes of OS [REDACTED], PFS [REDACTED], PFS2 [REDACTED], and TFST [REDACTED].
- The EAG considers that there is insufficient evidence to assume clinical equivalence between PARP inhibitors.
 - The EAG considers the equivalence testing performed by the company to be inappropriate, with an alternative statistically, and clinically, meaningful approach suggested.

- ITCs performed by the EAG have provided evidence that there is a statistically significant benefit of olaparib, relative to niraparib, for the endpoints of OS and PFS in the BRCAm population.

4 Cost effectiveness

This section presents a summary and critique of the cost-effectiveness evidence included in the company's submission. Section 4.1 focuses on the company's review of the cost-effectiveness evidence and section 4.2 covers the company's economic evaluation.

The company's deterministic and probabilistic base case results are presented in Table 44 and Table 45 for the BRCAm (breast cancer gene mutation) and BRCAwt (breast cancer wild type) populations, respectively. Probabilistic outcomes were generated using a Monte Carlo simulation, drawing from 5000 model iterations. The tables highlight that probabilistic outcomes showed close alignment to deterministic outcomes.

For both BRCAm and BRCAwt populations, health outcomes were found to be all but equivalent between niraparib and comparators, with any difference driven solely by adverse event disutilities. Niraparib was also found to be less costly than comparators in each respective population, with resulting ICERs being in either the southwest (BRCAm) or southeast (BRCAwt) quadrant of the cost-effectiveness plane.

Table 44. Company's base case results for the BRCAm population

	Total Costs (£)	Total LY	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)
Deterministic results							
Niraparib	■	8.21	■	-	-	-	-
Olaparib	£128,104	8.21	6.27	■	0.00	■	SW ICER (less costly, less effective)
Probabilistic results							
Niraparib	■	8.42	■	-	-	-	-
Olaparib	£128,656	8.42	6.41	■	0.00	■	SW ICER (less costly, less effective)
Abbreviations: BRCAm, breast cancer gene mutation; ICER, incremental cost-effectiveness ratio; INC, incremental; LY, life year; QALY, quality-adjusted life-year; SW, southwest.							

Table 45. Company's base case results for the BRCAwt population

	Total Costs (£)	Total LY	Total QALYs	Inc. costs (£)	Inc. LYs	Inc. QALYs	ICER (£/QALY)
Deterministic results							
Niraparib	██████	4.75	██████	-	-	-	-
Rucaparib	£ 117,230	4.75	3.50	██████	0.00	██████	SE ICER (less costly, more effective)
Probabilistic results							
Niraparib	██████	4.78	██████	-	-	-	-
Rucaparib	£ 117,264	4.78	3.52	██████	0.00	██████	SE ICER (less costly, more effective)
Abbreviations: BRCAwt, breast cancer wild type; ICER, incremental cost-effectiveness ratio; INC, incremental; LY, life year; QALY, quality-adjusted life-year; SE, southeast.							

The company considers a disease severity modifier of 1.0 to be appropriate.

4.1 Critique of the review of cost effectiveness evidence

As part of the company's submission (CS), a systematic literature review (SLR) was conducted to identify published relevant cost-effectiveness, quality of life and health care resource use studies to inform the economic model where appropriate.

The SLR was conducted using the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA),²⁷ general methodological requirements outlined in the Cochrane Handbook for Systematic Reviews of Interventions, and key health technology assessment (HTA) bodies, such as NICE and Canada's Drug Agency (CDA). A wide array of literature databases were searched using the Ovid platform. Databases included, but not limited to, MEDLINE, EMBASE, ECONLIT, NICE, SMC and ISPOR. The SLR was originally conducted in February 2019 and was subsequently updated in February 2020, March 2023 and February 2025.

The cost-effectiveness SLR identified 49 relevant studies after second screening, which assessed cost-effectiveness using a Markov (n=11), semi-Markov (n=6) or a partitioned survival model (n=30), with the remaining two studies using a trial-based cost-effectiveness approach. The company noted that previous NICE advanced ovarian cancer appraisals, (TA673⁷, TA598²⁸, TA962¹⁰, TA693²⁹, TA946⁹ and TA1055¹), all utilised a partitioned survival model with either three or four health states. The EAG notes that the company's model is also a partitioned survival model.

The health-related quality of life SLR identified four relevant studies evaluating 1L PARPi maintenance treatments with relevant HRQoL data. These studies related to the RCTs for niraparib, rucaparib² olaparib and olaparib plus bevacizumab main clinical trial publications. Data on EQ-5D were available from two randomised clinical trials (PAOLA-1¹⁶ and PRIMA³, and SOLO-1⁵ and PRIMA, respectively). The EAG notes that health state utility values used in the model were informed using niraparib's pivotal trial, PRIMA.

The health care resource use SLR identified 13 studies of relevance, including NICE TA962¹⁰, TA946⁹, and TA1055¹, which evaluated olaparib and rucaparib for the treatment of advanced ovarian cancer. The EAG notes that the costs and health care resources use included in the company's model are reflective of NICE TA TA962¹⁰, TA946⁹, and TA1055¹.

Table 46. Summary of the company's economic systematic literature review

Systematic review step	Section of CS in which methods are reported			EAG assessment of robustness of methods
	Cost-effectiveness evidence	HRQoL evidence	Resource use and costs evidence	
Search strategy	Appendix E.1.1.1	Appendix F.1.1.1	Appendix G.1.1.1	Appropriate
Inclusion/ exclusion criteria	Appendix E.1.1.2	Appendix F.1.1.2	Appendix G.1.1.2	Appropriate
Screening	Appendix E.1.1.3	Appendix F.1.1.3	Appendix G.1.1.3	Appropriate
Data extraction	Appendix E.1.1.4	Appendix F.1.1.4	Appendix G.1.1.4	Appropriate
Quality assessment of included studies	Appendix E.1.1.5	Appendix F.1.1.5	Appendix G.1.1.5	Appropriate
Abbreviations: CS, company submission; EAG, External Assessment Group; HRQoL, health related quality of life.				

4.2 Critique of the submitted economic evaluation

4.2.1 NICE reference case checklist

Table 47 summarises the EAG's assessment of the company's economic evaluation against the requirements set out in the NICE reference case checklist for the base-case analysis,³⁰ with reference to the NICE final scope outlined in Section 2.3.

Table 47. NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Adheres to the reference case.
Perspective on costs	NHS and PSS	Adheres to the reference case.
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Adheres to the reference case.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Lifetime. Adheres to the reference case.
Synthesis of evidence on health effects	Based on systematic review	Adheres to the reference case.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Adheres to the reference case.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Adheres to the reference case. EQ-5D-5L data collected from the key trial (PRIMA ³), mapped to EQ-5D-3L.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Adheres to the reference case. Uses UK value set to derive utility values.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Adheres to the reference case.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Adheres to the reference case.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Adheres to the reference case.
Abbreviations: EAG, External Assessment Group; EQ-5D-3L; EuroQol Five Dimensions 3 Level version; EQ-5D-5L; EuroQol Five Dimensions 5 Level version; NHS, National Health Service; PSS, personal social services; QALY, quality adjusted life year; UK, United Kingdom.		

4.2.2 Population

As discussed in Section 2.3.1, the company has submitted evidence for two populations; BRCAm and BRCawt, with cost-effectiveness results presented for each population.

The baseline characteristics of each population informing the company model, taken from PRIMA³, are shown below. The company also included scenarios in the model using the median age estimates from the niraparib SACT data.

Table 48. Baseline characteristic informing the company model

Characteristic	Mean	SE (N)
BRCAm		
Age at baseline (years)	■	■
Weight (kg)	■	■
BSA (m ²)	■	■
BRCAwt		
Age at baseline (years)	■	■
Weight (kg)	■	■
BSA (m ²)	■	■
Abbreviations: BRCAm, breast cancer gene mutation; BRCAwt, breast cancer gene wild type; BSA, body surface area; m ² , square meters; N, number; kg, kilograms; SE, standard error.		

4.2.2.1 EAG critique

While the EAG acknowledges that niraparib has marketing authorisation for the whole BRCAwt population (and BRCAm), the EAG considers that for the BRCAwt population, the company should have split the population by homologous recombination deficient (HRD) subgroups; HRD-positive (HRd) and HRD status negative (HRp), in line with the approach used in the rucaparib appraisal (TA1055¹). The EAG requested that this was done during clarification; however, updated analyses were not presented and the company maintained the BRCAwt and BRCAm populations, which the EAG considers to be a key limitation of the cost-effectiveness results provided (key issue 2 and 4b), also discussed further in the following sub-sections.

As mean age is not available in the SACT data for comparison to the PRIMA³ population, the EAG requested the median age for each population included in the company's model from PRIMA, shown below in Table 49. The EAG notes that in the olaparib plus bevacizumab appraisal (TA693²⁹) the committee concluded that it was more suitable to use the median age from the SACT data in the economic model. In addition, in the final guidance for olaparib monotherapy (TA962¹⁰), it is noted that the CDF lead was concerned about the impact of age on the generalisability of the SOLO-1⁵ trial data to NHS clinical practice (53 years in SOLO-1 compared to 61 years in olaparib SACT data). While

the committee acknowledged the concerns, they concluded that SOLO-1 data were sufficient for decision making, but would have preferred to see analyses on the impact of age. The EAG has conducted scenario analyses on their own base-case (see Section 5.2.4) to explore the impact of age, using the median age from the SACT dataset .

Table 49. Median age of patients in PRIMA versus SACT data for niraparib

	BRCAm population	BRCAwT population
PRIMA median age, years	■	■
SACT median age, years	■	■
Abbreviations: BRCAm, breast cancer gene mutation; BRCAwT, breast cancer gene wild type; SACT, systemic anti-cancer therapy.		

4.2.3 *Modelling approach and model structure*

The company developed a *de novo* economic model in Microsoft Excel® using a partitioned survival model (PSM) approach with three health states: progression-free survival (PFS); progressed disease (PD); and death (Figure 7). This approach is in line with the company’s model used in the original submission for niraparib, prior to entry into the Cancer Drugs Fund (CDF).³¹ The company stated that the PSM approach is in line with guidance from the NICE Decision Support Unit (DSU) and consistent with previously accepted NICE appraisals for first-line (1L) PARPi maintenance therapies for advanced ovarian cancer. However, upon review by the EAG, all previous NICE appraisals used a four-state PSM to account for second progression (PFS2).^{1, 9, 28, 29}

Cost-effectiveness analyses are presented separately by population subgroup: BRCAm population versus olaparib and BRCAwT population (not split by HRD status) versus rucaparib. Based on subgroup data from the PRIMA³ randomised controlled trial (RCT), patients entered the model at a mean age of ■ years in the BRCAm population and ■ years in the BRCAwT population.

Patients start in the PFS health state and receive either niraparib or olaparib (BRCAm subgroup)/rucaparib (BRCAwT subgroup). During each model cycle, patients in the PFS health state can be either on-treatment or off-treatment. From the progression-free health state, patients can transition to either the progressed health state when they experience disease progression or die

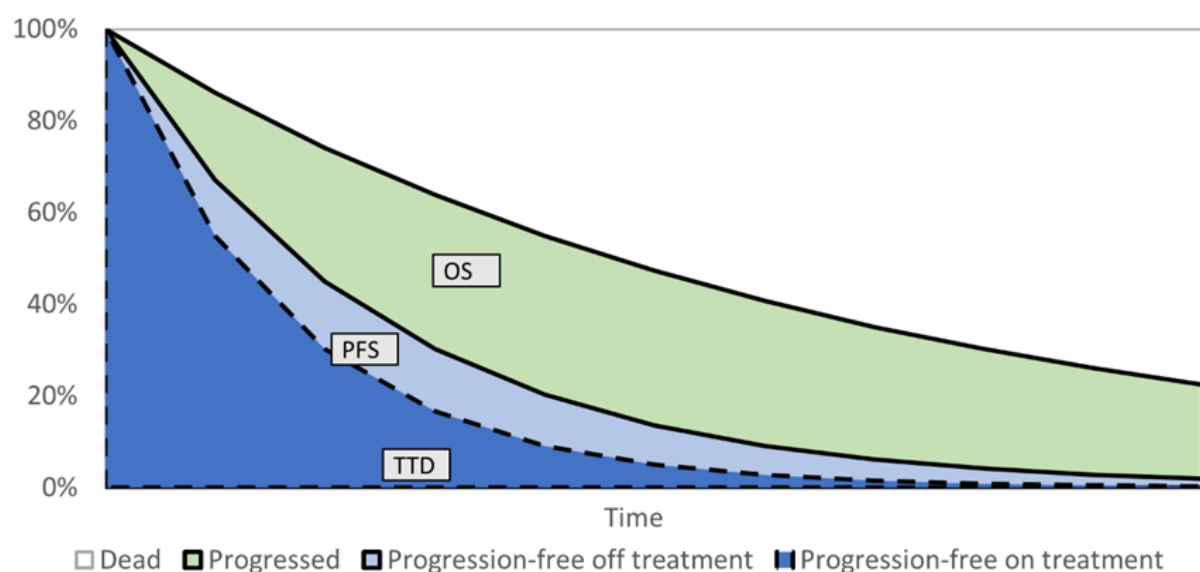
(thus transitioning to the dead health state). When patients transition to the progressed disease health state, they remain there until death.

In the niraparib arm of the model, PFS, overall survival (OS) and time to treatment discontinuation (TTD) are informed by parametric distributions fitted to time-to-event subgroup data (BRCAm or BRCAwt) from the PRIMA³ RCT. PFS and OS in the comparator arms of the model are estimated based on the application of a hazard ratio (HR) to the niraparib PFS and OS extrapolated estimates (see Section 4.2.4 for further details).

The probability of being in each model health state at each cycle is estimated based on:

- PFS: The cumulative PFS survivor function applied in the model;
- PD: The difference between the OS and the PFS cumulative probabilities;
- Death: The cumulative OS survivor function applied in the model ($1 - OS$), constrained to not fall below the PFS function.

Figure 7. Company model, reproduced from Figure 28 in CS)



Abbreviations: OS, overall survival; PFS, progression-free survival; TTD, time to treatment discontinuation

The company applied a constraint to ensure that neither PFS or OS exceeded that of the general population for the UK.

The company includes a long-term remission assumption in the economic model. Based on clinical expert advice, the company chose 10 years as the point in the model when the survival rate for PFS patients was set to the all-cause general population mortality. The same long-term remission time point was applied to all interventions included in the economic model, as this is assumed to be equal across the PARPi treatments.

The model used a lifetime horizon and a cycle length of one month, with a half-cycle correction implemented. The analysis was carried out from an NHS and Personal Social Services (PSS) perspective. Costs and health effects are discounted at an annual rate of 3.5%, in line with the NICE Reference Case.³⁰

4.2.3.1 EAG critique

The EAG agree with the use of a PSM used by the company to appropriately capture the disease pathway and key outcomes. However, the EAG has some concerns with the exclusion of PFS2 as an additional model state. The company noted that due to the treatment pathway following progression with a PARPi monotherapy being same across the included modelled treatments, the costs and outcomes from subsequent treatments are expected to be the same. In addition, the company noted a lack of relevant PFS2 data available stratified for high-risk population for the included model comparators. The EAG notes, however, that the company's economic model has been developed to include a PFS2 health state — it just isn't utilised. During clarification, the EAG therefore asked the company to include data on PFS2 in the economic model and update the base-case results.

While the EAG agrees that subsequent therapies should be the same in clinical practice following progression on 1LM PARPi therapies, if the PARPi therapies included in the economic model are not equivalent to one another in effectiveness, then excluding PFS2 will fail to capture an important difference between treatments. For example, if the time to second progression differs between the PARPi treatments included, this would not currently be captured in the model. In addition, as it would be expected that quality of life would differ between patients with a first and second progression, this would not currently be captured in the model. As discussed in Section 3.3.2.2, niraparib did not show a statistically significant difference compared to placebo in PFS2 based on the most recent PRIMA³ analysis. In response to a clarification request, the company included an option

to use a four-state model, however, this was not used in their updated base-case. As with the assumptions used for PFS and OS, the company assumed equivalence in PFS2 between all treatments. No additional ITCs were performed for PFS2, which the company stated was due to a lack of PFS2 data in high-risk populations for the comparators. While the EAG considers that the inclusion of PFS2 would have been more appropriate, due to a lack of evidence for the specific populations requested by the EAG in order to compare PFS2 against comparators (HRd/BRCawt and HRp/BRCawt), the EAG has not included PFS2 in the updated model but notes this as a limitation.

4.2.4 *Treatment effectiveness*

In this section, the EAG first provides a summary of the company's general approach to treatment effectiveness, with details of PFS, OS and TTD included in the economic model provided in the following subsections.

4.2.4.1 *General approach to treatment effectiveness*

Survival outcomes in the economic model for niraparib are calculated using extrapolations of PRIMA³ Kaplan-Meier (KM) PFS and OS data for the BRCAm and BRCawt subgroups. Due to a lack of direct trial evidence comparing niraparib to the included comparators, the company conducted ITC feasibility assessments to inform the relative treatment effectiveness of olaparib and rucaparib. As discussed in Section 3.4.2, the company considered that any ITCs comparing the key trials for niraparib (PRIMA and PRIME⁴) versus olaparib (SOLO-1⁵) or rucaparib (ATHENA-MONO²) are fundamentally flawed. However, the company undertook exploratory ITCs to explore the relative treatment effects and to inform the hazard ratio applied in the economic model. The company discussed the available real-world evidence (RWE) to support the assumptions made for comparator PFS and OS.

Based on the results of the ITCs of PRIMA vs SOLO-1⁵ in the high-risk population for the comparison against olaparib, which showed no statistically significant difference in PFS [REDACTED], the company assumed clinical equivalence between the two treatments, therefore implementing a HR of 1 in the model. Due to a lack of OS data for the high-risk population in SOLO-1, the company also assumed equivalence in OS between niraparib and olaparib based on the following:

- Comparison of SACT data for niraparib and olaparib showing overlapping OS up to 27 months before divergence, which the company states is due to small patient numbers in the tail of the KM.
- RWE for a South Korean study comparing olaparib and niraparib in BRCAm patients showing no statistically significant differences in PFS or OS.³²
- Expert opinion stating that based on the above data, it is reasonable to assume a 'class effect' for PARPi monotherapies.

The exploratory unadjusted Bucher ITC of PRIME⁴ versus ATHENA-MONO² showed no statistically significant difference in PFS or OS. Based on this and the above assumption of a class effect for PARPi monotherapies, the company also applied a HR of 1 for both PFS and OS in the comparison with rucaparib in the BRCAwt population. Further detail is discussed in the following subsections.

Extrapolations of the KM data were explored using independently fit standard (exponential, Weibull, Gompertz, log-normal, log-logistic, gamma and generalised gamma) and flexible (hazard, odds and normal spline with 1, 2, 3 knots) parametric models to the niraparib arm from PRIMA³ for OS and PFS in both the BRCAm and BRCAwt subgroups. To determine the most appropriate extrapolation, the company followed NICE DSU technical support document (TSD) 14 guidance³³ and assessed the following:

- Visual inspection of the curves;
- Fit of each modelled curve against the observed KM data using statistical goodness of fit statistics, including Akaike information criterion (AIC) and Bayesian information criterion (BIC) statistics;
- Assessment of the smoothed hazard plots and average hazard rate over time;
- Clinical plausibility of the extrapolation over the time horizon of the model using expert opinion.

The company noted that while a mixture cure model (MCM) was considered, the flexible spline models were preferred and noted that splines are likely to produce comparable extrapolations due to the mature survival data available. The EAG agree that the added complexity of a MCM approach is unlikely to have improved the reliability of the survival estimates.

Further details of the company's extrapolation choice for PFS, OS and TTD are provided in appendix J of the CS for both the BRCAm and BRCAwt populations, including hazard plots over time, AIC/BIC

statistics and landmark estimates of PFS/OS produced with each survival distribution. Table 50 presents an overview of the company's survival curve selection for each outcome by population and Sections 4.2.4.1 - 4.2.4.10 provides more detail on the company's approach to extrapolating PFS and OS. Please refer to Section 4.2.5 for further details on the TTD extrapolations.

The EAG notes that the company has implemented the following limits in the model to ensure that model outcomes pass clinical and face validity:

- Risk of progression or mortality risk per cycle cannot fall below age-matched general population mortality, based on ONS life tables from 2021-2023;³⁴
- OS cannot fall below PFS (i.e. OS is capped to PFS);
- PFS is set equal to the general population all-cause mortality at 10 years (long-term remission assumption);
- TTD cannot exceed PFS.

Table 50. Overview of company's survival curve selection by outcome and population

Outcome	BRCAm population		BRCAwt population	
	Niraparib	Olaparib	Niraparib	Rucaparib
PFS	Generalised gamma	Assumed equivalence	Generalised gamma	Assumed equivalence
OS	1-knot normal spline	Assumed equivalence	1-knot hazard spline	Assumed equivalence
TTD	KM + exponential	Generated from PFS and AE discontinuation	KM + log-logistic	Generated from PFS and AE discontinuation

Abbreviations: BRCAm, breast cancer gene mutated; BRCAwt, breast cancer gene wild type; KM, Kaplan-Meier; OS, overall survival; PFS, progression-free survival; TTD, time-to-treatment discontinuation

4.2.4.2 EAG critique

Overall, the EAG considers the company's general approach to extrapolating outcomes for PFS and OS to be appropriate. The EAG has a minor issue with the use of OS capped to PFS in the model (PFS is the upper limit). The EAG considers that typically, in PSMs, the cap used is that PFS cannot exceed OS (OS is the upper limit). The EAG queried this during clarification and in response the company stated that it was preferable to cap OS to PFS due to the maturity of the PFS data from PRIMA³ which is used to model the long-term remission (cure) point. It was noted if PFS is capped to OS this

would result in higher mortality than general population being applied to PF patients after the cure point, which is not in line with clinical expert advice and accepted in previous NICE appraisals. While a scenario was not provided capping PFS to OS, it is noted that if this was applied before the cure point it would have no impact on the company's base-case analyses as the OS-PFS crossing points are after the 10 years cure point.

Based on clinical expert advice, the company's economic model implements a long-term remission point at 10 years, upon which patients who remain progression-free have the general population mortality applied from thereafter. A clinical expert to the EAG also noted that they would consider a patient to be in long-term remission if they were progression-free at 10 years. The EAG notes that, the longest available data from PRIMA³ is up to seven years and therefore it is uncertain what happens to PFS beyond this point. The company presented the smoothed hazards over time for both PFS and OS in both subgroups (BRCAm and BRCAwt), appendix J, in which it shows the nature of the hazards is decreasing up to seven years. While the EAG considers it reasonable to infer that the trajectory of the hazard will continue to decrease up to 10 years and likely plateau, there is no objective observed evidence to confirm this.

The EAG notes that the company does not vary any of the HRs used to inform survival curves for the parameters in the probabilistic sensitivity analysis (PSA). As discussed in Section 3.4.5, the EAG considers there to be large uncertainty regarding the company's assumption of equivalence between treatments and therefore not varying the main treatment effect is highly inappropriate. The EAG addresses this in its own analyses.

As noted previously in Section 3.4.1, the EAG recognises the limitations of all of the ITCs due to differences in the PRIMA³ (and PRIME⁴) population compared to the relevant comparator trials. However, a lack of statistically significant results does not equal equivalence; non-statistically significant results are often the outcome for ITCs that are reliant on single trials for each comparator. The EAG also notes that when a direct comparison is available through an RCT, non-statistically significant differences between any KM curves for overall survival would likely be used to extrapolate outcomes in a PSM, rather than assuming clinical equivalence.

Despite the limitations, the EAG considers that the ITCs conducted and described in Section 3.4 represent the best available estimates of relative effectiveness between niraparib and the included comparators (key issue 4), summarised below (Table 51). This critique point is subsequently explored

in the EAG's exploratory analyses in Section 5.2.2, and described in the following sub-sections, when the EAG has changed the company's base-case assumption of equivalence between all included PARPIs to use the EAG-derived HRs.

Table 51. EAG-derived hazard ratios from Bucher ITCs, as described in Section 3 of EAG report (a HR<1 favours niraparib, and a HR>1 favours the comparator)

	EAG-derived hazard ratio (95% CI)	
	Progression free survival	Overall survival
Niraparib vs olaparib		
BRCAm		
Niraparib vs rucaparib		
BRCAwt (all)		N/A
HRd/BRCAwt	Not used in EAG preferred	
HRp/BRCAwt	Not used in EAG preferred	
* Analyses for the BRCAwt population was performed by using a hazard ratio reported for the PRIMA trial in the company's submission and a hazard ratio calculated using pseudo-IPD from a combination of the HRp/BRCAwt and HRd/BRCAwt populations, as discussed in Section 3.4 Abbreviations: BRCAm, Breast cancer gene mutation; BRCAwt, Breast cancer gene wild type; CI, confidence interval; EAG, External Assessment Group; HR, hazard ratio; HRd, homologous recombination deficient; HRp, homologous recombination proficient; ITC, indirect treatment comparison; N/A, not available.		

The EAG is aware that a constant hazard ratio derived from the ITC should be applied to baseline curves that support the proportional hazards assumption. However, as discussed further in the following sections and shown in appendix J of the CS, the relevant standard parametric models that do support PH (exponential, Weibull and Gompertz) did not produce reliable fits to the observed data. Therefore, the EAG was concerned that this would introduce further uncertainty and preferred to use baseline extrapolations that reflect the observed data and underlying nature of the hazards over time. The EAG notes that this is the same approach as used by the company in any scenario analyses in which they do not assume clinical equivalence. The EAG notes that the preferred option would have been to conduct ITCs using a fractional polynomial network meta-analysis (fpNMA) to capture the underlying complex hazard function. However, this was not feasible for the EAG to conduct due to time constraints. The company could have also undertaken a multi-level network meta-regression (ML-NMR) to inform the indirect comparisons; this was not possible for the EAG to undertake due to not having access to the individual patient data (IPD) for PRIMA³.

4.2.4.3 Progression-free survival – BRCAm population

The company considered non-monotonic standard parametric (log-logistic, log-normal and generalised gamma) and all spline models to be most reflective of the hazard over time, which showed an increasing then decreasing hazard profile. The one-knot normal spline model provided the best fit to the observed data and produced the lowest AIC/BIC, with all one and two-knot spline models also producing similar statistical fits to the observed data. In the base-case analysis, the company chose the generalised gamma, noting this was due to being the best fitting statistical model that produced landmark estimates of PFS at 10, 15 and 20 years most in line with its clinical experts.

The one-knot normal spline was implemented as a scenario analysis and noted to have slightly more optimistic survival predictions compared to the generalised gamma. The EAG notes that all estimates of predicted survival beyond 10 years used to compare against the company's clinical expert opinion included the 10-year cure point. Figure 8 and Figure 9 show the Kaplan-Meier (KM) data and base-case extrapolation curve, both with and without the 10-year long-term remission assumption applied, respectively.

As previously noted, PFS is set equal to the general population all-cause mortality at 10 years. In the BRCAm subgroup, an excess mortality of 1.26 is applied to the general population mortality hazard, based on data from Mai et al. 2009³⁵ to account for higher mortality risk for this population.

Figure 8. Progression-free survival in company's base case for the BRCAm population (generalised gamma, long-term remission assumption), produced from the company's model

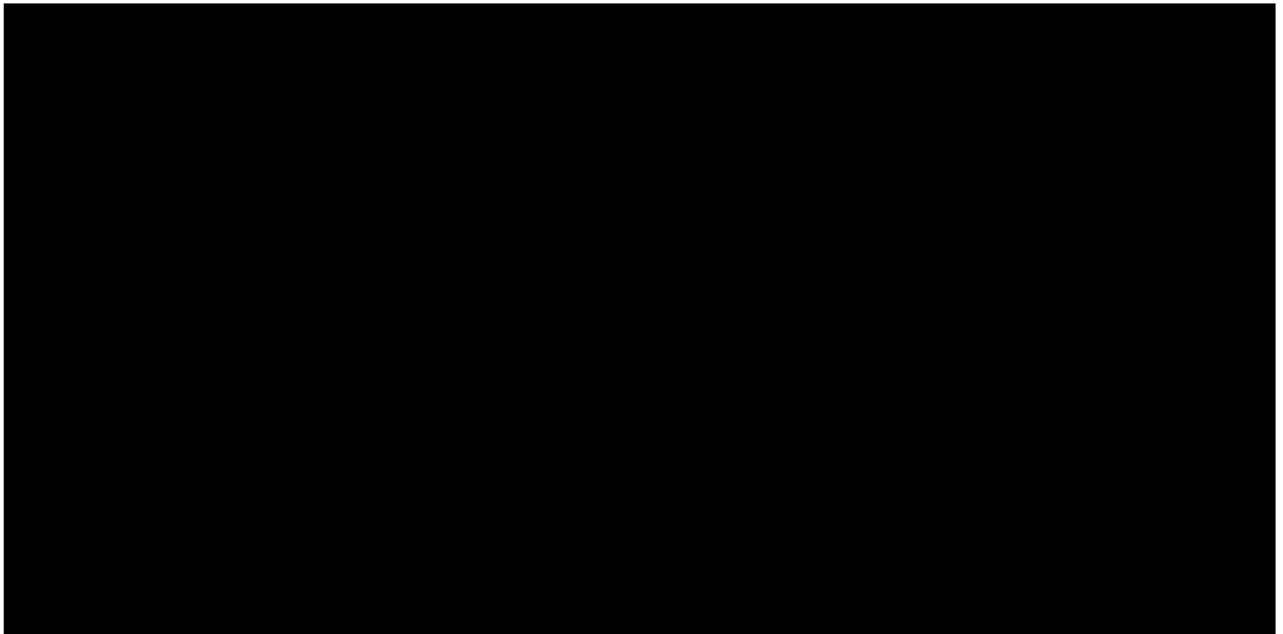
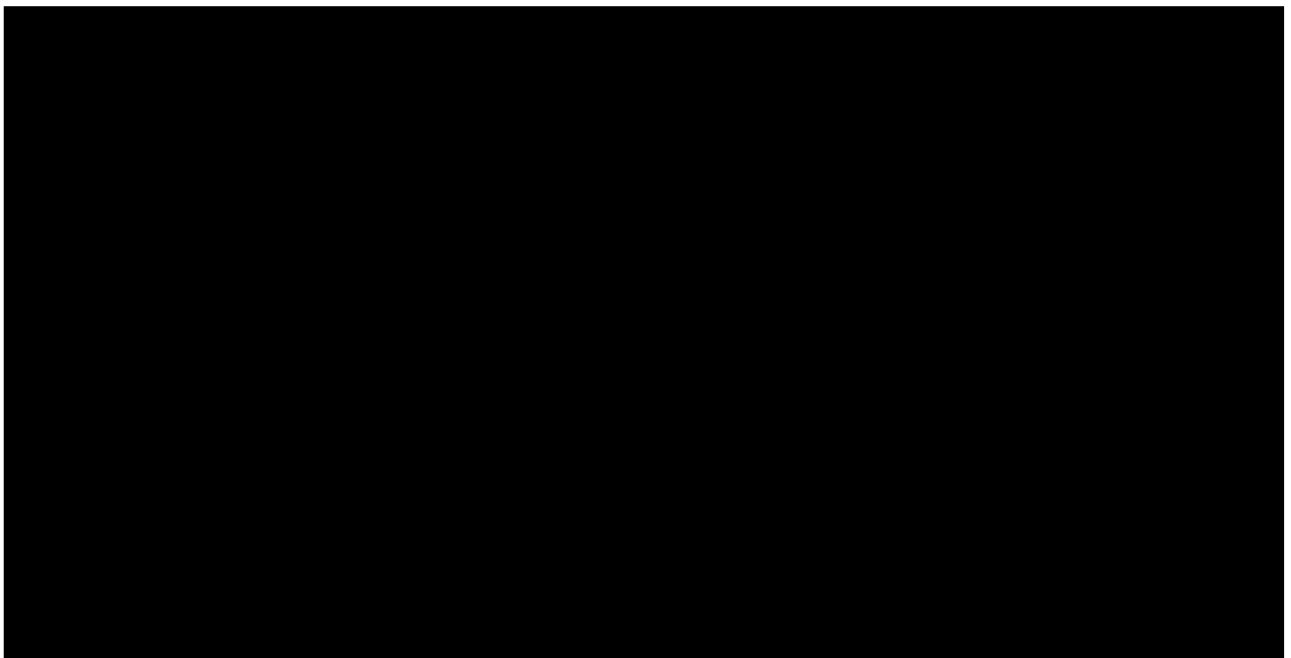


Figure 9. Progression-free survival in company's base case for the BRCAm population (generalised gamma, no long-term remission assumption), produced from the company's model



Based on the hazard ratio of 1 applied in the company's base case analysis, PFS curves are equal for both niraparib and olaparib. However, a scenario analysis applying a HR of [REDACTED] was applied based on the outputs of the exploratory Bucher ITC conducted of PRIMA³ versus SOLO-1⁵.

4.2.4.4 EAG critique

In relation to the best fitting survival curve to the PRIMA³ BRCam data, the EAG was generally satisfied with the company's approach to selection. The EAG notes that the company chose the generalised gamma over the one-knot normal spline, which had the best statistical fit, due to slightly more optimistic survival projections with the one-knot normal spline. The EAG notes due to the company's assumption of equivalence in PFS between niraparib and olaparib, applying the more conservative estimates using generalised gamma favours the company. This is due to TTD for comparators being generated from PFS and AE discontinuation, therefore, applying the more optimistic PFS with the one-knot normal spline would result in a slightly higher proportion of patients remaining on comparator treatments and therefore incurring drug acquisition costs.

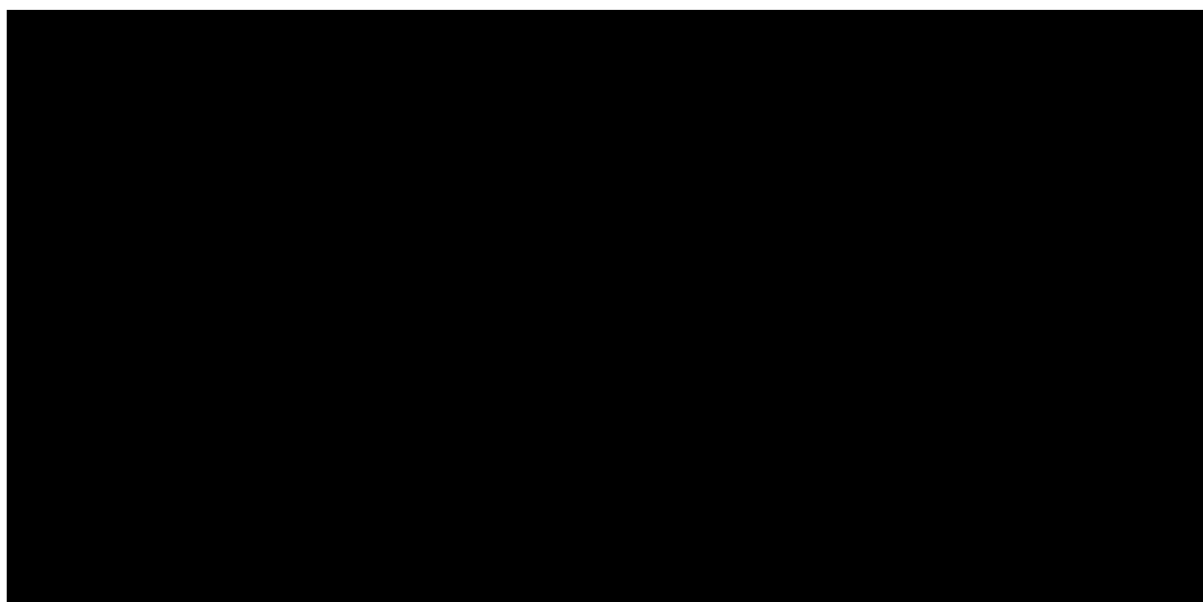
The clinical expert consulted by the EAG estimated a similar proportion of patients PF as those consulted by the company, with estimates largely in line with those predicted by the company's model.

As discussed in Section 3.4.5, the EAG considers clinical equivalence between niraparib and olaparib based on the presented analyses to be a strong assumption and highly uncertain (key issue 4a). The EAG analyses of PRIMA³ versus SOLO-1⁵ in the BRCam population showed a HR for PFS of [REDACTED]. While the EAG notes the wide confidence intervals, it is considered to be the most appropriate representation of the difference in PFS between niraparib and olaparib in the BRCam subgroup, and therefore the EAG applies this in the preferred base-case analysis (See Section 5.1.1). The EAG also conducted an ITC for the BRCam high-risk population with a resulting HR of [REDACTED]. As an ITC could only be conducted for the high-risk population for PFS and not OS, the EAG preferred to use the overall BRCam population HR in the base-case for consistency between the two outcomes and applied the high-risk HR in a scenario analysis (see Section 5).

The EAG notes that the application of the HR results in landmark estimates of PFS for olaparib that are closely aligned with the evidence from SOLO-1⁵, which showed 48.4% of patients progression-free at five years compared to [REDACTED]% estimated in the economic model. This is in comparison to [REDACTED]%

in the company's base case analysis, assuming clinical equivalence between niraparib and olaparib. Figure 10 below shows the PFS curves using the EAG's preferred assumption.

Figure 10. Progression-free survival using EAG preferred analysis for the BRCam population (generalised gamma, long-term remission assumption applied)



4.2.4.5 Overall survival – BRCam population

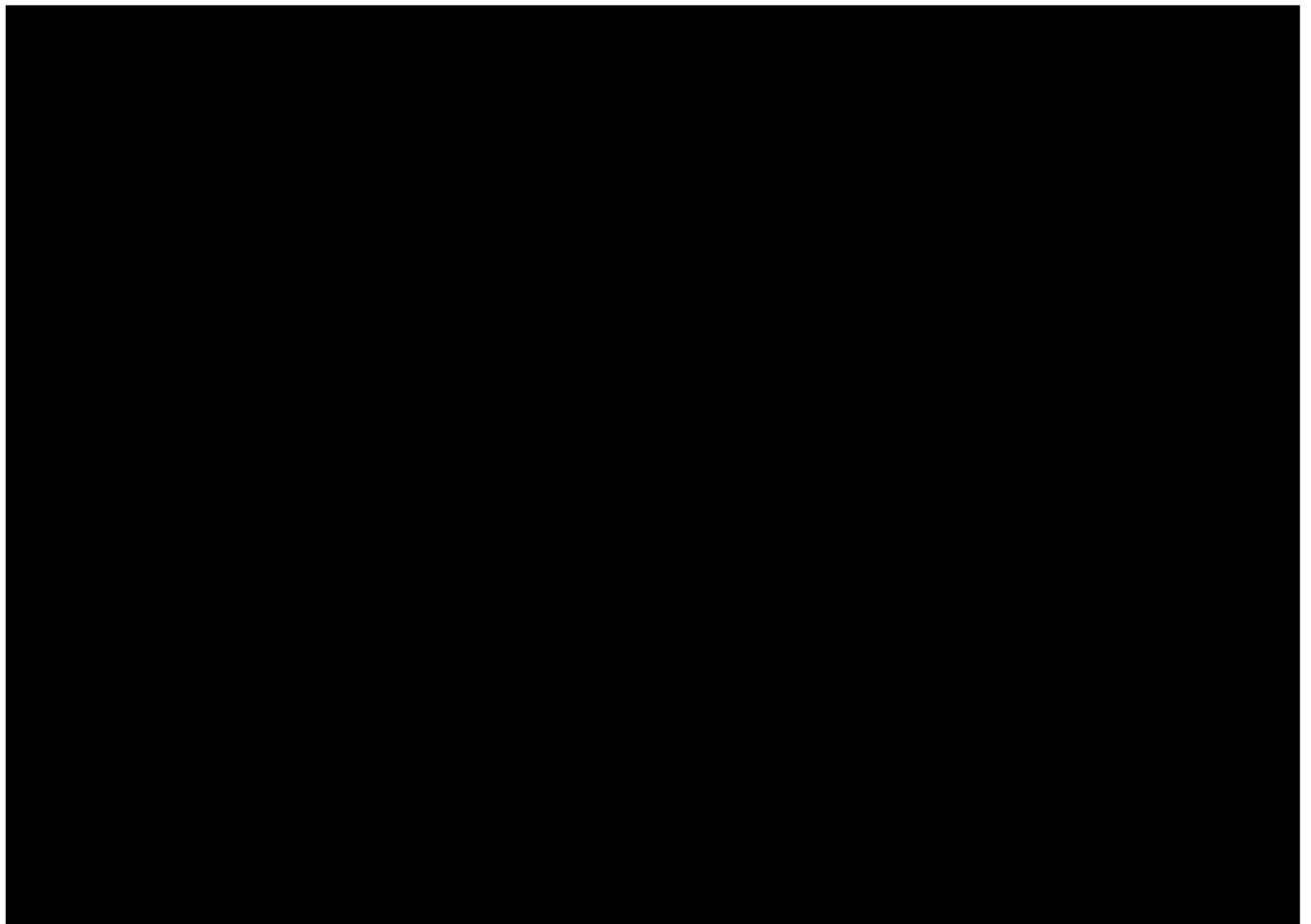
As with the PFS data, the non-monotonic standard parametric models (log-logistic, log-normal and generalised gamma) and spline models were considered to be most reflective of the hazard over time.

The generalised gamma and one-knot normal spline models produced the best statistical fit measured by AIC, while the log-normal produced the best fit in terms of BIC. However, the generalised gamma and all one-knot spline models had negligible differences in BIC compared to the log-normal.

Based on both statistical and visual fit to the KM curve and input from the company's clinical experts, the one-knot normal spline was chosen in the company's base-case to represent OS for niraparib. The EAG notes that the OS curve is capped by the base-case PFS survival curve (with the 10-year long-term remission assumption applied), and the company's clinical experts were presented with extrapolated curves with these constraints applied. Scenario analyses were

conducted applying the log-normal and generalised gamma to represent lower and upper bounds of OS, respectively. Figure 11 below shows the OS curve applied for niraparib in the base-case, noting that this is constrained from below by the chosen PFS curve, included the 10-year long-term remission assumption.

Figure 11. Overall survival in company's base case for the BRCAm population (one-knot normal spline), including base-case PFS extrapolation constraint. Produced from the company's model



As previously noted, the company assume clinical equivalence in OS between niraparib and olaparib and therefore the same survival curves are applied in both arms of the model. The company did not present any scenario analyses applying alternative assumptions regarding OS for olaparib in the CS. Following a request from the EAG during clarification, the company included the following scenario analyses:

- HR for OS based on a naïve comparison of SACT OS data () and HR for PFS based on previously presented Bucher ITC of PRIMA³ versus SOLO-1⁵, as noted in Section 4.2.4.3 (). HRs are applied to the same OS and PFS baseline curves niraparib based for on PRIMA.
- HRs applied as above but baseline OS curve fit to SACT OS data for niraparib (log-normal) and TTD for both niraparib and olaparib based on SACT KM curves. Starting dose distribution used to cost niraparib is also based on the SACT data in this scenario.

The EAG notes that the second scenario detailed above, which reflects a SACT based analysis, reduced the company's incremental net monetary benefit (NMB) at a £30,000 threshold from to . The EAG notes that NMB is presented by the company instead of the ICER as their base-case analysis results in a southwest quadrant ICER due to the very small incremental QALY differences.

4.2.4.6 EAG critique

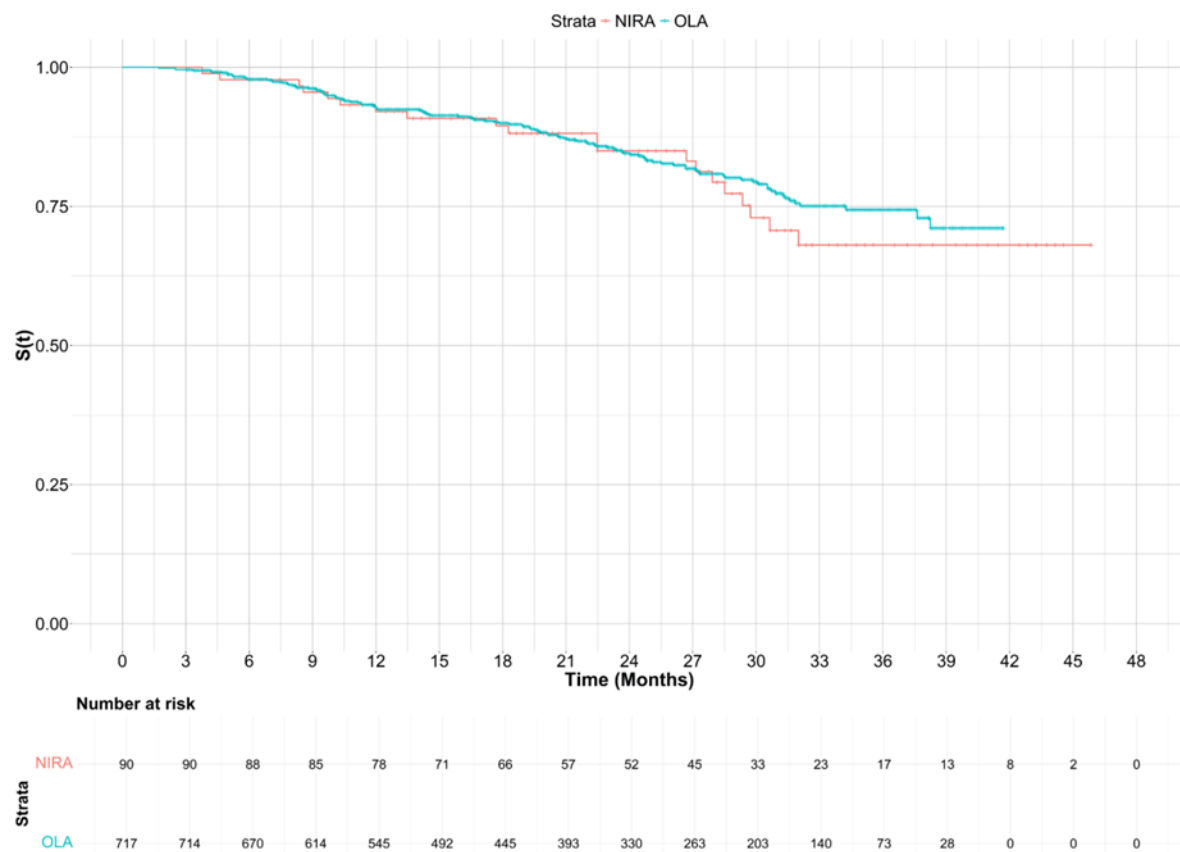
The EAG agrees with the use of the one-knot normal spline as the baseline OS curve for niraparib, as used by the company. However, as previously noted, the EAG does not agree with assuming clinical equivalence in OS for niraparib and olaparib.

The company presented RWE from SACT data for both olaparib and niraparib to assess if differences in OS can be expected between the two treatments in clinical practice, reproduced below in Figure 12. The company noted how the KM curves overlap for the first 27 months and state that divergences past this point and the numerical advantage for olaparib shown in a HR derived from a naïve comparison of SACT OS data (), provided during clarification, is a result of low patient numbers available for niraparib in the tail of the KM. While the EAG agrees that low patient numbers available in the niraparib arm may limit the reliability of any comparisons, the EAG considers this to be accounted for in the wide confidence intervals.

The EAG considers that it is likely that the comparison of SACT data could be confounded by different patient selection. When olaparib initially entered the CDF it may have been offered to all patients including those with the poorest prognosis. However, by the time niraparib entered the CDF, using a PARPi for maintenance therapy will have been considered established practice and therefore the OS data for niraparib may be a more generalisable population compared to olaparib.

The EAG considers that, as the SACT data are not contemporary datasets, any naïve comparison between the two is likely to be confounded. SACT data are available for niraparib between January 2021 and August 2024 compared to olaparib, with data from July 2019 to September 2022, with patients traced for vital status until January 2023. The EAG notes that a comparison of OS during the time period in which both treatments were available may be more informative.

Figure 12. Comparison of overall survival data from SACT for BRCAm patients: niraparib versus olaparib



Abbreviations: NIRA, niraparib; OLA, olaparib, S(t), survival

The EAG notes that in the final guidance for olaparib (TA962¹⁰) it was noted that divergence in OS curves between olaparib and placebo was not seen until 42 months in the SOLO-1⁵ trial. While the olaparib company was not able to provide a clinical rationale for this, the committee concluded that “...although the survival data for olaparib remained immature, the most recent data cutoff (March 2022) suggested that it improves overall survival compared with placebo.”. While it is acknowledged that OS was a secondary outcome in all PARPi monotherapy trials and may suffer from a lack of

statistical power for analysis, the EAG notes that niraparib was unable to demonstrate a similar improvement versus placebo in OS in PRIMA³ BRCAm population (or ITT), despite seven years follow-up data.

The EAG acknowledges that post-progression treatment with PARPi for placebo patients in PRIMA³ make comparisons of OS against placebo difficult; however, it is noted that in SOLO-1⁵, 44% of placebo patients had subsequent PARPi therapy. In the PRIMA trial for BRCAm patients, █% of patients in the placebo arm received a PARPi as subsequent second-line therapy and █% as subsequent third-line therapy. Despite a higher proportion of placebo patients receiving subsequent PARPi therapy in PRIMA than SOLO-1, it is uncertain if this difference is enough to explain any lack of OS benefit observed in PRIMA.

As previously discussed, while the EAG considers that despite the potential limitations of the ITCs, they are considered the most reliable estimates of relative effectiveness currently available. Based on the EAG calculated HR for OS between SOLO-1⁵ and PRIMA³ of xxxxxxxxxxxxxxxxxxxxxx,

Table 52 below shows the model-predicted landmark estimates of OS compared to those available from SOLO-1 and PRIMA. As shown, OS at seven years for olaparib estimated using the EAG preferred approach is much closer aligned to the most recent data available from SOLO-1 (67%) than the estimates using the company's approach (█), i.e. assuming clinical equivalence with niraparib.

Although the estimates at 10 and 20 years for olaparib using the EAG preferred approach seem high, the EAG does not consider them to be unreasonable given the observed OS at 7 years. This was confirmed by clinical experts to the EAG who stated that the resulting estimates are clinically plausible in light of the observed data.

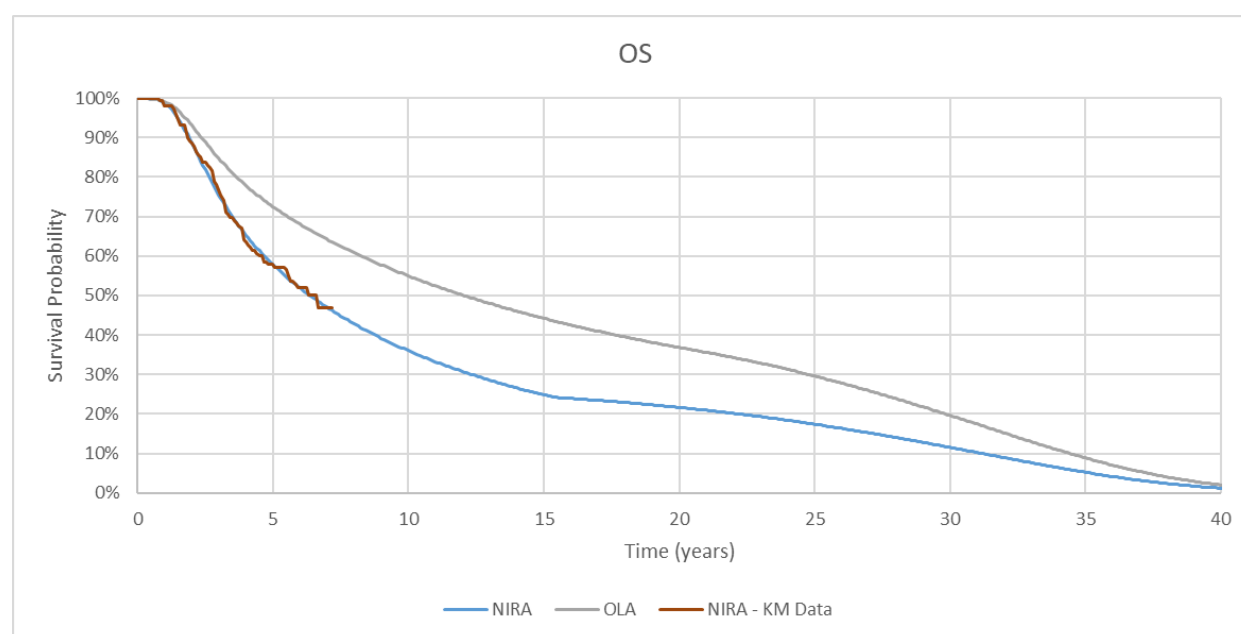
Table 52. Estimates of overall survival for the BRCam population, applying EAG derived HRs for both PFS and OS

Year	Observed data from PRIMA (niraparib)	Observed data from SOLO-1 (olaparib)	1-knot normal spline (company base case for niraparib and olaparib)*	1-knot normal spline with EAG HR for olaparib applied*
1	98.0%	-	██████	██████
3	76.8%	-	██████	██████
5	57.9%	73.1%	██████	██████
7	-	67.0%	██████	██████
10	-	-	██████	██████
20	-	-	██████	██████

* Long-term remission point of 10 years applied

Abbreviations: BRCam, breast cancer gene mutation; EAG, External Assessment Group; HR, hazard ratio; PFS, progression-free survival; OS, overall survival.

Figure 13. Overall survival using EAG preferred analysis for the BRCam population (HRs applied to estimate olaparib PFS and OS)



4.2.4.7 Progression-free survival – BRCAwt population

As with the BRCAm population, the company considered non-monotonic standard parametric (log-logistic, log-normal and generalised gamma) and all spline models to be most reflective of the hazard over time, which showed an increasing then decreasing hazard profile. The generalised gamma produced the best statistical fit based on AIC and BIC, with the one-knot normal spline producing a similar statistical fit with a negligible difference in both AIC and BIC. The generalised gamma was used in the company base-case as it produced estimates, which overlapped with the estimates from the company's three clinical experts, who agreed that around █% of patients' PF at 10 years was reasonable. The EAG notes that experts were shown the estimates predicted by the different parametric models with the 10 cure assumptions applied.

The two-knot normal spline joint fit model was implemented as a scenario analysis due to this providing the best statistical fit of the alternative models that produced estimates in line with the clinical expert opinion at 10 years. The company notes that one expert suggested estimates between █% and █% are plausible but the models that produced estimates less than █% were substantially lower with poor statistical and visual fits. The EAG agrees with the company's assessment. **Figure 14** and **Figure 15** show the Kaplan-Meier (KM) data and base-case extrapolation curve, both with and without the 10-year long-term remission assumption applied, respectively.

Figure 14. Progression-free survival in the company's base case for the BRCAwt population (generalised gamma, long-term remission assumption), produced from the company's model

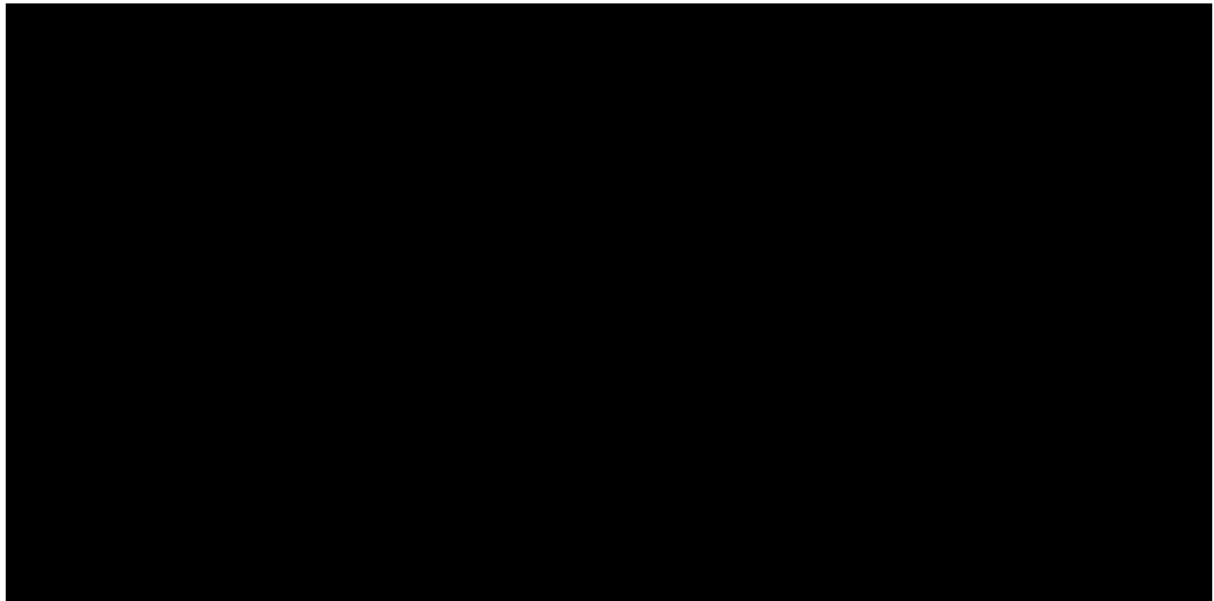
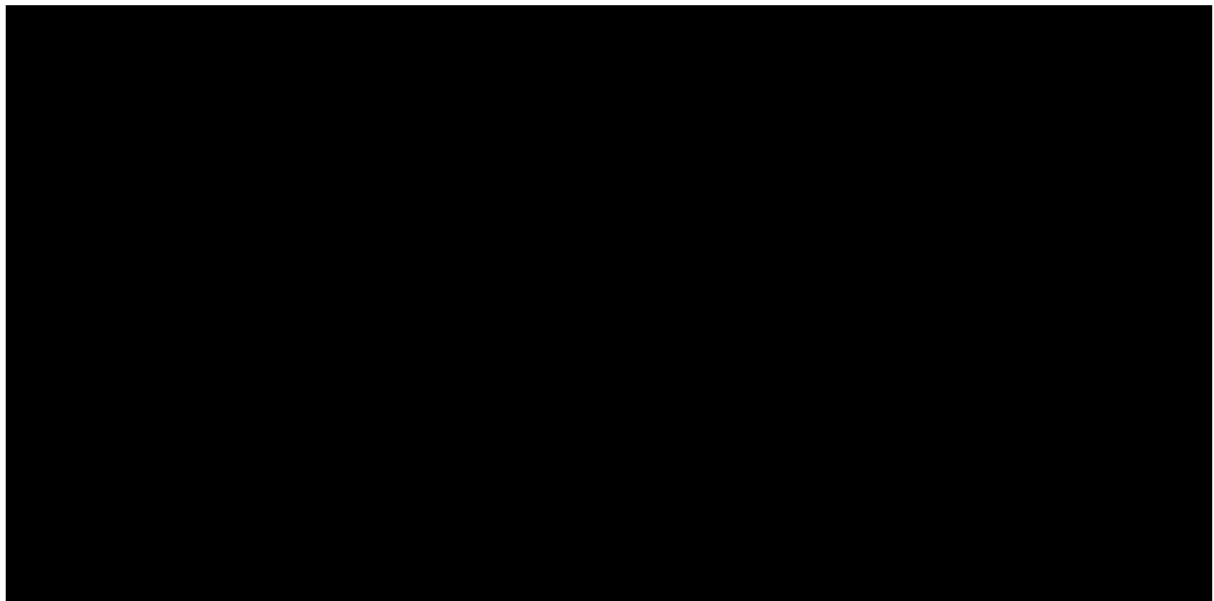


Figure 15. Progression-free survival in company's base case for the BRCAwt population (generalised gamma, no long-term remission assumption), produced from the company's model



4.2.4.8 EAG critique

As previously discussed (Section 4.2.2) the EAG considers that to produce the most robust comparison against rucaparib, the company should have split the BRCAwt population into

HRd/BRCawt and HRp/BRCawt subgroups and made use of the available data in PRIMA³ for these subgroups. The EAG requested this during clarification; however, this was not provided due to the company's argument that the high risk population of PRIMA is not comparable with ATHENA-MONO² to conduct reliable ITCs. Therefore, the EAG did not have access to all of the survival data available for the subgroups of interest from PRIMA (HRd/BRCawt and HRp/BRCawt) in order to implement these in the economic model. For example, although the PFS KM curve was available for the HRp/BRCawt population from PRIMA, the EAG did not have the equivalent for the HRd/BRCawt population. During factual accuracy it was brought the EAG's attention that these data were available in the supplementary material of Monk *et al.* 2024.¹⁷ However, during the time of the EAG report, this was not known to the EAG, and the company had not provided these data in their CS or response to clarification. Therefore, the EAG considers that this would be the most appropriate data to include for comparisons against rucaparib in the model for the most robust assessment. The EAG notes the preference for the company to implement this analysis in the economic model using available IPD, rather than requiring the EAG to digitise published KM curves. In addition, the company should also include additional data on file, not available to the EAG, related to each subgroup. For example, time to treatment discontinuation, niraparib dosage data (per cycle), proportion receiving subsequent treatment and corresponding distribution of patients receiving each type of subsequent treatment. The EAG consider this to be key issue 4b.

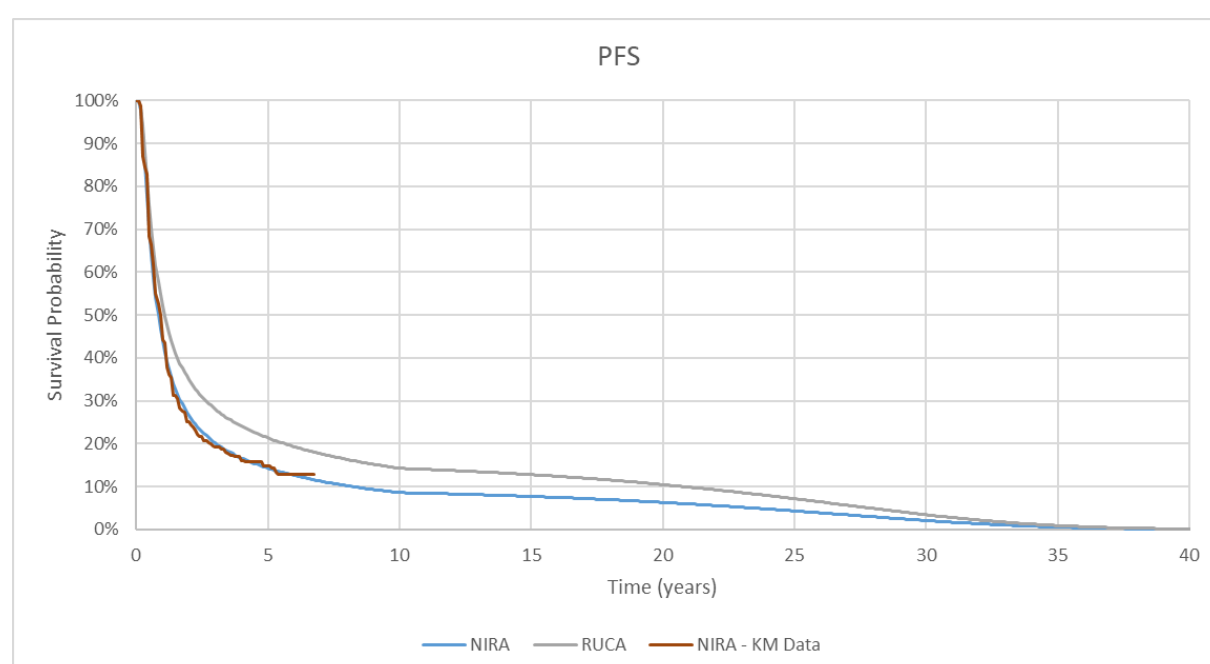
As such, in order to provide a meaningful analysis for the committee, the EAG generated a pooled BRCawt population from ATHENA-MONO² by combining published data from the HRd/BRCawt and HRp/BRCawt subgroups, as described in Section 3.4.4. The pooled BRCawt data were then used to calculate a hazard ratio comparing PFS between the rucaparib and placebo arms in the ATHENA-MONO trial, which permitted an indirect comparison of rucaparib to niraparib, for the BRCawt subgroup, to be performed. As a result, the EAG retained use of the overall BRCawt KM curve from PRIMA³ as the baseline extrapolated survival curve, as used in the company's economic model, and applied the ITC-derived HR of [REDACTED] as the preferred EAG base-case analysis. The EAG notes that as the proportion of patients with HRd/BRCawt is under-represented in ATHENA-MONO compared to PRIMA (33.22% vs 49.03%), the resulting PFS for rucaparib could be considered underestimated, as HRd/BRCawt patients would be expected to have a better prognosis (PFS) than HRp/BRCawt patients.

Upon testing the proportional hazards (PH) assumption of the EAG pooled BRCawt analysis using log-log plots and the Schoenfeld test, it appeared that the PH assumption may be violated. The EAG

recognises the limitations of applying a constant hazard ratio when PH do not hold but notes that based on the data and analyses available to the EAG during the critique stage, the EAG did not have an alternative option. However, despite this, the EAG considers that the PFS estimates produced from applying the HR to the niraparib curve are more in line with observed data for rucaparib than the company's estimates.

Figure 16 shows the PFS curves for the BRCAwt population using the EAG estimated HR of [REDACTED] to estimate PFS for the overall BRCAwt rucaparib population (10 year long-term remission applied).

Figure 16. Progression-free survival based on EAG analysis of BRCAwt population (generalised gamma, long-term remission assumption applied) with HR applied to estimate rucaparib



Landmark estimates of PFS are not available from ATHENA-MONO² for the overall BRCAwt population as this was split between HRd/BRCAwt and HRp/BRCAwt. However, the EAG has reproduced the observed estimates for the different populations available from ATHENA-MONO from years one to three, sourced from the committee papers for the rucaparib appraisal (TA1055),¹ shown in Table 53. The EAG notes that one of the company's experts noted a lower proportion may be expected to be alive at 10 years ($\approx$ [REDACTED]) but as previously noted, none of the parametric models that produced lower estimates at 10 years provided a good visual or statistical fit to the KM data. Therefore, as the baseline model may be considered optimistic, it is reasonable to expect that applying a HR to this baseline curve may produce estimates at 10 years that may also be slightly optimistic.

As shown in Table 53, the company's approach of assuming clinical equivalence for niraparib and rucaparib produces estimates of PFS for rucaparib that would not be in line with the observed data from ATHENA-MONO².

Table 53. Landmark estimate of PFS in the BRCAwt population from key clinical trials compared to model predicted PFS

Timepoint	1	2	3	10
Niraparib*				
PRIMA	44.3%	25.1%	19.2%	-
Generalised gamma (company baseline)	■	■	■	■
Rucaparib				
ATHENA MONO - HRd/BRCAwt	66.3%	45.1%	34.1%	-
ATHENA MONO - HRp/BRCAwt	52.70%	35.70%	22.40%	-
ATHENA-MONO- ITT	63.0%	45.1%	32.8%	-
Generalised gamma with EAG HR for overall BRCAwt applied	■	■	■	■
* also applied for rucaparib in company's base-case due to assuming equivalence				
Abbreviations: BRCAwt, breast cancer gene wildtype; EAG, External Assessment Group; HR, hazard ratio; HRd, homologous recombination deficient; HRp, homologous recombination proficient; ITT, intention to treat.; PFS, progression-free survival.				

The latest published estimates of median PFS at four years from ATHENA-MONO², presented at the European Society for Medical Oncology (ESMO) 2024,²¹ are also shown below in Table 54 compared to the EAG preferred model estimated value. The EAG notes that it is reassuring that the median estimates produced using their preferred approach to modelling rucaparib PFS lie in-between that reported for the HRd/BRCAwt and HRp/BRCAwt populations. While the EAG is unable to estimate where the model-predicted value should lie within that range, it is noted that it would be expected to be closer to (but higher than) that of the HRp/BRCAwt population.

Table 54. Median PFS for BRCAwt population from key trials compared to model-predicted

	Median PFS, months	Source
Niraparib		
PRIMA KM	10.9	PRIMA trial, Table 12 of CS
Generalised gamma (company baseline)	10	Model predicted
Rucaparib		
ATHENA MONO - HRd/BRCAwt	22.3	

ATHENA MONO - HRp/BRCAwT	12.1	ATHENA-MONO, Kristeleit <i>et al.</i> 2024 ²¹
ATHENA-MONO- ITT	20.2	
Generalised gamma with EAG HR for overall BRCAwT applied	13	Model predicted

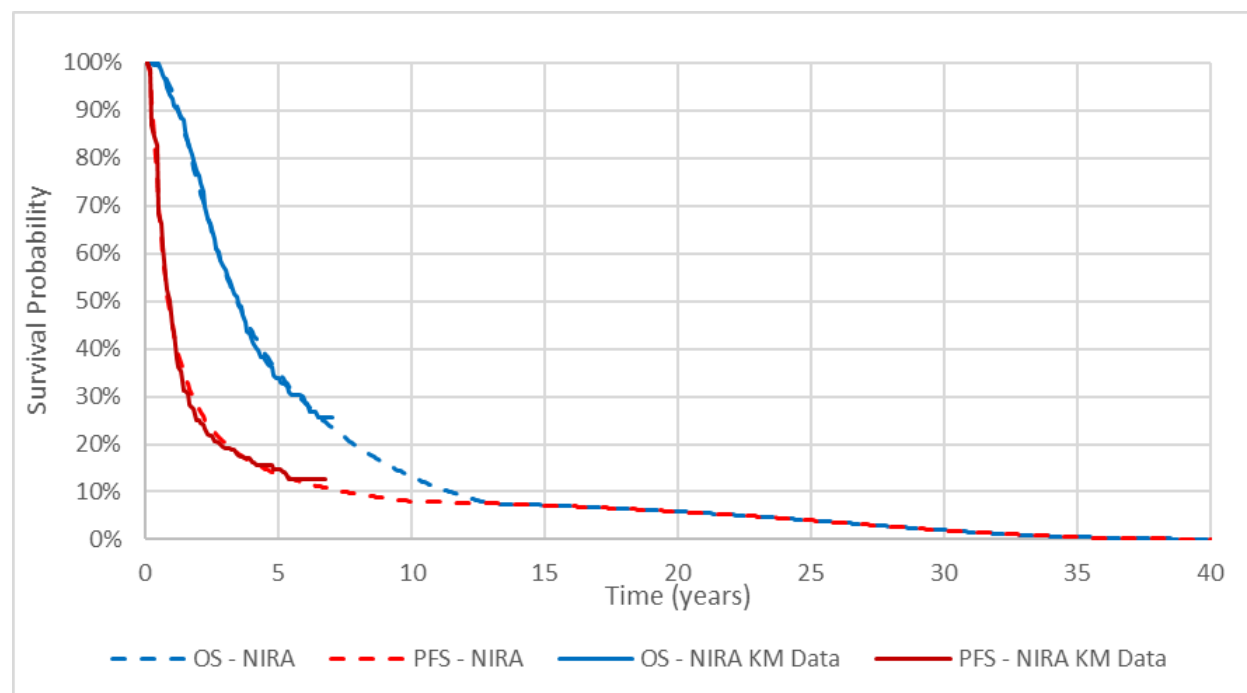
Abbreviations: BRCAwT, breast cancer gene wildtype; CS, company submission; EAG, External Assessment Group; HR, hazard ratio; HRd, homologous recombination deficient; HRp, homologous recombination proficient; ITT, intention to treat; PFS, progression-free survival.

At 20 years using the EAG preferred approach, █% of patients remain PF in the niraparib arm versus █% in the rucaparib arm.

4.2.4.9 Overall survival – BRCAwT population

The CS stated that a one-knot hazard spline was used for the base-case extrapolation of OS in the BRCAwT population based on a balance between clinical validity of the extrapolated outcomes and visual and statistical fit of the observed data. As OS is capped by PFS, which crossed at around █ this only impacted on timepoints before the crossing. While it had a small impact on the total costs for each treatment arm, due to the clinical equivalence of niraparib and rucaparib assumed by the company, it did not change the overall incremental differences. Figure 17 included below is based on the one-knot hazard spline being applied.

Figure 17. Overall survival in company's base case for the BRCAwt population (one-knot hazard spline), including base-case PFS extrapolation constraint. Produced from the company's model



As with PFS, the company assumed clinical equivalence of niraparib and rucaparib for OS in the BRCAwt population, which they state is supported by the outcomes of the Bucher ITCs of PRIME⁴ versus ATHENA-MONO² and clinical expert opinion supporting a class effect for PARPi therapies. Following clarification, the company provided the following two scenario analyses in which clinical equivalence was not assumed, based on either the ITT or HRd populations (not split by BRCA status); however, the HRs were still based on the PRIME versus ATHENA-MONO ITC rather than the EAG requested PRIMA³ versus ATHENA-MONO ITC:

- Applying a PFS HR of [REDACTED] and OS HR of [REDACTED] for niraparib versus rucaparib, based on Bucher ITC analyses for the ITT population. This increased the company's NMB by ≈£11,000 due to an increase in incremental QALYs and a decrease in incremental costs [REDACTED]
- Using a PFS HR of [REDACTED] and OS HR of [REDACTED] for niraparib versus rucaparib, based on Bucher ITC analyses for the HRd population. This reduced the NMB and resulted in [REDACTED]).

4.2.4.10 EAG critique

The EAG agrees with the use of the company's one-knot hazard spline in the base-case analysis but also notes that the log normal provided the best statistical fit to the observed data, albeit marginally. The company provided this as a scenario analysis. Due to the capping of OS by the PFS curve, most standard models and the one- and two-knot hazard splines had met the base case PFS curve by 15 years and therefore landmark estimates were equal from this time point onwards.

As noted in Section 3.4.5, the EAG does not agree with the company's argument that clinical equivalence between niraparib and rucaparib has been demonstrated and therefore does not consider applying the hazard ratio of 1 to be appropriate.

As discussed, the EAG did not have all the required data to present the preferred analysis for the BRCAwt population within the subgroups considered to be the most appropriate for this appraisal (HRd/BRCAwt and HRp/BRCAwt) (Key issue 4b). Therefore, as noted in Section 4.2.4.8, the EAG undertook an analysis to create a 'pooled' BRCAwt population for rucaparib for PFS in order to compare against the company's presented analysis for niraparib. However, the same data were not publicly available for OS and therefore the EAG was unable to perform the same analysis for OS. As an alternative approach, the EAG ran two separate analyses for the HRd/BRCAwt and the HRp/BRCAwt population. This involved using the baseline BRCAwt (all) OS curve used by the company for niraparib and applying the EAG derived HRs for each subgroup based on the ITC analyses presented in Section 3.4.4 and reproduced below (Table 20). The EAG acknowledges that this is not a preferred approach, but in light of the company not providing the requested analyses separately for HRp/BRCAwt and HRd/BRCAwt, the EAG was limited in the analysis they could provide in the available timeframe. The EAG considers this approach to provide a reasonable indication of the range of true ICER.

Table 55. EAG derived hazard ratios for OS for the comparison of niraparib to rucaparib, BRCAwt population

	EAG derived hazard ratio (95% CI)
HRd/BRCAwt	
HRp/BRCAwt	

Abbreviations: BRCAwt, breast cancer gene wildtype; CI, confidence interval; EAG, External Assessment Group; HRd, homologous recombination deficient; HRp, homologous recombination proficient; OS, overall survival.

The resulting survival curves for both niraparib and rucaparib with the HRs applied separately are shown below.

Figure 18. Overall survival for niraparib and rucaparib, applying EAG derived HR for HRd/BRCAwt population to baseline niraparib BRCAwt (all) curve

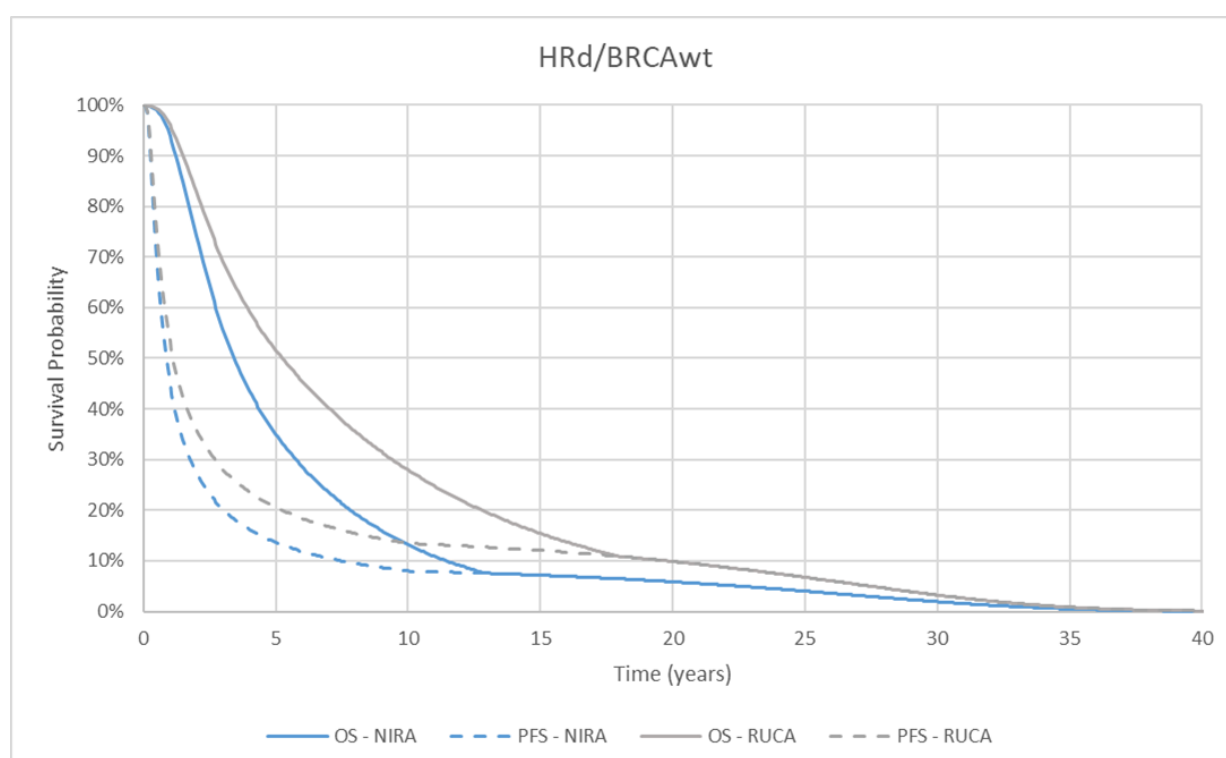
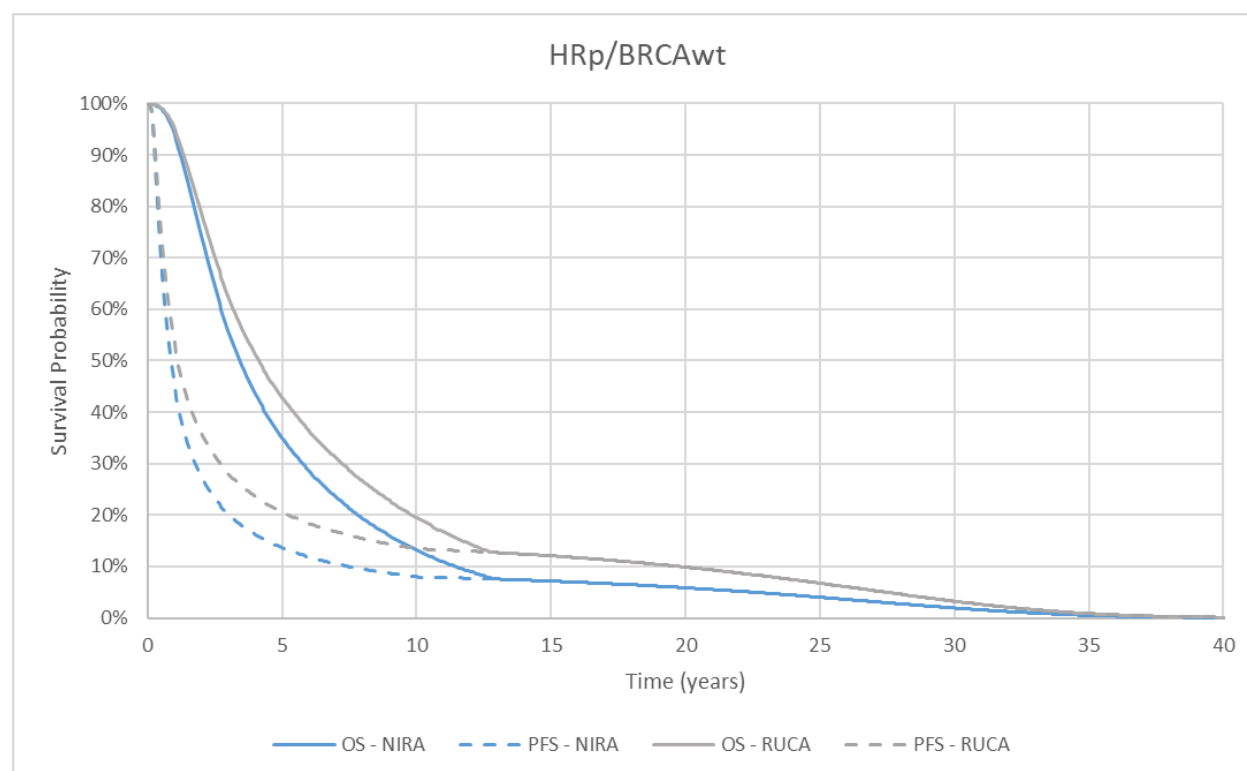


Figure 19. Overall survival for niraparib and rucaparib, applying EAG derived HR for HRp/BRCAwt population to baseline niraparib BRCAwt (all) curve



The EAG did not have access to landmark estimates of overall survival from the latest data cut of ATHENA-MONO² and therefore could not compare to the modelled outcomes for rucaparib. However, Table 56 below presents the estimates of overall survival in the niraparib arm and the rucaparib arm when the separate HRs are applied to the overall BRCAwt baseline curve. To note, as estimates of OS are capped by the PFS curve, the crossing point differs in the EAG approach for rucaparib due to also not assuming clinical equivalence for PFS, as discussed in Section 4.2.4.8. Based on the immature OS data available for rucaparib and the observed benefit for OS with niraparib in PRIMA³ being similar to placebo, a clinical expert to the EAG noted that the predicted OS outcomes for both rucaparib and niraparib at 10 and 20 years may be overly optimistic. However, the EAG considers the difference in benefit is still clinically plausible.

In order to allow a comparison against the BRCAwt (all) population provided for niraparib, the EAG has also calculated the weighted estimates of overall survival for rucaparib based on the observed split of HRd/BRCAwt (49.03%) and HRp/BRCAwt (50.97%) observed in the PRIMA³ trial for illustrative purposes.

Table 56. Estimates of overall survival for the BRCAwt population, applying EAG-derived HRs for the HRd/BRCAwt and HRp/BRCAwt populations

Timepoint	1	3	5	10	20
Niraparib*					
PRIMA	92.4%	56.6%	33.7%	-	-
One-knot hazard spline (company baseline)	████	████	████	████	████
Rucaparib					
One-knot hazard spline with EAG HR for HRd/BRCAwt	████	████	████	████	████
One-knot hazard spline with EAG HR for HRp/BRCAwt	████	████	████	████	████
Weighted estimates of OS based on HRd/BRCAwt:HRp/BRCAwt split in PRIMA	████	████	████	████	████
* also applied for rucaparib in company's base-case due to assuming equivalence Long-term remission point of 10 years applied to all estimates and capping by PFS. Abbreviations: BRCAwt, breast cancer gene wildtype; EAG, External Assessment Group; HR, hazard ratio; HRd, homologous recombination deficient; HRp, homologous recombination proficient; OS, overall survival.					

4.2.4.11 EAG preference to treatment effectiveness

As discussed, the EAG consider the company's approach to modelling the relative treatment effect of the included comparators to be flawed and do not consider a robust argument has been provided to support the assumption of clinical equivalence between the three PARPi therapies included for the corresponding populations. The EAG reiterates that making an assumption of clinical equivalence is a "high bar" requiring an appropriately powered RCT to demonstrate no clinically meaningful differences in PFS and OS; it is not an assumption to make in the presence of high uncertainty due to limited power in simple ITCs. In addition, the EAG considers the analysis provided for the BRCAwt population compared against rucaparib does not utilise all relevant populations and evidence available. Specifically, the EAG considers that the cost-effectiveness analysis should have included comparisons of niraparib and rucaparib in the HRd/BRCAwt and HRp/BRCAwt subgroups.. Due to time constraints and the company not performing the EAG preferred analysis for the BRCAwt population at clarification, the EAG has had to perform an exploratory analysis for the preferred base-case to provide an estimate of the ICERs likely range, but notes the preference would be for the company to conduct the requested analyses and implement these in the model. Below summarises the approach used by the EAG for the two included comparisons:

Niraparib versus olaparib – BRCAm

- Baseline PFS and OS curves for niraparib are equal to those used by the company;
- Olaparib PFS derived by applying HR of [REDACTED];
- Olaparib OS derived by applying a HR of [REDACTED].

Niraparib versus rucaparib – BRCAwt

- Baseline PFS and OS curves for niraparib are equal to those used by the company;
- Rucaparib PFS derived by applying EAG-derived HR for the BRCAwt (all) population based on analysis of rucaparib ATHENA-MONO² data; [REDACTED];
- As the equivalent data was not available to produce a BRCAwt (all) HR to derive rucaparib OS, the EAG applied two separate analyses to represent the range at which the ICER would lie:
 - HR for HRd/BRCAwt population of [REDACTED] applied to overall OS curve;
 - HR for HRp/BRCAwt population of [REDACTED] applied to overall OS curve.

The EAG acknowledges the aforementioned limitations in their approach (Section 4.2.4.2) yet considers it to provide a more informative comparison than those provided by the company.

4.2.5 Treatment discontinuation

Time to treatment discontinuation (TTD) is used to inform the proportion of patients in the PFS health state either on- or off-treatment. In the niraparib arm, the company use the subgroup data (BRCAm or BRCAwt) on TTD from the PRIMA³ trial for each respective comparison. Based on poor visual fit to the observed data of standard parametric model, the company use the KM data directly for the first 77-months of the model. Beyond this point, the proportion remaining on treatment is informed by the parametric extrapolation curve based on the best statistical fit (exponential for BRCAm, log-logistic for BRCAwt; further detail in Appendix J of the CS).

TTD KM data for the comparators were not available from the key trials used to inform effectiveness and had been redacted from previous NICE appraisal papers.. The company therefore state that to provide a consistent approach across the comparators, TTD curves were estimated by adjusting PFS

curves by adverse event discontinuation probabilities, from the corresponding trials, and assuming a constant discontinuation rate.

Despite no explicit stopping rule for niraparib in the SmPC, the company note how the PRIMA³ trial protocols implemented a 36-month stopping rule. Based on clinical opinion stating that, “*the proportion of patients remaining on niraparib treatment after 36 months is estimated to range from 5% to 10%*”, the company assume that at 36 months, 90% of patients discontinue treatment. This results in a sharp drop in the TTD curve, as shown in Figure 20 and Figure 21 for the BRCAm and BRCAwt, respectively.

The company also apply the same approach of 90% of patients discontinuing treatment for both olaparib and rucaparib. However, due to the earlier stopping rule of these treatments at two years, this is implemented earlier (24 months).

The company also applied a range of scenario analyses around TTD assumptions applied for both niraparib and the comparators, including use of SACT data for niraparib and olaparib, detailed in Section 3.4.7 of the CS.

Figure 20. Time to treatment discontinuation used in the company base for niraparib and olaparib, BRCAm population. Reproduced from Figure 34 of the CS

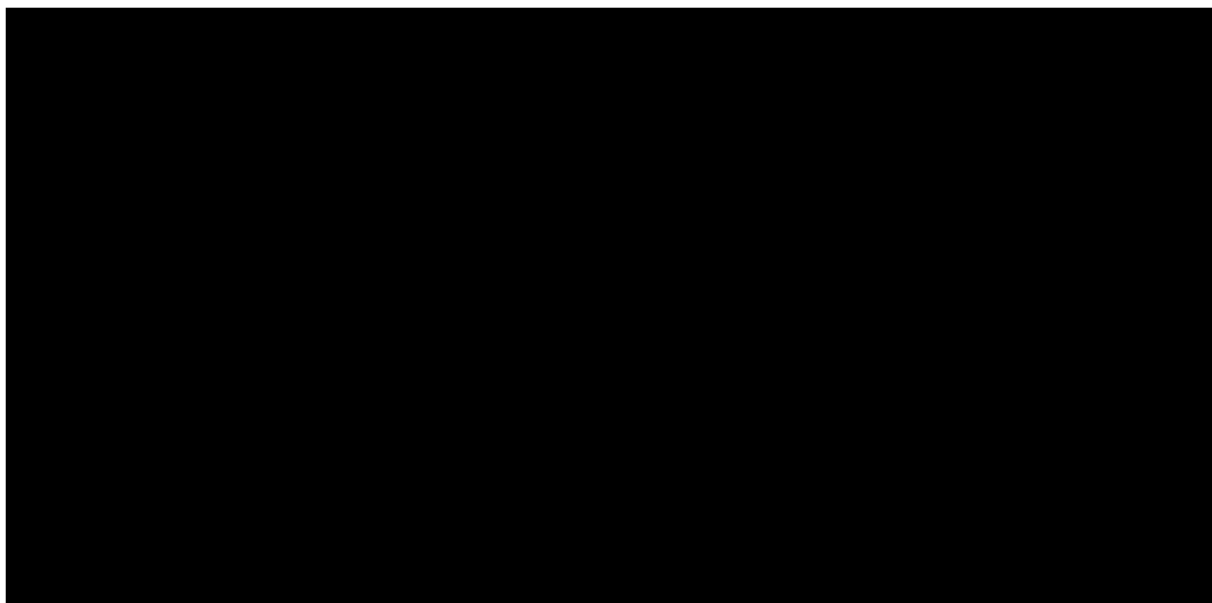
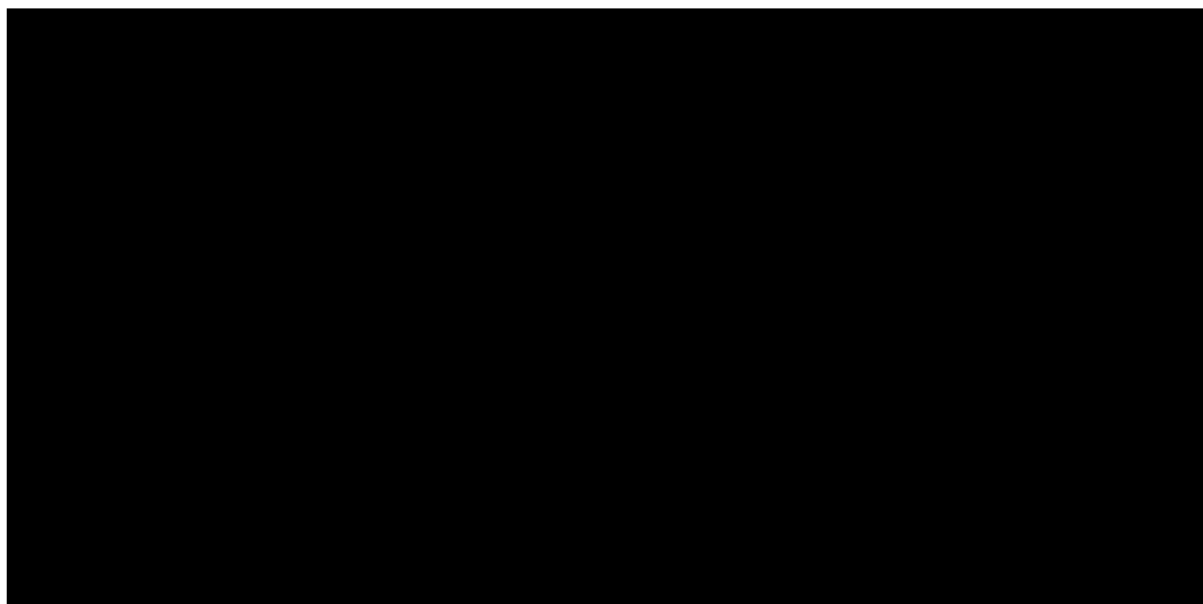


Figure 21. Time to treatment discontinuation used in the company base for niraparib and niraparib, BRCAwt population. Reproduced from Figure 35 of the CS



4.2.5.1 EAG critique

The company state in the CS that a published TTD curve is available from SOLO-1⁵; however, this was not used as the equivalent is not available for rucaparib, therefore, the company uses PFS and AE discontinuations to estimate TTD for olaparib to use a consistent approach with rucaparib. The EAG notes that this is not consistent across all treatments included in the model because the TTD curve for niraparib is used. The EAG considers it more appropriate to use the direct trial data when available. However, the EAG was unable to identify the SOLO-1 TTD KM curve in a publicly available source as this was redacted in the NICE committee papers for the olaparib appraisal¹⁰ and it was also not provided by the company upon request during a clarification. However, it is noted in the NICE appraisal for olaparib that there was a sharp drop in TTD at 2 years and only small patient numbers available in the tail, with 5% of patients remaining on treatment at 5 years. The company stated that as the model already has an option to use the median TTD estimate from SOLO-1 (24.6 months) with an exponential curve fit, this will provide similar and more conservative estimates than using the SOLO-1 TTD curve directly. The EAG notes that this scenario reduced the incremental costs in the BRCAm population by ≈£9,000 compared to the company base-case using PFS and AE discontinuations.

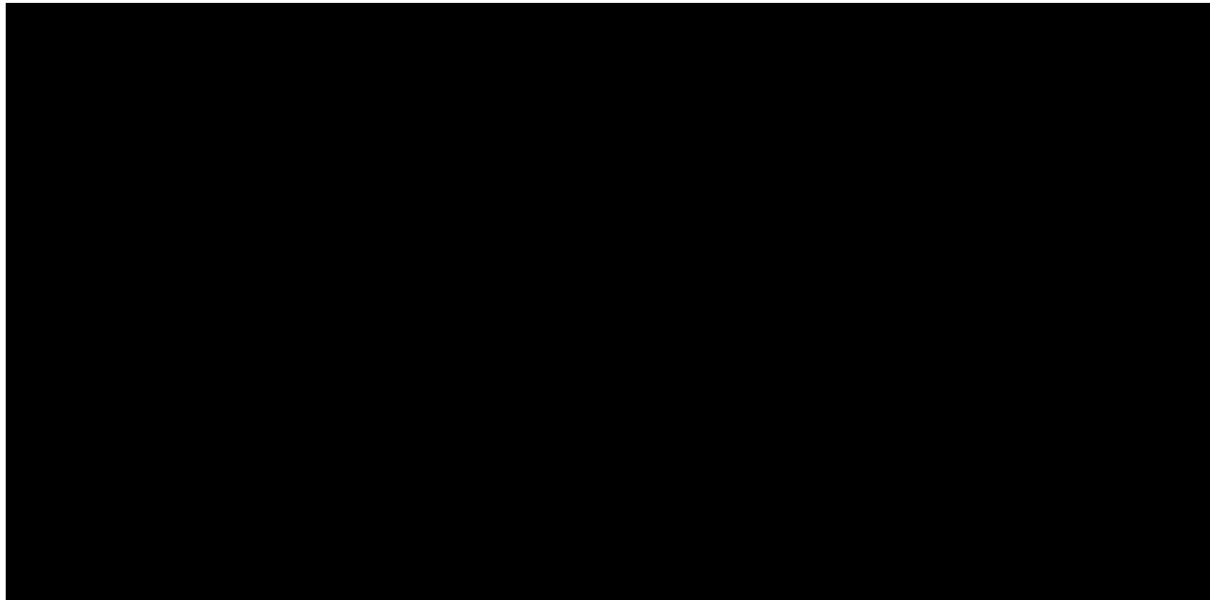
Based on a lack of TTD data from olaparib and rucaparib, the EAG explored applying a constant hazard ratio based on TTD:PFS observed in PRIMA³, estimated by recreating IPD data from the provided KM curves in the CS for TTD and PFS, to the EAG preferred PFS curves used for rucaparib and olaparib. However, the EAG notes that when implementing this approach, it resulted in a large initial decrease in TTD within the first month of treatment that would not be in line with clinical practice. Therefore, in light of a lack of KM data for the comparators, and to maintain consistency with the accepted approach in the recent appraisal of rucaparib (TA1055¹), the EAG has applied the same approach as the company based on PFS and AE discontinuations in the base case. The EAG notes that this could underestimate discontinuations as patients will discontinue for reasons other than adverse events. However, as AEs are most likely to occur at the beginning of treatment, applying a constant rate of discontinuations throughout may account for this to a degree. The EAG notes that using the PFS and AE approach is a more conservative option than using the median TTD from the SOLO-1⁵ trial for olaparib.

Based on the application of the stopping rule applied in the company's approach, this results in a sharp decrease in patients on treatment at two years for the comparators and three years for niraparib, as shown in Figure 20 and Figure 21. The EAG notes that the company's approach means that only 10% of those who were already remaining on treatment at 36 months continue beyond this time point, rather than it being 10% of all patients, which is what the EAG considers is implied by the company's statement that, "*the proportion of patients remaining on niraparib treatment after 36 months is estimated to range from 5% to 10%*". The EAG notes that in the BRCAwt population, this results in it decreasing from ■% of patients on treatments at 36 months to just ■% the following month. However, the EAG notes that in the company's expert meeting minutes, it is stated that continuation for a patient who is progression-free beyond 36 months would be extremely rare. The EAG's clinical expert noted that they expect the proportion of patients continuing beyond 36 months with niraparib to be lower than shown in the PRIMA³ trial in clinical practice, as these patients are likely fitter and would not expect any patients to continue beyond 5 years.

Both the PRIMA³ trial and SACT data for the BRCAm population show a proportion remain on treatment beyond 36 months, with SACT data for niraparib showing that there is 27.5% at three years and 17% of patients still receiving niraparib at 3.5 years, shown in Figure 22. For olaparib, SACT data showed a decrease in patients around two years with 13% still on treatment at three years. The company applied a scenario analysis using SACT TTD data but noted that due to the sharp drop at

two years for olaparib, standard parametric curves failed to provide a reasonable fit. The EAG notes that more flexible models may have rectified this but were not explored by the company.

Figure 22. Time to treatment discontinuation from SACT data for niraparib and olaparib, BRCam population. Produced from the company's economic model



In the recent appraisal for rucaparib, the two-year stopping rule was implemented for rucaparib, in line with the SmPC.³⁶ For the comparison with olaparib plus bevacizumab in the rucaparib appraisal, the company (and EAG) base-case also stopped treatment with olaparib at two years. While the EAG acknowledges the evidence for continued treatment beyond 2 and 3 years for olaparib and niraparib, respectively, to maintain consistency with the most recent appraisal and across the three PARPi therapies included in the current appraisal, in the EAG preferred analysis, all patients on rucaparib/olaparib discontinue at two years and three years for niraparib. In light of the uncertainty (key issue 5) regarding the proportion of patients remaining on treatment with niraparib beyond three years, the EAG also applies a scenario (in both the BRCam and BRCAwt populations) in which niraparib TTD is informed by the full mature KM curve, with no stopping rule applied. An additional scenario analysis is also explored on the EAG base-case, directly applying the KM curves from the SACT data for niraparib and olaparib in the BRCam population (Section 5.2.4).

None of the standard parametric curves provided a good visual fit to the observed KM TTD curve for niraparib, with models underpredicting TTD between 30 and 60 months in the BRCam population and between approximately 30 to 55 months in the BRCAwt population. Based on the EAG

preference to apply the stopping rule at 36 months, it was considered more appropriate to apply the observed KM up to this point, rather than impose a poorly fitting model.

The EAG preferred analysis for TTD is therefore as follows:

- Niraparib TTD KM curve applied up to 36 months, upon which all patients discontinue;
- Rucaparib and olaparib TTD informed by PFS and AE discontinuations up to 24 months, upon which all patients discontinue.

4.2.6 Adverse Events

Adverse events (AEs) were included in the model if they were grade 3+, were treatment-related, and occurred in more than five per cent of patients in either treatment arm.

Niraparib AE incidence was informed using the MONITOR-UK⁶ study, while olaparib and rucaparib were informed by their respective clinical trials (Table 57).

Table 57. Grade 3+ AE incidence included in the model (reproduced from Table 42 in the CS)

Adverse event	Niraparib		Rucaparib	Olaparib
	MONITOR-UK (n=165)	PRIMA (n=484)	ATHENA MONO (n=425)	SOLO-1 (n=260)
Anaemia	9.80%	████	28.70%	21.90%
Hypertension	15.20%	████	0.00%	0.00%
Increased ALT/AST	0.00%	████	10.60%	0.00%
Neutropenia	0.00%	████	14.60%	8.50%
Neutrophil count decreased	7.70%	████	0.00%	0.00%
Platelet count decreased	11.00%	████	0.00%	0.00%
Thrombocytopenia	0.00%	████	7.10%	0.80%

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CS, company submission.

While niraparib AE incidence may have also been informed using niraparib's pivotal trial, the company preferred AE incidence from MONITOR-UK⁶ as in the company's base case RWE was also used to inform the starting dose of niraparib (200mg vs 300mg) at baseline. In consultation with the company's clinical experts, their clinicians stated that AE frequencies observed in MONITOR-UK were appropriate and more reflective of niraparib use in UK clinical practice.

In consideration of the use of phase 3 trial data to inform comparator AE incidence, and the RWD to inform intervention AE incidence, the company stated that RWD for olaparib is similar to that of SOLO-1⁵, which was used to inform olaparib AE incidence. Comparatively, the difference in PRIMA³ and real-world evidence can be attributed to differences in starting doses, with a higher proportion of patients expected to start on lower doses (200mg) in clinical practice and therefore experience fewer AEs. The company additionally noted that niraparib is the only PARPi treatment for which the marketing authorisation mandates weekly blood count tests for the first month, followed by monthly tests for the following nine months. Additionally, a GSK sponsored patient support program is in place which provides blood testing at home for patients being treated with niraparib, helping to manage the incidence of AEs.

4.2.6.1 *EAG critique*

While the EAG appreciates the company's arguments for informing AE incidence for niraparib using MONITOR-UK⁶, the EAG considers that as treatments effects and treatment discontinuations are intrinsically linked to dose, and that PRIMA³ has been used to inform both of these parameters, PRIMA is also the most appropriate source to inform starting doses in the model. For this reason, the EAG also considers PRIMA to be the most appropriate source to inform AE incidence for niraparib, with PRIMA being used in the EAG's preferred base case assumptions. The health-related quality of life and cost implications of AEs are discussed in detail in Sections 4.2.7.2 and 4.2.8.4, respectively.

The EAG notes that due to the company assuming equivalence in clinical outcomes between the three included PARPi therapies, adverse events account for the only differences observed in quality-adjusted life years (QALYs).

4.2.7 *Health-related quality of life*

4.2.7.1 *Health state utility values*

Health state utility values were informed using EQ-5D-5L responses from the PRIMA³ trial. EQ-5D-5L responses were converted to 3L using the Hernandez-Alava *et al.* 2020 cross-walk algorithm,³⁷ as preferred in the NICE reference case.³⁰ The company used a multivariable linear model, which considered covariate combinations of progression status, BRCA status, HRD status and treatments to derive health state utility values. To address the positive correlation of utility scores across repeated patient visits, the company employed a Generalised Estimating Equation (GEE), assuming compound symmetry or autoregressive correlation to ensure model convergence. Of the models with differing

covariate combinations, the model which only included disease progression as a covariate resulted in the lowest quasi-information criteria (QIC) and was therefore used in the company's base case. Table 58 presents a summary of the health state utilities assumed in the model.

Table 58. Health state utility values (reproduced from Table 45 in the CS)

Health States	Mean	SE	Reference Age (Years)	Source
Progression Free	██████	██████	██████	PRIMA
Progressed	██████	██████		

Abbreviations: CS, company submission; SE, standard error.

Utility values were adjusted by age to reflect decreases in health-related quality of life over time. Adjustments were made using UK general population utility norms, which were sourced from the Hernandez-Alava *et al.* 2022 NICE DSU report.³⁸

4.2.7.2 Adverse event disutility

Adverse event disutilities were calculated as the product of adverse event incidence (Table 57) and disutility (Table 59) and applied as a one-off QALY loss at the start of the model (Table 60).

Table 59. Adverse event disutilities (reproduced from Table 43 in the CS)

Adverse Events	Disutility	SE	Duration (weeks)	SE	Estimated QALY Loss Per AE	Source
Anaemia	-0.0800	0.0080	1.0000	0.1000	-0.0015	NICE TA1055 ¹
Hypertension	-0.1300	0.0130	1.5714	0.1571	-0.0039	NICE TA1055 ¹
Increased ALT/AST	-0.0900	0.0090	1.6000	0.1600	-0.0028	NICE TA1055 ¹
Neutropenia	-0.0900	0.0090	1.3286	0.1329	-0.0023	NICE TA1055 ¹
Neutrophil count decreased	-0.0900	0.0090	1.3286	0.1329	-0.0023	NICE TA1055 ¹
Platelet count decreased	-0.0900	0.0090	1.3286	0.1329	-0.0023	Assumed same as neutropenia
Thrombocytopenia	-0.0900	0.0090	1.3286	0.1329	-0.0023	Assumed same as neutropenia

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CS, company submission; QALY, quality-adjusted life year; SE, standard error.

Table 60. One-off adverse event disutility (reproduced from Table 44 in the CS)

Treatment	One-off AE-related QALY loss
Niraparib	-0.00117
Rucaparib	-0.00123
Olaparib	-0.00055
Abbreviations: AE, adverse event; CS, company submission; QALY, quality-adjusted life year	

4.2.7.3 EAG critique

The EAG considers that the methods used to derive health state utility values are robust, that the values reflect those of the original submission, and are appropriate for use.

The EAG notes that the CS lacks detail around how EQ-5D data was captured, specifically, at what time points during the PRIMA³ trial EQ-5D scores were recorded and the change in the number of scores over time. However, given the face validity of the health state utility values, the EAG considers that while this additional information would be beneficial for transparency, its absence is unlikely to compromise the validity of the derived utilities.

With respect to adverse events, given the assumption of equal efficacy in the company's base case, the difference in QALYs is solely driven by the differences in adverse events. As stated in Section 4.2.6, the company has preferred to inform niraparib adverse event incidence using MONITOR-UK,⁶ a RWE study, as opposed to PRIMA³, the niraparib study that is used to inform the model's treatment effects. As such, the EAG considers that PRIMA is the more appropriate source to inform adverse event (and so adverse event disutilities). When assuming the PRIMA AE incidence for niraparib, the one-off QALY loss applied in the first cycle [REDACTED] to [REDACTED], [REDACTED]. The PRIMA AE incidences are assumed in the EAG base case.

4.2.8 Resource use and costs

Based on the company's review of published economic studies and prior NICE appraisals, the company's submission included drug acquisition, administration, healthcare resource use, adverse events, subsequent treatments and terminal care costs. The following sub-sections describe the inputs and underlying assumptions used to inform the model for each specific cost.

4.2.8.1 Acquisition costs

Treatment acquisition costs were informed using the cost per package and dosing regimens (from prescribing information and/or clinical trials). Cost per package information was obtained from the British National Formulary and electronic market information tool (eMIT).^{39, 40} In addition to the patient access scheme (PAS) discount for niraparib, confidential prices are available for olaparib and rucaparib, and so the EAG has produced a confidential appendix to this report.

In the CS, the company noted that the recommended starting dose of niraparib is 200mg, taken once orally daily. However, 300mg is recommended for patients who weight $\geq 77\text{kg}$ and have a baseline platelet count of $\geq 150,00/\mu\text{l}$. Therefore, in the company's base case the SACT data set was used to inform the distribution of 200mg and 300mg doses received by patients at baseline. The SACT data were considered the most appropriate source to inform the dose distribution by the company as the data aligned with dosing in the MONITOR-UK study,⁶ which clinical experts consulted by the company stated was a more accurate reflection of niraparib use in UK clinical practice. Relative dose intensity (RDI) was also included in the model, with PRIMA³ informing niraparib RDI. In the company's base case, RDI for rucaparib and olaparib was assumed to be 100%. This was due to the lack of available data to inform mid-cycle dose adjustments. However, the company conducted a scenario analysis using the RDIs for olaparib and rucaparib from NICE TA1055¹, which were 96% and 88% for the BRCAm and BRCAwt populations, respectively. However, the EAG notes that in the appraisal for rucaparib (TA1055¹), in relation to the EAG removing RDI multipliers from all analyses, the CDF lead recalled that *"...rucaparib had the same cost per pack regardless of the strength per tablet. So, dose reductions are not expected to be associated with substantial cost savings if applied in practice"*. It was also noted that this was the case in the olaparib appraisal and therefore the EAG considers assuming 100% RDI for the comparators to be appropriate.

Table 61 presents a summary of the distribution of 200mg and 300mg patients at baseline in addition to treatment-specific RDIs.

Table 61. Dosing distribution at baseline and relative dose intensities

	Niraparib		Rucaparib	Olaparib
Dosing type	Fixed	Fixed	Fixed	Fixed
Route	Oral	Oral	Oral	Oral
Dose	200 mg	300 mg	600mg	300mg
% of patients at baseline	87% BRCAm 83% BRCAwt	13% BRCAm 17% BRCAwt	-	-

Relative dose intensity	■■■■ BRCAm ■■■■ BRCAwt	■■■■ BRCAm ■■■■ BRCAwt	■■■■	■■■■
Abbreviations: BRCAm, breast cancer gene mutation; breast cancer gene wildtype.				

In addition, the company conducted the following scenario analyses;

- Informing the distribution of 200mg vs 300mg patients at baseline using the PRIMA³ trial;
- Applying the average niraparib dose received in the PRIMA³ trial (■■■■ for BRCAm, ■■■■ for BRCAwt);
- Applying the proportion of patients receiving each of the three niraparib doses (100 mg, 200 mg, 300 mg) per month over the PRIMA³ trial duration (shown in Appendix K of the company submission);
- Using the relative 200mg (82.8%) vs 300mg (17.2%) starting dose distribution based on data from the MONITOR-UK study.⁶

Using the treatment package costs and dosing information, Table 62 presents the calculated acquisition costs per model cycle for the BRCAm and BRCAwt populations.

Table 62. Acquisition costs per model cycle (reproduced from Table 49 in the CS)

Population	Treatment	Dose	Acquisition cost per model cycle
BRCAm	Niraparib	200mg	£■■■■
	Niraparib	300mg	£■■■■
	Olaparib	300mg	£4,837
BRCAwt	Niraparib	200mg	£■■■■
	Niraparib	300mg	£■■■■
	Rucaparib	600mg	£6,361
Abbreviations: BRCAm, breast cancer gene mutation; breast cancer gene wildtype; CS, company submission.			

4.2.8.2 Administration costs

Following approaches in previous TAs (TA946⁹ and TA962¹⁰), oral drugs administered at home were assumed not to incur any administration-related costs and therefore all PARPi therapies included had no administration costs applied. However, an option was included in the model to apply oral chemotherapy administration costs to all PARPi therapies, either as a one-off or a monthly cost (as per administration).

Subsequent treatments received on progression (Section 4.2.8.5) had administration costs applied to intravenous (IV) drugs, with a different cost applied depending on the administration visit (initial vs subsequent attendance) and complexity of administration, shown below in Table 63.

Table 63. Drug administration costs used in company base model

Administration type	Unit cost	Source
Deliver Exclusively Oral Chemotherapy	£240	NHS reference costs 2023/24; ⁴¹ Outpatient procedures: Medical Oncology Service. HRG (SB11Z). Deliver Exclusively Oral Chemotherapy
IV Simple administration – First attendance	£133	NHS reference costs 2023/24; ⁴¹ Outpatient procedures: Medical Oncology Service. HRG (SB12Z) Deliver simple parenteral chemotherapy at first attendance
IV Complex Administration – First attendance	£184	NHS reference costs 2023/24; ⁴¹ Outpatient procedures: Medical Oncology Service. HRG (SB13Z) Deliver more complex parenteral chemotherapy at first attendance
IV Subsequent administration	£198	NHS reference costs 2023/24; ⁴¹ Outpatient procedures: Medical Oncology Service. HRG (SB15Z) Deliver subsequent elements of a chemotherapy cycle
Abbreviations: HRG, health resource group; IV, intravenous; NHS, national health service.		

4.2.8.3 Health care resource use

Resource use was calculated and applied separately for each of the model's health states, namely;

- Progression-free - On maintenance treatment;
- Progression-free - Off maintenance treatment;
- Progressed disease.

The company noted that in the absence of available data to differentiate monitoring frequencies by treatment within health states, the same frequencies of health care resource use were assumed across all treatments. An exception to this was the addition of a one-off monitoring session for niraparib patients in the first cycle of the model, which included four additional blood tests.

Health care resource use frequencies assumed in the model are presented in Table 64, with Table 65 presenting the resource use costs per cycle. As per In line with NICE TA962¹⁰ and TA946⁹, a 7-year stopping rule was applied in the base case for progression free patients, meaning these patients no longer incurred resource use costs after this time point. The company additionally conducted a scenario analysis where no stopping rule was applied to progression-free patients.

Table 64. Health state resource use and frequencies (reproduced from Table 50 in the CS)

Health state	Outpatient Oncologist Visit	Complete Blood Count	CT scan	Source
Progression free- on treatment – first cycle (niraparib only)	-	2.67	-	NICE TA1055 ¹ and NICE TA946 ⁹ Niraparib SmPC ⁴²
Progression free - on treatment (up to 7 years)	1.33	1.33	0.17	
Progression free - off treatment	0.33	0.33	0.08	
Progressed disease	1.33	1.33	0.33	
Unit cost	£ 191.00	£ 7.66	£ 110.42	
Source	NHS Reference Cost (WF01A) ⁴¹	NHS Reference Cost (PATH05) ⁴¹	NHS Reference Cost (RD20A - RD27Z) ⁴¹	
Abbreviations: CS, company submission; CT, computed tomography; NHS, National Health Service; SmPC, summary of product characteristics.				

Table 65. Health care resource use per health state per cycle (reproduced from Table 52 in the CS)

Health states	Cost per Cycle
Progression free - on treatment – first cycle (niraparib only)	£ 20.43
Progression free - on treatment	£ 283.32
Progression free - off treatment	£ 75.39
Progressed disease	£ 301.65
Abbreviations: CS, company submission.	

4.2.8.4 Adverse events

Adverse event (AE) costs were applied as a one-off cost in the first model cycle. AE costs were informed using NHS reference costs and AE incidence (Table 57).

Table 66 presents the costs associated with each AE and the one-off cost applied in the first cycle for each treatment.

Table 66. AE unit and treatment costs

Adverse event	Cost of AE Per Episode	NHS Reference Codes
Anaemia	£802.00	SA04G
Hypertension	£759.00	EB04Z
Increased ALT/AST	£15.00	PATH04

Neutropenia	£636.47	SA08G
Neutrophil count decreased		SA08H
Platelet count decreased	£752.58	SA12G
Thrombocytopenia		SA12H SA12J SA12K
Treatment arm	One-off cost	
Niraparib	£ 325.38	
Rucaparib	£ 377.78	
Olaparib	£ 235.47	
Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; NHS, National Health Service.		

4.2.8.5 Subsequent treatments

After experiencing a progression event in the model, a proportion of patients move on to subsequent treatments, such as platinum- and non-platinum-based chemotherapies. Due to PARPi re-treatment not being recommended in UK clinical practice, as noted in NICE TA962¹⁰, TA946⁹ and TA1055¹, PARPi re-treatment was not considered in the model.

The proportion of patients receiving each subsequent treatment was derived from treatment usage observed in the PRIMA³ trial. However, the company noted that PARPi retreatment was permitted in the PRIMA trial, and therefore these patients were redistributed equally amongst the other subsequent treatments.

Table 67 presents the proportions of patients receiving subsequent treatments in the model. Combining these proportions with the cost of treatment administration and the appropriate dosing schedules (Table 57 and 58 in the company submission), results in the one-off subsequent treatment cost applied at the point of progression for each patient (Table 68).

Table 67. Distribution of subsequent treatments applied in the economic model – base case (PRIMA) (reproduced from Table 55 in the CS)

Subsequent treatment	BRCAm		BRCAwt	
	2L	3L+	2L	3L+
Proportion of first progression patients experiencing second progression	-	■%	-	■%
Proportion of progressed patients receiving subsequent treatment				

Carboplatin	███%	███%	███%	███%
Cisplatin	███%	███%	███%	███%
Cyclophosphamide	███%	███%	███%	███%
Paclitaxel	███%	███%	███%	███%
Doxorubin (PLD)	███%	███%	███%	███%
Gemcitabine	███%	███%	███%	███%

Abbreviations: 2L, second-line; 3L+, third-line or later; BRCAm, breast cancer gene mutation; BRCAwt, breast cancer gene wildtype; CS, company submission; PLD, pegylated liposomal doxorubicin.

Table 68. Summary of subsequent treatment costs (reproduced from Table 58)

Population	Total Subsequent Treatment Cost	
	2L	3L+
BRCAm	£ 5,444.25	£ 4,646.92
BRCAwt	£ 4,713.10	£ 5,026.01

Abbreviations: 2L, second line; 3L+, third line or later; BRCAm, breast cancer gene mutation; breast cancer gene wildtype.

4.2.8.6 Terminal care costs

In the model, patients incur a one-off terminal care cost applied at the time of death. The terminal care cost (£8,053.63) was derived from NICE TA946⁹ and TA962¹⁰, which used an estimate from Guest *et al.* 2006,⁴³ and was inflated to the 2024 cost year using the PSSRU inflation indices.⁴⁴

The model additionally assumed that 51.28% of patients would receive end-of-life care, based on a UK study by Gao *et al.* 2013⁴⁵, as also assumed in TA946⁹ and TA962¹⁰

Table 69 outlines the terminal care costs assumed in the model.

Table 69. Terminal care costs (reproduced from Table 59 in the CS)

End of Life Costs	Mean	SE	Source	Notes
Unit Cost	£ 9,248.28	£ 924.83	Guest <i>et al.</i> 2006 ⁴³	Inflated from NICE TA946 ⁹ /NICE TA962 ¹⁰ estimate to 2024 costs

Proportion of patients receiving end-of-life care	51.28%	5.1%	Gao <i>et al.</i> 2013	In line with all recent NICE PARPi TAs
Average terminal care cost per death	£ 4,742.52			
Abbreviations: CS, company submission; NICE, National Institute for Health and Care Excellence; PARPi, poly(ADP-ribose) polymerase inhibitor; SE, standard error; TA, technology appraisal.				

4.2.8.7 EAG critique

The EAG agrees with the methods used by the company to derive treatment acquisition costs per model cycle but disagrees with the use of the SACT data to inform the distribution of 200mg and 300mg niraparib patients at baseline. The EAG considers that as PRIMA³ has been used to inform model treatment effects, and robust evidence exists for the starting dose distribution of niraparib from PRIMA, PRIMA should be used to inform the distribution of niraparib dosing at baseline. While more patients received a higher starting dose in PRIMA than in the SACT dataset, which the company considers more reflective of clinical practice, not using the PRIMA dose distribution ignores the intrinsic link between dose and treatment effect. Therefore, in the EAG base case the dose distribution of niraparib at baseline has been informed using PRIMA and each cycle is informed by the observed proportion of patients receiving each of the three niraparib doses (100 mg, 200 mg, 300 mg) for either the BRCam or BRCAwt population. The EAG notes that this is also the approach accepted by committee in the company's original submission, prior to entry into the CDF.³¹

The EAG considers that the health care resources and their respective frequencies align with the company's original submission and are appropriate. However, compared to the previous appraisal, long-term remission for the progression-free patients has been updated to 10 years, opposed to the previous 7 years. Therefore, given the health care resource use stopping rule for progression-free patients was based on long-term remission, the EAG considers that the 7 year stopping rule should be updated to 10 years to reflect the updated long-term remission assumption. At the clarification stage, the company was requested to clarify why the stopping rule for progression free patients had not been updated, and to conduct a scenario analysis assuming a 10-year stopping rule. In response, the company agreed that the stopping point should coincide with the "cure point" and updated the model and the company base case accordingly. The company noted that the updated stopping rule had a limited impact on the results.

With respect to subsequent treatments, on validating the costs, the EAG identified that lower costs were available for many of the included subsequent treatments. On sharing the lower list prices with the company at the clarification stage, the company noted that the latest version of the eMIT database was released after the submission date, leading to the misalignment of costs. As such, the company updated the cost of subsequent treatments, using the more recent eMIT costs (Table 70).⁴⁰

Table 70. Updated subsequent treatment costs (reproduced from Table 13 in the company's response to clarification questions)

Drugs	Unit size 1 (mg)	Pack size 1	List price per pack for pack size 1 (£)	Unit size 2 (mg)	Pack size 2	List price per pack for pack size 2 (£)	Source
Carboplatin	450.0 mg	1	£ 22.92	50.0 mg	1	£ 5.07	eMIT
Cisplatin	50.0 mg	1	£ 24.33	10.0 mg	1	£ 3.68	eMIT
Cyclophosphamide	50.0 mg	100	£ 73.95	---	---	---	eMIT
Paclitaxel	100.0 mg	1	£ 9.48	30.0 mg	1	£ 4.31	eMIT
Doxorubin (PLD)	50.0 mg	1	£ 9.89	20.0 mg	1	£ 6.94	eMIT
Gemcitabine	1800.0 mg	1	£ 283.88	200.0 mg	1	£ 150.60	eMIT
Abbreviations: eMIT, electronic market information tool; PLD, pegylated liposomal doxorubicin.							

The EAG notes that opposed to applying subsequent treatments in the combinations they would be applied in clinical practice, subsequent treatments have been applied individually. As such, the EAG considers that a more robust method would have been to have costed subsequent treatments in their respective combinations at 1st and 2nd progression events, as was done in TA1055¹. However, while a difference in approach may have led to more accurate subsequent treatment costs, as the same approach has been used for all treatment arms, the EAG considers that the company's approach is unlikely to bias in favour of a particular treatment. Similarly, subsequent treatment costs are equal between the niraparib and the comparators.

The EAG notes that end-of-life costs for cancer are available from the latest PSSRU Unit Costs of Health and Social Care 2024 Manual.⁴⁴ Therefore, the company was requested to conduct a scenario using the PSSRU costs, with the company commenting on the limited impact on the ICER. The EAG consider the PSSRU end-of-life costs to be most appropriate and use this in the EAG preferred analysis (Section 5).

5 Cost effectiveness results

5.1.1 BRCAm subgroup

Table 71 presents the cost-effectiveness results of the company's updated (i.e. post clarification) base case deterministic and probabilistic analyses for the BRCAm subgroup. The company performed a probabilistic sensitivity analysis (PSA) to assess the joint parameter uncertainty around base case results. Incremental results from the company's PSA are based on 5,000 simulations.

In the base case probabilistic analysis, the incremental quality-adjusted life-year (QALY) difference between niraparib and olaparib is [REDACTED] with [REDACTED], which results in a [REDACTED]. As the ICER is driven by [REDACTED], the company presented net monetary benefit (NMB), which the EAG agrees is a useful measure [REDACTED]. The NMB based on the probabilistic results using the £20,000 and £30,000 threshold is [REDACTED] and [REDACTED], respectively. The net health benefit (NHB) based on the deterministic results using the £20,000 and £30,000 threshold is [REDACTED] and [REDACTED], respectively. A positive NHB implies that overall population health would be increased because of the new intervention.

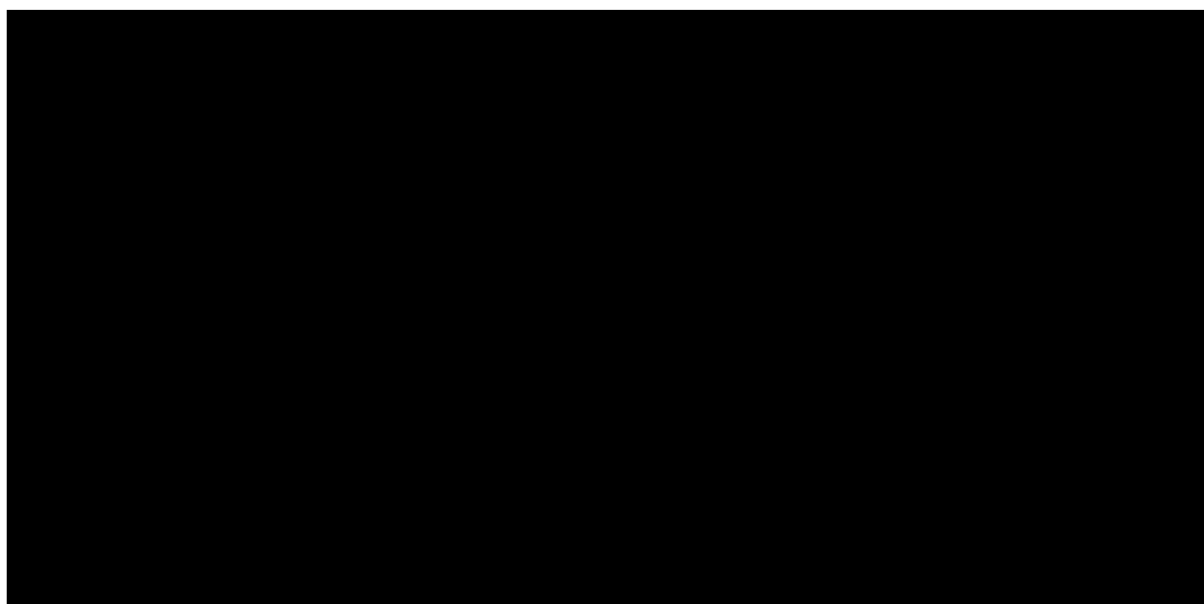
Table 71. Company's base case results (post clarification) – BRCAm subgroup

Interventions	Total Costs (£)	Total LY	Total QALYs	Δcosts (£)	ΔLYs	Δ QALYs	NMB at £20,000 (£)	NMB at £30,000 (£)
Deterministic results								
Olaparib	128,104	8.21	6.27	-	-	-	-	-
Niraparib	[REDACTED]	8.21	[REDACTED]	[REDACTED]	0.00	[REDACTED]	[REDACTED]	[REDACTED]
Probabilistic results								
Olaparib	128,656	8.42	6.41	-	-	-	-	-
Niraparib	[REDACTED]	8.42	[REDACTED]	[REDACTED]	0.00	[REDACTED]	[REDACTED]	[REDACTED]
Abbreviations: Δ, incremental; BRCAm, breast cancer gene mutation; ICER, incremental cost-effectiveness ratio; LY, life year; NMB, net monetary benefit; QALY, quality-adjusted life-year.								

The company considers a disease severity modifier of 1.0 and the EAG agrees.

A PSA scatterplot is presented in Figure 23. The company did not present a cost-effectiveness acceptability curve (CEAC) because at all cost-effectiveness thresholds, [REDACTED]. However, the EAG cautions the interpretation of the CEAC as it is primarily driven by the assumption of clinical equivalence between niraparib and olaparib [REDACTED].

Figure 23. Scatterplot of PSA estimates on a cost-effectiveness plane, niraparib versus olaparib - BRCAm subgroup (Figure 20 of the company's clarification response document)



5.1.2 BRCAwT subgroup

Table 72 presents the cost-effectiveness results of the company's updated (i.e. post clarification) base case deterministic and probabilistic analyses for the BRCAwT subgroup. The company performed a probabilistic sensitivity analysis (PSA) to assess the joint parameter uncertainty around base case results. Incremental results from the company's PSA are based on 5,000 simulations.

In the base case probabilistic analysis, the incremental QALY difference between niraparib and rucaparib is [REDACTED] with [REDACTED], which results in a [REDACTED]. However, the EAG advises caution when interpreting the ICER, [REDACTED]. The incremental QALY gain is equivalent to [REDACTED] as a result of differences in the safety profile of niraparib compared with rucaparib and as such differences in treatments are based solely on incremental costs, as shown with the NMB results. The NMB based on the probabilistic results using the £20,000 and £30,000 threshold is [REDACTED] and [REDACTED], respectively. The net health benefit (NHB) based on the deterministic results using the

£20,000 and £30,000 threshold is [REDACTED] and [REDACTED], respectively. A positive NHB implies that overall population health would be increased because of the new intervention.

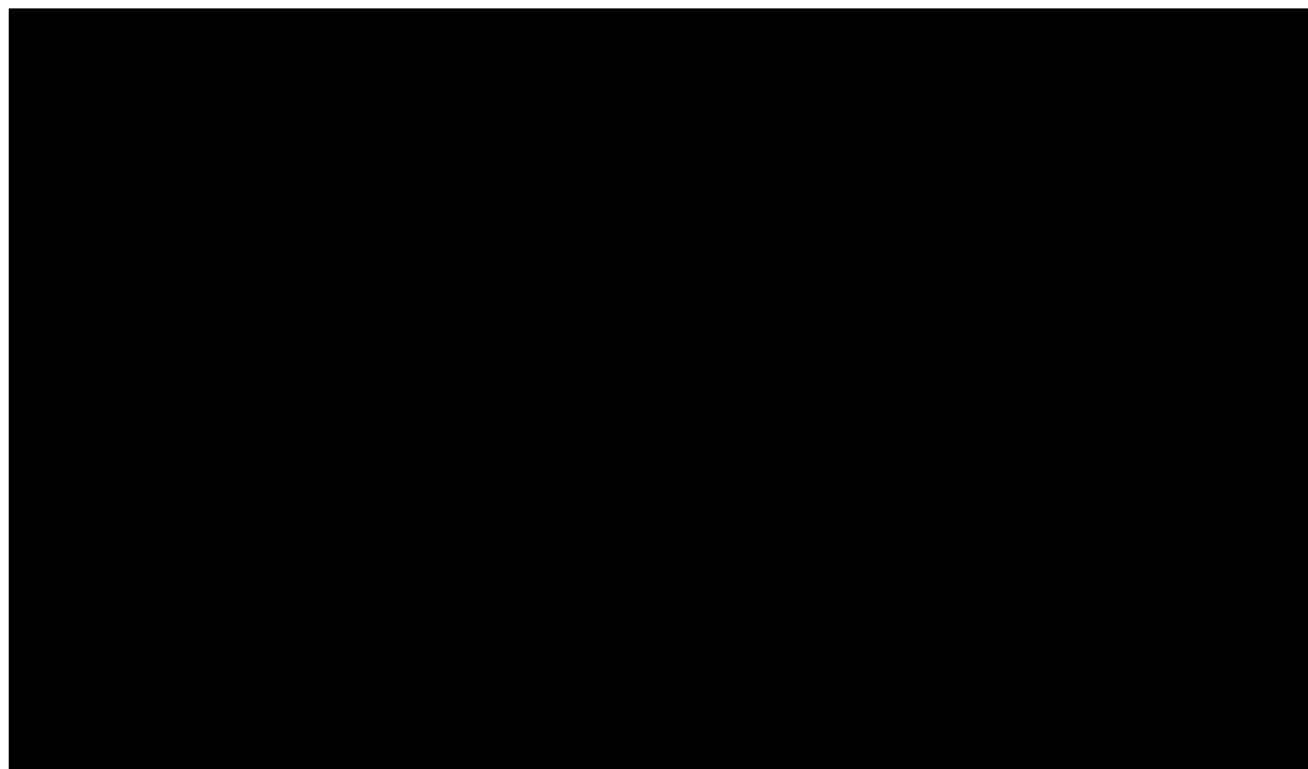
Table 72. Company's base case results (post clarification) – BRCAwt subgroup

Interventions	Total Costs (£)	Total LY	Total QALYs	Δcosts (£)	ΔLYs	Δ QALYs	NMB at £20,000 (£)	NMB at £30,000 (£)
Deterministic results								
Rucaparib	117,230	4.75	3.50	-	-	-	-	-
Niraparib	[REDACTED]	4.75	[REDACTED]	[REDACTED]	0.00	[REDACTED]	[REDACTED]	[REDACTED]
Probabilistic results								
Rucaparib	117,264	4.78	3.52	-	-	-	-	-
Niraparib	[REDACTED]	4.78	[REDACTED]	[REDACTED]	0.00	[REDACTED]	[REDACTED]	[REDACTED]
Abbreviations: Δ, incremental; BRCAwt, breast cancer gene wildtype; ICER, incremental cost-effectiveness ratio; LY, life year; NMB, net monetary benefit; QALY, quality-adjusted life-year.								

The company considers a disease severity modifier of 1.0 and the EAG agrees.

A PSA scatterplot is presented in Figure 23. The company did not present a cost-effectiveness acceptability curve (CEAC) because at all cost-effectiveness thresholds, [REDACTED]. However, the EAG cautions the interpretation of the CEAC as it is primarily driven by the assumption of clinical equivalence between niraparib and olaparib [REDACTED].

Figure 24. Scatterplot of PSA estimates on a cost-effectiveness plane, niraparib versus rucaparib - BRCAwt subgroup (Figure 21 of the company's clarification response document)



5.1.3 *Company's sensitivity analyses*

5.1.3.1 *One-way sensitivity analysis*

The company conducted one-way sensitivity analyses (OWSAs) to assess the impact on the ICER of varying specific parameters in isolation and to identify the main model drivers. The results are illustrated in the tornado diagrams presented in Figure 25 for niraparib versus olaparib (BRCAm subgroup) and Figure 26 for niraparib versus rucaparib (BRCAwt subgroup). As with the base case results, the OWSAs are presented using NMB [REDACTED] [REDACTED] for both subgroups.

For the BRCAm subgroup, the ICER was most sensitive to the progression-free survival (PFS) parametric fit coefficients for niraparib, the adverse event (AE) discontinuation probability for olaparib and the time to treatment discontinuation (TTD) random sample parameter for niraparib. For the BRCAwt subgroup, the ICER was most sensitive to PFS parametric fit coefficients for niraparib and the TTD random sample parameter for niraparib.

Figure 25. Tornado plot using net monetary benefit – niraparib versus olaparib (BRCAm subgroup)

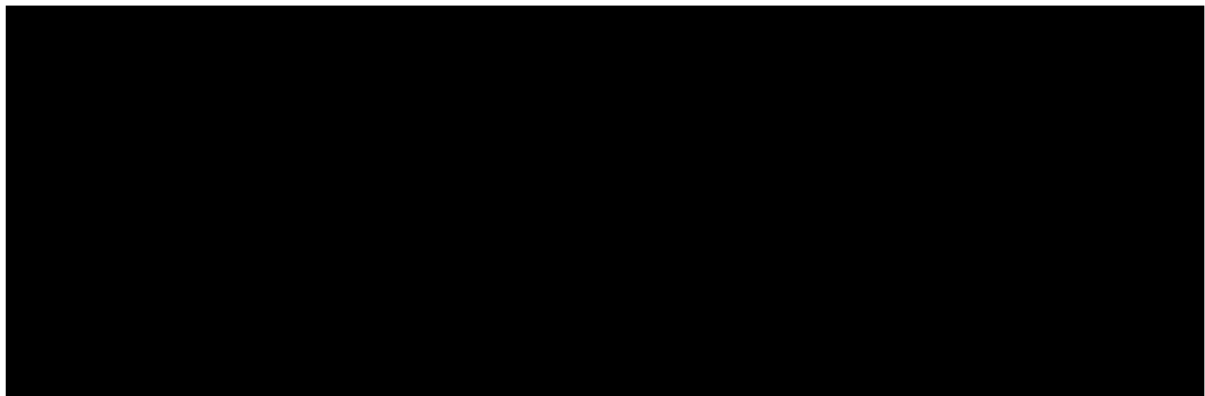
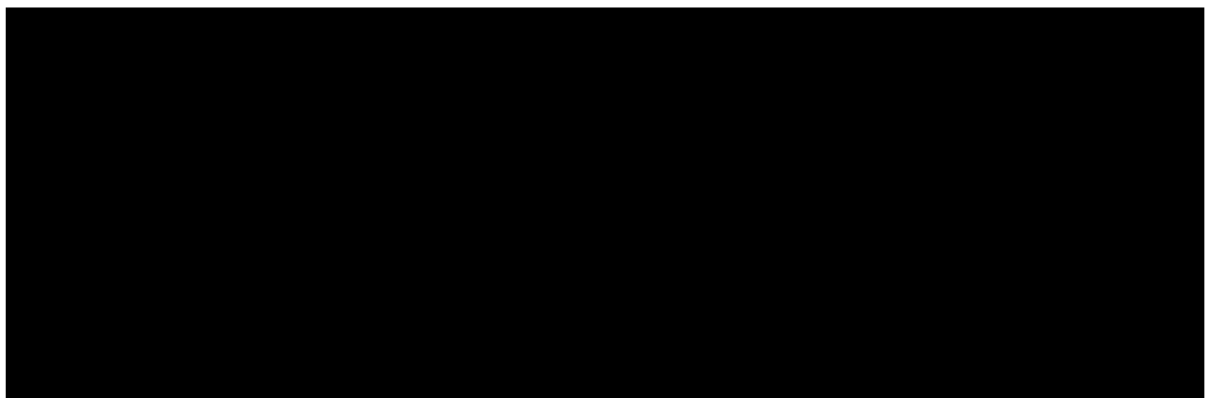


Figure 26. Tornado plot using net monetary benefit – niraparib versus rucaparib (BRCAwt subgroup)



5.1.3.2 Scenario analysis

The company undertook an extensive series of scenario analyses, with several at the request of the EAG, to assess the impact of applying alternative assumptions to key model parameters. The company scenarios are presented in Table 22 and Table 23 of the company's clarification response document for both the BRCAm and BRCAwt subgroups. However, the EAG notes that because of the company's assumption of clinical equivalence between niraparib and olaparib for the BRCAm subgroup and niraparib and rucaparib for the BRCAwt subgroup, the majority of the scenarios have minimal impact on the incremental QALYs and the net monetary benefit. As such, the EAG presents the company scenarios where there has been a substantial impact on the incremental costs and/ or the incremental QALYs.

The EAG notes that deterministic scenario analyses are presented for pragmatism as the PSA run times are extremely long. However, the EAG considers that the deterministic and probabilistic

Table 73. Company scenario analysis – niraparib versus olaparib (BRCAm subgroup) (extracted from Table 22 of the company’s clarification response)

Table 74. Company scenario analysis – niraparib versus rucaparib (BRCAwt subgroup) (extracted from Table 23 of the company's clarification response)

BMJ TAG

1	RDI = 88% as in NICE TA 1055	████	████	████	████
Additional scenarios following EAG requests during clarification					
2	Applies Bucher ITC HRs for niraparib vs rucaparib for PFS (████) and OS (████) based on ITT population analysis of PRIME ⁴	████	████	████	████
3	Applies Bucher ITC HRs for NIRA vs RUCA for PFS (████) and OS (████) based on HRd population (not split by BRCA status) analysis of PRIME ⁴	████	████	████	████ ████
Abbreviations: BRCAwt, breast cancer gene wildtype; EAG, External Assessment Group; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; ITC, indirect treatment comparison; ITT, intention to treat; NICE, National Institute for Health and Care Excellence; NMB, net monetary benefit; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life-year; RDI, relative dose intensity; SACT, Systemic Anti-Cancer Treatment; SW, south-west; TA, technology appraisal; TTD, time to treatment discontinuation.					

5.2 EAG additional analyses

5.2.1 Model validation and face validity check

Section 3.14 in the company submission outlines the company's approach to the validation of the economic model. The EAG is satisfied that the company's approach was thorough and robust, with a wide range of internal and external validation being undertaken. The EAG undertook its own validation of the model and checked the face validity of the assumptions and inputs with clinical experts, as well as checking model formulae/code.

The EAG notes that the company's survival analysis is undertaken in a VBA macro, which allows for parameterisation based on a range of statistical packages used to undertake survival analysis (e.g. R, SAS, STATA). The EAG cross-checked the resulting survival analysis outputs based on the company's chosen statistical package (R) and after further clarification from the company was satisfied that the VBA code produced correct extrapolations. The EAG notes that they did not perform checks of the VBA code for the parameterisation of survival models using statistical packages other than R.

During clarification, the EAG highlighted that less expensive drug prices were available via the Drugs and pharmaceutical electronic market information tool (eMIT)⁴⁰ than those used in the company's model, which were subsequently updated by the company and incorporated into the post-clarification base-case.

5.2.2 *EAG's exploratory analyses using the company's base case*

In Section 4 of the report the EAG detailed several areas of uncertainty that warrant further exploration. However, as previously noted in Section 5.1.3.2, due to the company's assumption of clinical equivalence between niraparib and olaparib for the BRCAm subgroup and niraparib and rucaparib for the BRCAwt subgroup, the majority of the scenarios have minimal impact on the incremental QALYs and the net monetary benefit. Therefore, the EAG has taken the pragmatic decision to only present exploratory analyses on the company's base case for scenarios that have a large change in the cost-effectiveness results, with additional exploratory analyses then presented on the EAG preferred base case in Section 5.2.4.

The scenarios performed by the EAG around the company base case (post-clarification) are summarised in Table 75. The results of the analyses are presented in Table 76 and Table 77 for the BRCAm and BRCAwt populations, respectively.

Due to long model run times for the PSA, the EAG has run the exploratory analyses deterministically. However, the EAG ran its preferred analysis both deterministically and probabilistically and results are consistent with each other.

Table 75. Summary of EAG's exploratory analyses using company's base case

	Company’s base case assumption	EAG scenario	Justification for EAG assumption	Section in EAG report
BRCAm population				
1	Assumed clinical equivalence in PFS between niraparib and olaparib	Olaparib PFS informed by applying EAG-derived HR of █████ for PFS to baseline niraparib PFS curve.	The EAG does not consider that the company has provided robust evidence to conclude olaparib and niraparib are clinically equivalent	4.2.4.4
2	Assumed clinical equivalence in OS between niraparib and olaparib	Olaparib OS informed by applying EAG-derived HR of █████ for OS to baseline niraparib OS curve.		4.2.4.6
3	Assumed clinical equivalence in OS between niraparib and olaparib	Olaparib PFS informed by applying EAG-derived HR of █████ for PFS to baseline niraparib PFS curve, based on the EAG Bucher ITC of SOLO-1 ⁵ versus PRIMA ³ in the high risk population.		4.2.4.4
BRCAwt population				
1	Assumed clinical equivalence in PFS between niraparib and rucaparib	Rucaparib PFS informed by applying EAG-derived HR of █████ for PFS to baseline niraparib PFS curve.	The EAG does not consider that the company has provided robust evidence to conclude rucaparib and niraparib has are clinically equivalent	4.2.4.8
2	Assumed clinical equivalence in OS between niraparib and rucaparib	Rucaparib OS informed by applying EAG-derived HR of █████ for OS to baseline niraparib OS curve, based on the EAG analysis of ATHENA-MONO ² versus PRIMA ³ in the HRd/BRCAwt population.	The EAG does not consider that the company has provided robust evidence to conclude rucaparib and niraparib are clinically equivalent. As the EAG was unable to derive a HR for the ‘pooled’ BRCAwt population using ATHENA-MONO ² data, and the company did not present analyses based on PRIMA ³ for the HRd/BRCAwt and HRp/BRCAwt populations separately, the hazard ratio for the HRd/BRCAwt population was applied to illustrate the ICER impact.	4.2.4.10

	Company's base case assumption	EAG scenario	Justification for EAG assumption	Section in EAG report
3	Assumed clinical equivalence in OS between niraparib and rucaparib	Rucaparib OS informed by applying EAG-derived HR of [REDACTED] for OS to baseline niraparib OS curve, based on the EAG analysis of ATHENA-MONO ² versus PRIMA ³ in the HRp/BRCAwT population.	As above. The HR for the HRp/BRCAwT population was also applied to baseline OS in order to derive the range of the true ICER when observed alongside scenario 1 above.	4.2.4.10
4	Adverse event probability informed from real-world evidence study, MONITOR-UK ⁶	Apply adverse events from PRIMA ³ study	The EAG considers that adverse events should be informed from the same source as the treatment effectiveness and discontinuation data for niraparib, which both use the PRIMA ³ study	4.2.6.1
Abbreviations: BRCAm, breast cancer gene mutation; BRCAwT, breast cancer gene wildtype; EAG, External Assessment Group; HR, hazard ratio; HRd, homologous recombination deficient; HRp, homologous recombination proficient; ICER, Incremental Cost Effectiveness Ratio; ITC, indirect treatment comparison; OS, overall survival; PFS, progression-free survival.				

Table 76. Results of EAG's exploratory analyses using the company's base case, BRCAm population (deterministic)

Exploratory analysis number	Scenario applied to company's base case	Incremental costs (£)	Incremental QALYs	NMB at £30,000	ICER (£/QALY)
Company base case	-	██████	██████	██████	██████
1	PFS HR = █████ based on EAG derived HR for SOLO-1 ⁵ vs PRIMA ³	██████	██████	██████	██████
2	OS HR = █████ based on EAG derived HR for SOLO-1 ⁵ vs PRIMA ³	██████	██████	██████	██████
3	PFS HR = █████ based on EAG derived HR for SOLO-1 ⁵ vs PRIMA ³ , high-risk population only	██████	██████	██████	██████

Abbreviations: BRCAm, breast cancer gene mutation; EAG, External Assessment Group; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; NMB, net monthly benefit; OS, overall survival; PFS, progression free survival; QALY, quality-adjusted life-year; SW, south-west

Table 77. Results of EAG's exploratory analyses using the company's base case, BRCAwt population (deterministic)

Exploratory analysis number	Scenario applied to company's base case	Incremental costs (£)	Incremental QALYs	NMB at £30,000	ICER (£/QALY)
Company base case	-	██████	██████	██████	██████
1	PFS HR = █████ based on EAG derived HR for ATHENA-MONO ² vs PRIMA ³	██████	██████	██████	██████
2	OS HR = █████ based on EAG derived HR for ATHENA-MONO ² vs PRIMA ³ in the HRd/BRCAwt population	██████	██████	██████	██████
3	OS HR = █████ based on EAG derived HR for ATHENA-MONO ² vs PRIMA ³ in the HRp/BRCAwt population	██████	██████	██████	██████
4	AEs informed by PRIMA ³ trial	██████	██████	██████	██████

Abbreviations: AE, adverse events; BRCAwt, breast cancer gene wildtype; EAG, External Assessment Group; HR, hazard ratio; HRd, homologous recombination deficient; homologous recombination proficient; ICER, incremental cost-effectiveness ratio; NMB, net monthly benefit; OS, overall survival; PFS, progression free survival; QALY, quality-adjusted life-year; SW, south-west

5.2.3 EAG preferred assumptions

As discussed in both Section 3.4.5 and Section 4.2.4, the EAG does not consider there to be robust evidence to support the company's assumption of clinical equivalence between all PARPi treatments included in the economic model. Therefore, in the BRCAm population, the EAG prefers to inform treatment effectiveness of olaparib based on the hazard ratios from the EAG indirect treatment comparison with SOLO-1⁵.

As previously discussed, the key trial for rucaparib of ATHENA-MONO² stratified patients by HRD classification (BRCAm, HRd/BRCAwt, HRp/BRCAwt and HRD unknown/BRCAwt). In the recent appraisal for rucaparib (TA1055¹), comparisons for the BRCAwt population were presented based on HRD classification. In addition, the PRIMA³ trial was stratified for HRD status and not BRCA status. Accordingly, any subgroup analyses of BRCA status would resolve in trial randomization being broken. Therefore, the EAG considers that the most appropriate comparison with rucaparib in the current appraisal for the BRCAwt population, and therefore the EAG preference, would use the same approach and compare ATHENA-MONO against the PRIMA trial for niraparib, with results presented separately for the HRd/BRCAwt and HRp/BRCAwt populations as this is the most robust use of the data from both ATHENA-MONO and PRIMA. As this was not provided by the company during clarification, the EAG did not have all of the outcomes from the PRIMA trial for each subgroup to conduct the analysis themselves. As such, in order to provide a meaningful analysis for committee, the EAG has maintained the company's approach of using the BRCAwt population as a whole (and not split by HRD classification). The EAG was able to construct an overall BRCAwt population from ATHENA-MONO data to allow an ITC against PRIMA for PFS. However, the equivalent data were not available for overall survival. Therefore, the EAG has instead applied separate HRs for OS in the HRd/BRCAwt and HRp/BRCAwt populations in order to provide a range for the ICER that would be expected for the combined BRCAwt population.

The EAG preferences are outlined in the following subsections for the BRCAm and BRCAwt population.

5.2.3.1 BRCam population

Table 78. Results using the EAG's preferred model assumptions in the BRCam population, deterministic

Preferred assumption	EAG report section	Cumulative incremental costs	Cumulative incremental QALYs	Cumulative NMB at £20,000 (£)	Cumulative NMB at £30,000 (£)	Cumulative ICER £/QALY
Company base case (post-clarification)	Not applicable	██████	██████	██████	██████	██████ ██████ ██████
Olaparib PFS informed by application of HR = █████	Section 4.2.4.4	██████	██████	██████	██████	██████ ██████
Olaparib OS informed by application of HR = █████	Section 4.2.4.6	██████	██████	██████	██████	██████ ██████
Treatment discontinuation: all patients discontinue at 3 years for niraparib and 2 years for olaparib.	Section 4.2.5	██████	██████	██████	██████	██████ ██████
Niraparib dosing informed by PRIMA ³ per cycle dosing	Section 4.2.8.7	██████	██████	██████	██████	██████ ██████
Adverse events for niraparib based on PRIMA ³	Section 4.2.6.1	██████	██████	██████	██████	██████ ██████
End of life care costs sourcedd from PSSRU ⁴⁴	Section 4.2.8.7	██████	██████	██████	██████	██████ ██████
Abbreviations: BRCam, breast cancer gene mutation; EAG, External Assessment Group; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; PSSRU, Personal Social Services Research Unit; SW, south-west.						

Table 79. EAG base case results for BRCAm population

Interventions	Total Costs (£)	Total LY*	Total QALYs	Incremental costs (£)	Incremental LYs*	Incremental QALYs	ICER (£/QALY)
Deterministic results							
Olaparib	123,144	15.94	8.27	-	-	-	
Niraparib	██████	11.30	██████	██████	██████	██████	██████ ██████
Probabilistic results							
Olaparib	123,218	NR	8.32	-	-	-	-
Niraparib	██████	NR	██████	██████	██████	██████	██████ ██████
*Undiscounted Abbreviations: BRCAm, breast cancer gene mutation; ICER, incremental cost-effectiveness ratio; LY, life year; NR, not reported; QALY, quality-adjusted life-year; SW, south-west							

The EAG considers a disease severity modifier of 1.0 is appropriate. As shown in Table 79, the EAG preferred analysis in the BRCAm population produces a ████████ ICER of ██████ (probabilistic). This has a corresponding net health benefit (NHB) of █████ and █████ at a WTP threshold of £20,000 and £30,000, respectively.

5.2.3.2 BRCAwt population

As discussed above, the EAG has provided what it considers to be an upper and lower range of the ICER in the BRCAwt population, based on applying alternative HRs for overall survival in the HRd/BRCAwt and HRp/BRCAwt populations. Therefore, these alternative assumptions are applied last in order to show the cumulative impact separately, depending on the HR applied. The EAG therefore considers the true ICER to lie between these values.

Table 80. Results using the EAG's preferred model assumptions, BRCAwt population

Preferred assumption	EAG report section	Cumulative incremental costs	Cumulative incremental QALYs	Cumulative NMB at £20,000 (£)	Cumulative NMB at £30,000 (£)	Cumulative ICER £/QALY
Company base case (post-clarification)	Not applicable	██████	██████	██████	██████	██████
Rucaparib PFS informed by application of HR = █████	Section 4.2.4.8	██████	██████	██████	██████	██████ ██████
Treatment discontinuation: all patients discontinue at 3 years for niraparib and 2 years for rucaparib.	Section 4.2.5	██████	██████	██████	██████	██████ ██████
Niraparib dosing informed by PRIMA ³ per cycle dosing	Section 4.2.8.7	██████	██████	██████	██████	██████ ██████
Adverse events for niraparib based on PRIMA ³	Section 4.2.6.1	██████	██████	██████	██████	██████ ██████
End of life care costs sourcedd from PSSRU ⁴⁴	Section 4.2.8.7	██████	██████	██████	██████	██████ ██████
OS HR = █████ based on EAG derived HR in the HRd/BRCAwt population	Section 4.2.4.10	██████	██████	██████	██████	██████ ██████
OS HR = █████ based on EAG derived HR in the HRp/BRCAwt population	Section 4.2.4.10	██████	██████	██████	██████	██████ ██████

Abbreviations: BRCAwt, breast cancer gene wildtype; EAG, External Assessment Group; HR, hazard ratio; HRd, homologous recombination deficient; HRp, homologous recombination proficient; ICER, Incremental Cost Effectiveness Ratio; NMB, net monthly benefit; OS, overall survival; PFS, progression-free survival; PSSRU, Personal Social Services Research Unit; QALY, quality-adjusted life-year.

Table 81 and Table 82 below present the EAG preferred base case results separately for when alternative HRs are applied for OS (either based on HRd/BRCAwt or HRp/BRCAwt, respectively) and as previously noted the EAG considers that the preferred ICER lies within this range. Results indicate a █████ between █████ and █████ with corresponding NHB between █████ and █████ at a

£20,000 WTP threshold and [REDACTED] and [REDACTED] at a WTP threshold of £30,000. The EAG has also calculated a 'weighted' ICER (probabilistic) in which the incremental costs and QALYs for each of the two scenarios are weighted based on the observed split of HRd/BRCawt (49.03%) and HRp/BRCawt (50.97%) observed in the PRIMA³ trial, in order to provide an illustrative ICER for the combined BRCawt population. This results in a [REDACTED] ICER of £[REDACTED].

Table 81. EAG base case results, BRCawt with HRd/BRCawt HR for overall survival applied

Interventions	Total Costs (£)	Total LY*	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Deterministic results							
Rucaparib	[REDACTED]	8.19	[REDACTED]	-	-	-	-
Niraparib	[REDACTED]	5.71	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Probabilistic results							
Rucaparib	[REDACTED]	NR	[REDACTED]	-	-	-	-
Niraparib	[REDACTED]	NR	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
*Undiscounted							
Abbreviations: BRCawt, breast cancer gene wildtype; EAG, External Assessment Group; HR, hazard ratio; HRd, homologous recombination deficient; ICER, incremental cost-effectiveness ratio; LY, life year; NR, not reported; QALY, quality-adjusted life-year; SW, south-west.							

Table 82. EAG base case results, BRCawt with HRp/BRCawt HR for overall survival applied

Interventions	Total Costs (£)	Total LY*	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Deterministic results							
Rucaparib	[REDACTED]	7.12	[REDACTED]	-	-	-	-
Niraparib	[REDACTED]	5.71	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Probabilistic results							
Rucaparib	[REDACTED]	NR	[REDACTED]	-	-	-	-
Niraparib	[REDACTED]	NR	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
*Undiscounted							
Abbreviations: BRCawt, breast cancer gene wildtype; EAG, External Assessment Group; HR, hazard ratio; HRp, homologous recombination proficient; ICER, incremental cost-effectiveness ratio; LY, life year; NR, not reported; QALY, quality-adjusted life-year; SW, south-west.							

5.2.4 Scenario analyses using EAG's preferred assumptions

The EAG conducted a number of scenario analyses to explore the impact on the ICER of alternative assumptions. Table 83 below details the additional scenarios applied to the EAG base case.

Table 83. Summary of EAG's scenario analyses using the EAG preferred assumptions

	EAG's base case assumption	EAG's scenario
Applied to both BRCAm and BRCAwt analyses		
1	Time to treatment discontinuation for niraparib applies KM curve up to three years, upon which all patients discontinue	Time to treatment discontinuation for niraparib applies full KM curve, upon which all patients discontinue – i.e. no stopping rule applied
2	Model start age informed by PRIMA ³ trial (mean)	Model start age informed by niraparib SACT data (median)
3	Long-term remission applied at 10 years	Long-term remission applied at 12 years
4	Utility values based on EQ-5D (EQ-5D-5L mapped to EQ-5D-3L) from PRIMA ³	Utility values based on those used in NICE TA962 ¹⁰ : progression free= 0.81 and progressed = 0.76
BRCAm population only		
5	Time to treatment discontinuation for niraparib applies KM curve up to three years, upon which all patients discontinue. Time to treatment discontinuation for olaparib based on PFS and AEs from SOLO-1 ⁵	Time to treatment discontinuation informed by respective niraparib and olaparib KM curves from SACT data, after which all patients were assumed to discontinue.
6	Olaparib PFS informed by applying EAG-derived HR of [REDACTED] for PFS to baseline niraparib PFS curve, based on EAG Bucher ITC of SOLO-1 ⁵ versus PRIMA ³ .	Olaparib PFS informed by applying EAG-derived HR of [REDACTED] for PFS to baseline niraparib PFS curve, based on the EAG Bucher ITC of SOLO-1 ⁵ versus PRIMA ³ in the high-risk population.
7	Key model informed by data from PRIMA ³	Key model inputs informed by SACT data: - OS based company derived HR for comparison on olaparib vs niraparib SACT data [REDACTED] applied to SACT KM with lognormal fit - PFS same as EAG base case - TTD based on SACT KM curves - Start dose based on SACT data (as used in company base case) - Start age based on SACT in BRCAm population (65). - AEs based on company approach to use RWE (MONITOR-UK⁶ study)
8	Key model informed by data from PRIMA ³	As above, but due to EAG concerns with comparison of olaparib and niraparib SACT OS (see Section 4.2.4.6), olaparib OS is instead derived by applying HR based on 'trial based' analysis, as in EAG preferred base-case (HR = [REDACTED])

	EAG's base case assumption	EAG's scenario
BRCAwt population only		
5	Proportions of HRd/BRCAwt and HRp/BRCAwt patients used to produce EAG weighted ICER for overall BRCAwt based on PRIMA ³ : • HRd/BRCAwt = 49.03% • HRp/BRCAwt = 50.97%	Proportions of HRd/BRCAwt and HRp/BRCAwt patients used to produce EAG weighted ICER for overall BRCAwt based on ATHENA-MONO ² : • HRd/BRCAwt = 33.22% • HRp/BRCAwt = 66.78%
Abbreviations: AE, adverse event; BRCAm, breast cancer gene mutation; BRCAwt, breast cancer gene wildtype; EAG, External Assessment Group; EQ-5D, European Quality of Life 5 Dimensions; EQ-5D-3L, European Quality of Life 5 Dimensions 3 Level Version; EQ-5D-5L, European Quality of Life 5 Dimensions 5 Level Version; HR, hazard ratio; HRd, homologous recombination deficient; HRp, homologous recombination proficient; ICER, Incremental Cost Effectiveness Ratio; ITC, indirect treatment comparison; KM, Kaplan-Meier; OS, overall survival; PFS, progression-free survival; SACT, systemic anti-cancer therapy; TTD, time to treatment discontinuation.		

5.2.4.1 BRCAm population

Table 84 below shows the results of the EAG's exploratory analyses on the EAG preferred base case for the BRCAm population. Due to long model run times, these are presented deterministically only, however, the EAG consider the probabilistic and deterministic results closely aligned.

Table 84. Results of EAG's exploratory analyses using EAG's preferred assumptions, BRCAm population (deterministic only)

Scenario analysis number	Scenario applied to EAG's base case	Incremental costs (£)	Incremental QALYs	NMB at £30,000	ICER (£/QALY)
-	EAG preferred analysis	████	████	████	████ ████
1	Time to treatment discontinuation for niraparib applies full KM curve, upon which all patients discontinue – i.e. no stopping rule applied	████	████	████	████ ████
2	Model start age informed by niraparib SACT data	████	████	████	████ ████
3	Long-term remission applied at 12 years	████	████	████	████ ████
4	Utility values based on those used in NICE TA962 ¹⁰ : progression free= 0.81 and progressed = 0.76	████	████	████	████ ████
5	TTD informed by respective niraparib and olaparib KM curves from SACT data, after which all patients assumed to discontinue.	████	████	████	████ ████
6	Olaparib PFS informed by applying EAG-derived HR of █████ for PFS (high risk population).	████	████	████	████ ████
7	SACT based analysis, applying company derived HR for OS of █████.	████	████	████	████ ████
8	SACT based analysis, applying 'trial based' HR for OS of █████	████	████	████	████ ████

Abbreviations: BRCAm, breast cancer gene mutation; EAG, External Assessment Group; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; KM, Kaplan-Meier; NICE, National Institute for Health and Care Excellence; NMB, net monetary benefit; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life-year; SACT, systemic anti-cancer therapy; SW, south-west; TTD, time to treatment discontinuation.

5.2.4.2 BRCAwt population

Table 85 presents the results of the EAG's exploratory analyses on the EAG preferred base case for the BRCAwt population. Due to the EAG presenting a range for the preferred ICER in the BRCAwt population, exploratory analyses are presented on each the upper and lower range of the ICER estimate (i.e. when the HR for OS for either the HRd/BRCAwt or HRp/BRCAwt is applied).

The EAG also re-calculated the 'weighted' ICER (probabilistic) in which the incremental costs and QALYs for each of the base case scenarios are instead weighted based on the observed split of HRd/BRCAwt (33.22%) and HRp/BRCAwt (66.78%) observed in the ATHENA-MONO² trial rather than PRIMA³. This results in a [REDACTED] ICER of £[REDACTED].

Table 85. Results of EAG's exploratory analyses using EAG's preferred assumptions, BRCAwt population (deterministic only)

Scenario analysis number	Scenario applied to EAG's base case	Incremental costs (£)	Incremental QALYs	NMB at £30,000	ICER (£/QALY)	Incremental costs (£)	Incremental QALYs	NMB at £30,000	ICER (£/QALY)
		HRd/BRCAwt population (rucaparib HRd BRCAwt OS)				HRp/BRCAwt population (rucaparib HRp BRCAwt OS)			
-	EAG preferred analysis	████	██	████	████ ████	████	██	████	████ ████
1	Time to treatment discontinuation for niraparib applies full KM curve, upon which all patients discontinue – i.e. no stopping rule applied	████	██	████	████ ████	████	██	████	████ ████
2	Model start age informed by niraparib SACT data	████	██	████	████ ████	████	██	████	████ ████
3	Long-term remission applied at 12 years	████	██	████	████ ████	████	██	████	████ ████
4	Utility values based on those used in NICE TA962 ¹⁰ : progression free= 0.81 and progressed = 0.76	████	██	████	████ ████	████	██	████	████ ████

Abbreviations: BRCAwt, breast cancer gene wildtype; EAG, External Assessment Group; HRd, homologous recombination deficient; HRp, homologous recombination proficient; ICER, incremental cost-effectiveness ratio; KM, Kaplan-Meier; NICE, National Institute for Health and Care Excellence; NMB, net monthly benefit; OS, overall survival; QALY, quality-adjusted life-year; SACT, systemic anti-cancer therapy; SW, south-west.

5.3 Decision Modifiers

5.3.1 *QALY weighting for severity*

The company has not made a case for a severity modifier to be applied to the base case QALY estimate and the EAG considers that to be appropriate.

5.3.2 *Uncaptured benefits*

Outlined in section 6.2.36 of the NICE health technology evaluations manual, committees can consider uncaptured benefits when making recommendations about a technology if:

- its decisions have a bearing on broader social considerations and the extent that these are covered by principles on social value judgements on the NICE website.
- there are strong reasons to suggest that the health benefits of the technology have been inadequately captured and may therefore misrepresent the health utility gained.
- a substantial proportion of the costs (savings) or benefits are incurred outside of the NHS and personal and social services, or are associated with significant benefits other than health, only when requested specifically by the Department of Health and Social Care as part of the remit.

The company has considered uncaptured benefits of niraparib that are not captured in the QALY calculation include:

- Having more than one treatment option available to delay disease progression as individuals respond differently to medication due to a number of reasons;
- The availability of diverse treatment options encourages innovation and competition.

The EAG considers that company's summary of uncaptured benefits does not meet the criteria outlined above. Therefore, the EAG considers that the committee should rely on estimates of the ICER as the basis for decision making.

5.3.3 *Health inequalities*

The company has not presented any information regarding health inequalities.

5.4 Confidential comparator and subsequent treatment prices

The EAG has produced a confidential appendix to the EAG report which takes into account the confidential arrangements for olaparib and rucaparib. Analyses included in the confidential appendix include the company base case results, scenario analyses and EAG base case and scenario analyses.

5.5 Conclusions of the cost effectiveness sections

The EAG considers the company's submission lacks an unbiased estimate of the ICER for niraparib. The company has assumed clinical equivalence between niraparib and the included comparators (olaparib and rucaparib) in their respective populations; however, the EAG does not consider that this is an appropriate assumption based on the evidence provided (key issue 3). Furthermore, the company did not vary any differences in treatment effectiveness between niraparib and the included comparators in the probabilistic sensitivity analysis (PSA). While the EAG acknowledges the company's argument that the ITCs are fundamentally flawed, the EAG still consider that the ITCs conducted by the EAG represent the best available estimates of relative effectiveness between niraparib and the included comparators. The EAG has included these in its preferred analyses; this is the key driver of the ICERs (key issue 4a and 4b).

The EAG notes that the preferred option would have been to conduct ITCs using a fractional polynomial network meta-analysis (fpNMA) to capture the underlying complex hazard function. However, this was not feasible for the EAG to conduct due to time constraints. The company could have also undertaken a multi-level network meta-regression (ML-NMR) to inform the indirect comparisons; this was not possible for the EAG to undertake due to not having access to the individual patient data (IPD) for PRIMA³.

As noted in Section 4.2.4, the EAG does not consider the comparison presented by the company against rucaparib to appropriately use the available data in the BRCAwt population based on HRD classification (key issue 2). As the company did not provide the requested analyses for the HRd/BRCAwt and HRp/BRCAwt populations in the economic model, the EAG could not present its preferred analyses for the BRCAwt populations (key issue 4b) as the EAG did not have access to all KM curves for the key model outcomes for each subgroup. As such, in order to provide a meaningful analysis for committee, the EAG has maintained the company's approach of using the BRCAwt population as a whole (and not split by HRD classification). The EAG was able to construct an overall BRCAwt population from ATHENA-MONO² data to allow an ITC against PRIMA³ for PFS. However, the

equivalent data were not available for overall survival. Therefore, the EAG has instead applied separate HRs for OS in the HRd/BRCAwt and HRp/BRCAwt populations in order to provide a range for the ICER that would be expected for the combined BRCAwt population, but notes that this is not the EAG's preferred approach.

The EAG notes a number of remaining uncertainties in the company's model assumptions which impact on the ICER, but to a lesser extent than the assumption of clinical equivalence, summarised below.

- The EAG notes that there is uncertainty in the proportion of patients remaining on treatment beyond the stopping rules for each included PARPi, which will impact the estimated drug acquisition costs. The EAG imposed a stopping rule at two years for olaparib and rucaparib and three years for niraparib, after which all patients discontinue. Scenario analyses have been presented applying different assumptions to inform TTD and explore the impact on the ICER (key issue 5).
- The company informed niraparib adverse event rates used in the economic model from a real-world evidence (RWE) study (MONITOR-UK⁶). The EAG considers that adverse events should be informed from the same source as the treatment effectiveness and discontinuation data for niraparib, which both use the PRIMA³ study. Therefore, this was updated in the EAG's preferred analysis. If the company preferred to use RWE for AEs, the EAG consider that a more appropriate dataset should have been consistently identified for all treatments considered in the analysis and not preferentially for only one treatment, to ensure a "like-for-like" comparison.
- The company used a three-state partition survival model (PSM) structure, despite all recent appraisals in the same disease area using a four-state PSM to include PFS2.^{1, 9, 10} While the EAG considers that the inclusion of PFS2 would have been more appropriate, due to a lack of evidence for the specific populations requested by the EAG in order to compare PFS2 against comparators (HRd/BRCAwt and HRp/BRCAwt), the EAG has not included PFS2 in the updated model but notes this as a limitation.
- The company informed starting dose distribution of niraparib using SACT data. As the treatment effectiveness and discontinuation used in the model is informed by the PRIMA³ trial, in the EAG base case the dose distribution of niraparib at baseline has been informed using PRIMA and each cycle is informed by the observed proportion of patients receiving each of the three niraparib doses (100 mg, 200 mg, 300 mg) for either the BRCAm or

BRCAwt population. The EAG notes that this is also the approach accepted by committee in the company's original submission, prior to entry into the cancer drugs fund (CDF).

In conclusion, the EAG considers the company's analysis to be flawed and present a biased estimate of the cost-effectiveness of niraparib compared to olaparib and rucaparib. The EAG considers that its preferred analyses address some of the key uncertainties but notes limitations in the EAG approach used due to lack of data provided by the company in the EAG's preferred populations for the BRCAwt subgroup.

6 References

1. 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 [TA1055], 2025. Available from: <https://www.nice.org.uk/guidance/ta1055/evidence/draft-consultation-guidance-committee-papers-pdf-15303262573>. Date accessed: September 2025.
2. Monk BJ, Parkinson C, Lim MC, O'Malley DM, Oaknin A, Wilson MK, et al. A Randomized, Phase III Trial to Evaluate Rucaparib Monotherapy as Maintenance Treatment in Patients With Newly Diagnosed Ovarian Cancer (ATHENA-MONO/GOG-3020/ENGOT-ov45). *J Clin Oncol* 2022; **40**: 3952-64.
3. González-Martín A, Pothuri B, Vergote I, DePont Christensen R, Graybill W, Mirza MR, et al. Niraparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. *The New England journal of medicine* 2019; **381**: 2391-402.
4. Li N, Zhu J, Yin R, Wang J, Pan L, Kong B, et al. Treatment With Niraparib Maintenance Therapy in Patients With Newly Diagnosed Advanced Ovarian Cancer: A Phase 3 Randomized Clinical Trial. *JAMA oncology* 2023; **9**: 1230-7.
5. DiSilvestro P, Banerjee S, Colombo N, Scambia G, Kim BG, Oaknin A, et al. Overall Survival With Maintenance Olaparib at a 7-Year Follow-Up in Patients With Newly Diagnosed Advanced Ovarian Cancer and a BRCA Mutation: The SOLO1/GOG 3004 Trial. *J Clin Oncol* 2023; **41**: 609-17.
6. Hasson SP, Bowen R, Ang JE, McGrane J, Vazquez I, George A, et al. 52P MONITOR-UK: An initial analysis of a multi-centre, observational study of maintenance niraparib in ovarian cancer. *ESMO Open* 2024; **9**.
7. National Institute for Health and Care Excellence. Niraparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy [TA673], 2021. Available from: <https://www.nice.org.uk/guidance/ta673/evidence/committee-papers-pdf-9014692142>. Date accessed: September 2025.
8. González-Martín A, Harter P, Leary A, Lorusso D, Miller RE, Pothuri B, et al. Newly diagnosed and relapsed epithelial ovarian cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Annals of Oncology* 2023; **34**: 833-48.
9. National Institute for Health and Care Excellence. Olaparib with bevacizumab for maintenance treatment of advanced high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer [TA946], 2024. Available from: <https://www.nice.org.uk/guidance/ta946/evidence/appraisal-consultation-committee-papers-pdf-13302703837>. Date accessed: September 2025.
10. National Institute for Health and Care Excellence. Olaparib for maintenance treatment of BRCA mutation-positive advanced ovarian, fallopian tube or peritoneal cancer after response to first-line platinum-based chemotherapy [TA962], 2024. Available from: <https://www.nice.org.uk/guidance/ta962/evidence/committee-papers-pdf-13366759933>. Date accessed: September 2025.
11. Graybill WS, Pardo Búrdalo B, O'Malley DM, Vergote I, Monk BJ, Auranen A, et al. Predictors of long-term progression-free survival in patients with ovarian cancer treated with niraparib in the PRIMA/ENGOT-OV26/GOG-3012 study. *International journal of gynecological cancer : official journal of the International Gynecological Cancer Society* 2024; **34**: 1041-50.

12. Monk BJ, Coleman RL, Fujiwara K, Wilson MK, Oza AM, Oaknin A, et al. ATHENA (GOG-3020/ENGOT-ov45): a randomized, phase III trial to evaluate rucaparib as monotherapy (ATHENA-MONO) and rucaparib in combination with nivolumab (ATHENA-COMBO) as maintenance treatment following frontline platinum-based chemotherapy in ovarian cancer. *International journal of gynecological cancer : official journal of the International Gynecological Cancer Society* 2021; **31**: 1589-94.
13. Wu X, Liu J, Wang X, Wang J, Wang L, Zhu J, et al. LBA36 Efficacy and safety of senaparib as maintenance treatment in patients with newly diagnosed advanced ovarian cancer (FLAMES study): A randomized, double-blind, placebo-controlled, phase III trial. *Annals of Oncology* 2023; **34**: S1277-S8.
14. Oda K, Shintani D, Mori M, Matsumura N, Kato K, Nagao S, et al. 777P A phase II study of the efficacy of olaparib maintenance monotherapy for patients with HRD-positive, newly diagnosed, advanced, high-grade ovarian cancer, evaluated by whole-exome sequencing (MSBM-OL). *Annals of Oncology* 2024; **35**: S585.
15. Hardesty MM, Krivak TC, Wright GS, Hamilton E, Fleming EL, Belotte J, et al. OVARIO phase II trial of combination niraparib plus bevacizumab maintenance therapy in advanced ovarian cancer following first-line platinum-based chemotherapy with bevacizumab. *Gynecologic oncology* 2022; **166**: 219-29.
16. Ray-Coquard I, Leary A, Pignata S, Cropet C, González-Martín A, Marth C, et al. Olaparib plus bevacizumab first-line maintenance in ovarian cancer: final overall survival results from the PAOLA-1/ENGOT-ov25 trial. *Ann Oncol* 2023; **34**: 681-92.
17. Monk BJ, Barretina-Ginesta MP, Pothuri B, Vergote I, Graybill W, Mirza MR, et al. Niraparib first-line maintenance therapy in patients with newly diagnosed advanced ovarian cancer: final overall survival results from the PRIMA/ENGOT-OV26/GOG-3012 trial^{☆}. *Annals of Oncology* 2024; **35**: 981-92.
18. Banerjee S, Moore KN, Colombo N, Scambia G, Kim B-G, Oaknin A, et al. Maintenance olaparib for patients with newly diagnosed advanced ovarian cancer and a BRCA mutation (SOLO1/GOG 3004): 5-year follow-up of a randomised, double-blind, placebo-controlled, phase 3 trial. *The Lancet Oncology* 2021; **22**: 1721-31.
19. Flaherty C. Maintenance Therapy With Rucaparib Upholds PFS Benefit in Newly Diagnosed Ovarian Cancer Subgroups. 2024. Available from: <https://www.oncnursingnews.com/view/maintenance-therapy-with-rucaparib-upholds-pfs-benefit-in-newly-diagnosed-ovarian-cancer-subgroups>. Date accessed: August.
20. GSK. MEETING REPORT GSK UK PRIMA CDF Exit Health Technology Assessment Advisory Board. 2025 30th April 2025. Report No.
21. Kristeleit R, O'Malley D, Lim MC, McNeish I, Herzog TJ, Wilson M, et al. 49MO Updated progression-free survival (PFS) in patients (pts) with newly diagnosed advanced ovarian cancer (OC) treated with rucaparib (RUC) in ATHENA-MONO. *ESMO Open* 2024; **9**.
22. Ghamande S, Miller RE, Solovyeva E, Prendergast E, Del Mar Gordon Santiago M, Kim Y-M, et al. ATHENA-MONO Post-Progression Survival Data Update In Patients With Newly Diagnosed Advanced Ovarian Cancer. *International Journal of Gynecological Cancer* 2025; **35**.
23. Oaknin A, Moore K, Colombo N, Scambia G, Kim BG, Friedlander M, et al. 995PD - Time to second progression (PFS2) and second subsequent therapy (TSST) for patients (pts) with newly diagnosed, advanced ovarian cancer (OC) and a BRCA mutation (BRCAm) treated with maintenance (mt) olaparib (ola): Phase III SOLO1 trial. *Annals of Oncology* 2019; **30**: v405.
24. Guyot P, Ades AE, Ouwens MJ, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. *BMC medical research methodology* 2012; **12**: 9.
25. Kaul S, Diamond GA. Making sense of noninferiority: a clinical and statistical perspective on its application to cardiovascular clinical trials. *Prog Cardiovasc Dis* 2007; **49**: 284-99.

26. Lee D, Allen A, Lovell A, Abdelsabour A, Wilson ECF, Melendez-Torres GJ. How similar is similar enough? Assessment of indirect treatment comparisons to support similarity for NICE's cost comparison route. *Value in Health* 2025.
27. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021; **372**: n71.
28. National Institute for Health and Care Excellence. Olaparib for maintenance treatment of BRCA mutation-positive advanced ovarian, fallopian tube or peritoneal cancer after response to first-line platinum-based chemotherapy [TA598], 2019. Available from: <https://www.nice.org.uk/guidance/ta598>. Date accessed: September 2025.
29. National Institute for Health and Care Excellence. Olaparib plus bevacizumab for maintenance treatment of advanced ovarian, fallopian tube or primary peritoneal cancer [TA693], 2021. Available from: <https://www.nice.org.uk/guidance/TA693>. Date accessed: September 2025.
30. National Institute for Health and Care Excellence. NICE health technology evaluations: the manual [PMG36], 2022. Available from: <https://www.nice.org.uk/process/pmg36/resources/nice-health-technology-evaluations-the-manual-pdf-72286779244741>. Date accessed: 26/06/2025.
31. National Institute for Health and Care Excellence. Niraparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy. TA673, 2021. Available from: <https://www.nice.org.uk/guidance/ta673/evidence>. Date accessed.
32. Kim JH, Kim SI, Park EY, Kim ET, Kim H, Kim S, et al. Comparison of survival outcomes between olaparib and niraparib maintenance therapy in BRCA-mutated, newly diagnosed advanced ovarian cancer. *Gynecologic oncology* 2024; **181**: 33-9.
33. Latimer N. NICE DSU Technical Support Document 14: Survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data. 2013. Available from: <http://nicedsu.org.uk/wp-content/uploads/2016/03/NICE-DSU-TSD-Survival-analysis.updated-March-2013.v2.pdf>. Date accessed: May 2021.
34. Office for National Statistics. Estimates of the population for England and Wales 2024.
35. Mai PL, Chatterjee N, Hartge P, Tucker M, Brody L, Struwing JP, et al. Potential excess mortality in BRCA1/2 mutation carriers beyond breast, ovarian, prostate, and pancreatic cancers, and melanoma. *PLoS One* 2009; **4**: e4812.
36. Electronic Medicines Compendium (EMC). Rubraca 200 mg film-coated tablets (rucaparib). 2024. Available from: <https://www.medicines.org.uk/emc/product/14967/smpc#gref>. Date accessed.
37. Hernández Alava M, Pudney S, Wailoo A. Estimating the Relationship Between EQ-5D-5L and EQ-5D-3L: Results From an English Population Study [EEPRU Report]. 2020. University of Sheffield & University of York.
38. Hernandez-Alava M, Pudney S, Wailoo A. Estimating EQ-5D by age and sex for the UK. 2022. Report No.
39. National Institute for Health and Care Excellence. British National Formulary. 2025. Available from: <https://bnf.nice.org.uk/>. Date accessed: August 2025.
40. Department of Health and Social Care. Drugs and pharmaceutical electronic market information tool (eMIT), 2025. Available from: <https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit>. Date accessed: August 2025.
41. NHS England. National Schedule of NHS Costs 2023/24. Available from: <https://www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/>. Date accessed: March 2025.
42. Electronic Medicines Compendium (EMC). Zejula 100 mg hard capsules (niraparib). 2025. Available from: <https://www.medicines.org.uk/emc/product/8828/smpc#gref>. Date accessed.

43. Guest JF, Ruiz FJ, Greener MJ, Trotman IF. Palliative care treatment patterns and associated costs of healthcare resource use for specific advanced cancer patients in the UK. *Eur J Cancer Care (Engl)* 2006; **15**: 65-73.
44. PSSRU. Unit Costs of Health and Social Care Programme (2022–2027). 2024. Available from: <https://www.pssru.ac.uk/unitcostsreport/>. Date accessed: June 2025.
45. Gao W, Ho YK, Verne J, Glickman M, Higginson IJ, on behalf of the GCp. Changing Patterns in Place of Cancer Death in England: A Population-Based Study. *PLOS Medicine* 2013; **10**: e1001410.

7 Appendices

7.1 Price sources for treatments included in the confidential appendix

Table 86. Source of the confidential prices used in the confidential appendix

Treatment	Source of price/type of commercial arrangement
Olaparib	Indication-specific discount
Rucaparib	Simple PAS

Abbreviations: PAS, patient access scheme.

Single Technology Appraisal

Niraparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy (review of TA673) [ID6403]

EAG report – factual accuracy check and confidential information check

“Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release.” (Section 5.4.9, [NICE health technology evaluations: the manual](#)).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Friday 10 October 2025** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as **confidential** should be highlighted in turquoise and all information submitted as **depersonalised data** in pink.

Issue 1 Inaccuracies related to clinical effectiveness section

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<u>Referencing error (p. 34):</u> In the section describing the disease entity ("<i>Ovarian cancer is a general term that is used to refer (...) following groups</i>"), the publication cited for PRIMA Gonzalez-Martin 2019 does not contain the described information.	Update citation to: González-Martín A, Harter P, Leary A, et al. Newly diagnosed and relapsed epithelial ovarian cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol 2023;34(10):833-848. (In eng). DOI: 10.1016/j.annonc.2023.07.011.	The amendment is necessary to correct the citation error.	Thank you for highlighting this factual inaccuracy. The proposed amendment has been added to the report.
<u>Referencing error (e.g., p. 68, 72, 75, 77):</u> In several places, the EAG report references Gonzalez-Martin 2019 for the latest PRIMA results (OS, PFS, TFST), even though these results are not available. This is incorrect.	Update the report to use the correct references for the latest PRIMA results (OS, PFS, TFST), specifically Monk 2024 or the CSR from the final OS analysis.(1, 2)	The appropriate references for the latest PRIMA results are Monk 2024 or the CSR from the final OS analysis. The referencing should be updated to ensure that the report accurately cites the PRIMA trial results.	As requested, the referencing for the PRIMA trial has been updated from Gonzalez-Martin et al. (2019) to Monk et al. (2024) for the requested sections.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<u>Factual error (pp. 38, 46):</u> The EAG report wrongly indicates that in the PRIME study, the starting dose was fixed at 300 mg per day. However, this is incorrect.	Update the report to reflect that unlike PRIMA, an individualised starting dose was applied following a trial protocol amendment, the PRIME study prospectively implemented the individualised dosing based on body mass and platelet count from the outset.	Amendment is necessary as the current information is incorrect. In PRIME, individualised dosing based on body mass and platelet count was used from the beginning of the study (300 mg for patients with a body weight of ≥ 77 kg and platelet count $\geq 150,000$ per cubic millimetre or 200 mg for patients with a body weight of < 77 kg and/or platelet count $< 150,000$ per cubic millimetre).(3)	Thank you for highlighting this factual inaccuracy. The report has been adjusted to state the correct starting dosages in the PRIME trial.
<u>Factual error (p. 48):</u> On page 48, the EAG report states, "<i>However, for the PRIME trial, only PFS-INV was reported,</i>" This is incorrect.	Update the sentence to reflect that in the PRIME trial, "PFS was assessed by BICR in the ITT population and appropriate subgroups. Additionally, PFS-INV in the ITT population was presented as part of a sensitivity analysis".	In the PRIME trial, PFS was assessed by BICR in the ITT population and relevant biomarker subgroups. Additionally, PFS assessed by INV in the ITT population and was presented as part of a sensitivity analysis.(3)	Thank you for highlighting this factual inaccuracy. The report has been adjusted to state that PFS-INV was available, as a sensitivity analysis, for the PRIME trial.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<u>Factual error (p. 49):</u> On page 49, the EAG report states, “<i>However, PFS-BICR is only available for the HRd subgroup in the PRIMA trial</i>”, which is incorrect.	Update the report to reflect that in the primary analysis, “results for PFS-BICR were presented for all HRD subgroups of interest”.	In the primary analysis of the PRIMA trial (data cut-off: 17 May 2019), PFS-BICR results were reported within the pivotal trial publication, González-Martín 2019,(4) for BRCAm, HRd/BRCAwt, HRp, and HRD status not determined. These results were previously presented in TA673 and also included in the company's response to the EAG's clarification questions – Appendix: KM Curves for Subgroups.	Thank you for highlighting this factual inaccuracy. The text has been adjusted to clarify that PFS-BICR is available for the PRIMA trial.
<u>Factual error (pp. 57, 110):</u> The EAG report states, “<i>Firstly, within the SOLO-1 trial comparing olaparib to placebo, the hazard ratio for progression-free survival reported for the high-risk subgroup was 0.33, which was nearly</i>	Update the report to reflect that the hazard ratio for the ITT population in SOLO-1 was 0.33, and the hazard ratio for the high-risk subgroup was 0.34.	This amendment ensures the report accurately reflects the correct hazard ratios for progression-free survival in the SOLO-1 trial, thereby maintaining the accuracy of the data presented.	Thank you for highlighting this factual inaccuracy. The proposed amendment has been added to the report .

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<i>identical to the reported hazard ratio of 0.34 for the ITT population (i.e., an all-risk population)," which is incorrect.</i>			
<u>Factual error (p. 58):</u> The EAG report states, “Randomisation was double-blinded and performed using an interactive web-response system, with stratification according to four factors” for the PRIMA trial, which is incorrect.	Update the report to reflect the three stratification factors that were used in the PRIMA trial.	Three stratification factors were used in the PRIMA trial (clinical response after first-line platinum-based chemotherapy, receipt of neoadjuvant chemotherapy, and status regarding tumour homologous recombination).(4)	Thank you for highlighting this factual inaccuracy. The proposed amendment has been added to the report.
<u>Factual error (pp. 63, 65):</u> On page 63, the EAG report notes that 32 patients dropped out of the PRIME trial (27 patients in the niraparib arm and 5 patients in the placebo arm) and there is no information available	GSK asks the EAG to review this paragraph considering the availability of the statistical analysis plan for the PRIME trial which pre-specifies how missing data were handled.	These patients were included in the analyses and censored at the date of last radiographic assessment (primary analyses). Moreover, all methods of handling patients withdrawal are available in the statistical analysis plan, which is	Thank you for highlighting this factual inaccuracy. The text has been adjusted to note that the EAG considers the handling of missing data to be appropriate.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
regarding how the missing data for these patients were accounted for within the trial analyses. This statement is incorrect.		publicly available (Li 2023, supplement 2).(3)	
<u>Alignment of observation periods and reported results (p. 67, 72):</u> The EAG report shows a result of [REDACTED] for PFS and [REDACTED] for OS for BRCAwt from the PRIMA trial from an unknown observation period, instead of 0.77 (0.62, 0.95) for PFS and 1.01 (0.80 to 1.27) for OS from the latest observation period as of 8 April 2024 (as reported for other subgroups).	Update the report to reflect the latest result for BRCAwt from the PRIMA trial, as reported in Monk et al. 2024.(1)	The quoted figures in the EAG report are derived from the naive Cox model applied for economic modelling. For reporting the outcomes of the trial, we recommend using the figures as reported in the supplemental appendix of the clinical trial publication (Monk et al. 2024).(1) This amendment ensures the report accurately reflects the most recent and relevant data for BRCAwt from the PRIMA trial.	Thank for highlighting the availability of hazard ratios for the BRCAwt subgroup from the PRIMA trial for the cut-off date of 8 April 2024. We have updated the hazard ratio data for this subgroup accordingly.
<u>Factual error (p. 67 and 76):</u>	Update the sentence to correctly state that there were nominally more HRd patients in the PRIME ITT population	This amendment ensures the report accurately reflects	Thank you for highlighting this factual inaccuracy. The text has been adjusted to

Description of problem	Description of proposed amendment	Justification for amendment	EAG response				
On page 67 and 76, the EAG notes that there were substantially more HRd patients in the PRIMA ITT population compared to the PRIME ITT population, which is incorrect.	compared to the PRIMA ITT population.	HRd distribution in PRIMA and PRIME trials.	state that there was a greater proportion of HRd patients in the PRIME trial compared to the PRIMA trial.				
<u>Factual error (p. 70):</u> On page 70, the EAG report states, " <i>PFS-BICR was not considered within the economic model; however, it is presented here due to the absence of data for the PRIME trial for PFS-INV,</i> " which is incorrect.	Remove the sentence.	In the PRIME trial, PFS-INV results were available as a sensitivity analysis.	Thank you for highlighting this factual inaccuracy. The text has been adjusted to remove the incorrect statement regarding the absence of PFS-BICR data for the PRIME trial.				
<u>Factual error (Table 20 p. 70):</u> Table 20 (p70) lists many patient subgroups of the PRIMA trial as not reported. This is incorrect.	Update the PRIMA column of Table 20, as follows: <table><tr><td>Population</td><td>PRIMA hazard ratio (95% CI)</td></tr><tr><td>BRCAm</td><td>0.40 (0.27 to 0.62)</td></tr></table>	Population	PRIMA hazard ratio (95% CI)	BRCAm	0.40 (0.27 to 0.62)	PFS-BICR results for the subgroups BRCAm, HRd/BRCAwt, BRCAwt, and HRp/BRCAwt are available in the Gonzalez-Martin 2019(4) publication and were presented in the	Thank you for highlighting this factual inaccuracy. The proposed amendment has been added to the report.
Population	PRIMA hazard ratio (95% CI)						
BRCAm	0.40 (0.27 to 0.62)						

Description of problem	Description of proposed amendment		Justification for amendment	EAG response
	HRd/BRCAwt	0.50 (0.31 to 0.83)	previous submission TA673, and therefore not considered confidential.(5)	
	BRCAwt	Not reported		
	HRp/BRCAwt	0.68 (0.51 to 1.43)		
<u>Factual error (p. 70):</u> On page 70, the EAG report states, "In contrast to the PRIME trial, PFS-BICR data were only available for the PRIMA trial for ITT and HRd populations," which is misleading.	Update the sentence to ensure that the report reflects the data availability of PRIMA results.		PFS-BICR results for the subgroups BRCAm, HRd/BRCAwt, BRCAwt, and HRp/BRCAwt are available in the Gonzalez-Martin 2019(4) publication and were presented in the previous submission TA673.(5)	Thank you for highlighting this factual inaccuracy. The report has been adjusted to discuss the hazard ratios for PFS-BICR for all available subgroups.
<u>Factual error (p. 73):</u> On page 73, the EAG report states, " <i>For all available hazard ratios, the associated 95% CIs overlapped 0, indicating that there was no statistically significant difference in OS between the niraparib and placebo</i>	Update the report to reflect that the associated 95% CIs overlapped 1 .		The states text should be corrected with “overlapped 1”.	Thank you for highlighting this factual inaccuracy. The proposed amendment has been added to the report.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<i>arms for any subgroup in either trial," which is incorrect.</i>			
<u>Factual error (p. 75):</u> On page, 75, the EAG report states, "<i>The HRd population (0.87; 95% CI: 0.656 to 1.165) had the largest improvement in TFST for niraparib, compared to placebo. In contrast, the ITT population (0.96; 95% CI: 0.794 to 1.167) had the smallest, statistically nonsignificant, improvement in TFST for niraparib compared to placebo,</i>" which is incorrect as it refers to PFS2.	Change "TFST" to " PFS2 "	This amendment ensures the report accurately reflects the correct endpoint.	Thank you for highlighting this factual inaccuracy. The proposed amendment has been added to the report.
<u>Factual error (p. 76):</u> On page 76, the EAG report incorrectly states	Update the report to reflect the correct 95% CI for TFST from the PRIMA trial, which is 0.622 to 0.887 .	This amendment ensures the report accurately reflects the correct results.	Thank you for highlighting this factual inaccuracy. The

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
the 95% CI for TFST from the PRIMA trial (0.74; 95% CI: 0.34 to 0.59), instead of (0.74; 95% CI: 0.622 to 0.887).			proposed amendment has been added to the report.
<u>Factual error (p. 80):</u> Table 25 indicates that 260 patients and 131 patients treated with olaparib and placebo, respectively, had HRd and BRCA (n), whereas the analysed group consisted of 146 and 73 patients (N).	Update the table to accurately reflect the analysed group sizes.	This amendment ensures the relevant rows of the table accurately represents the correct number of patients analysed.	Not a factual inaccuracy, no change required. The population sizes of 260 patients and 131 patients treated with olaparib and placebo, respectively correspond to the overall population sizes in the SOLO-1 trial. However, as stated in the title of Table 25, these sample sizes correspond to the subgroup of high-risk patients only. The EAG notes that these numbers were taken from Table 93 of the company's submission.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<u>Factual error (p. 82):</u> On page 82, the EAG report states, "Additionally, there was a 12.3% difference in the prevalence of FIGO stage III patients in the SOLO-1 trial," and "Additionally, when comparing data between the PRIMA and SOLO-1 trials, the prevalence of FIGO stage III patients considerably varied from [REDACTED] to [REDACTED], a range of 21.9%", which is incorrect.	Update the report to reflect the correct differences in prevalence rates and between trial ranges.	The difference in the prevalence of stage III patients between the treatment and the placebo arms in SOLO-1 was 8.3% (72.6% vs 64.3%, respectively). The prevalence of FIGO stage III patients in PRIMA and SOLO-1 was [REDACTED] to 72.6% ([REDACTED]).(4, 6)	Thank you for highlighting this factual inaccuracy. The proposed amendment has been added to the report.
<u>Factual error (p. 83):</u> On page 83, the EAG report compares the proportion of patients who achieved a complete response to first-line chemotherapy between the PRIME and ATHENA-MONO trials, without	Update the report to acknowledge the differences in definitions between trials.	In the PRIMA trial, patients without evidence of disease following surgery and first-line platinum-based chemotherapy were not further subdivided into complete responders (CR) and no evidence of disease (NED) categories, as was	Thank you for highlighting the difference in definitions between the ATHENA-MONO and PRIME trials. Accordingly, the corresponding text has been updated to include the following discussion:

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
considering that ATHENA-MONO patients with NED are those who achieved CR due to surgery alone while patients with CR are those who achieved CR to platinum chemotherapy as they had measurable disease after surgery and prior to chemotherapy.		done in the ATHENA-MONO trial. Therefore, when comparing baseline characteristics across trials, the proportion of CR patients at baseline in the PRIMA trial should be compared to the combined proportion of CR and NED patients from the ATHENA-MONO trial."	<i>"However, in the PRIME trial, complete response at baseline included all patients with either no evidence of disease or who had achieved a complete response. In contrast, in the ATHENA-MONO trial, complete response at baseline did not include patients with no evidence of disease. Within the ATHENA-MONO trial, 52.5% and 57.7% of patients had no evidence of disease at baseline in the rucaparib and placebo arms, respectively. As such, in the ATHENA-MONO trial, 69.6% and 67.6% of patients had no evidence of disease or a complete response at baseline in the rucaparib and placebo arms, respectively. Accordingly,</i>

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
			<i>there is a considerable difference between the proportion of patients, at baseline, with no evidence of disease or complete response between the PRIME and ATHENA-MONO trials."</i>
<u>Factual error (p. 92):</u> On page 90, the EAG report states, <i>"Additionally, the EAG performed an ITC for the BRCAm population which comprised both low-risk and high-risk patients in the ATHENA-MONO"</i>, which is incorrect.	Change "ATHENA-MONO" to "SOLO-1".	The SOLO-1 study should be referred to in this statement to ensure the report accurately reflects the correct trial.	Thank you for highlighting this factual inaccuracy. The proposed amendment has been added to the report.
<u>Factual error (p. 93, 95):</u> On page 93, the EAG report states, <i>"The EAG's analysis, using data from the PRIMA trial, indicated that there was a</i>	Change "HRd/BRCAt" to "BRCAm".	For the data being referred to by the EAG, olaparib and niraparib were compared in the BRCAm population.	Thank you for highlighting this factual inaccuracy. The proposed amendment has been added to the report.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<i>statistically significant hazard ratio ([REDACTED]) that indicated a relative benefit of olaparib compared to niraparib in the HRd/BRCAwt population", which is incorrect.</i> A similar issue was noted on page 95 for the sentence: <i>"The EAG's analysis, using data from the PRIMA trial, indicated that there was a non-statistically significant hazard ratio ([REDACTED]) that indicated a relative benefit of olaparib compared to niraparib in the HRd/BRCAwt population".</i>			
<u>Factual error (p. 101):</u> The EAG report states, <i>"However, the results of the PFS-BICR analysis for</i>	Change "HRd/BRCAwt" to "HRp/BRCAwt".	These data are referring to the ITC of niraparib and rucaparib in the HRp/BRCAwt subgroup.	Thank you for highlighting this factual inaccuracy. The proposed amendment has been added to the report.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<i>the HRd/BRCAt population did not align with the results of the EAG's ITC for PFS-INV," which is incorrect.</i>			

Issue 2 Bucher ITC analysis of high-risk PRIMA population data with all-risk population data from SOLO-1 and ATHENA-MONO

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<u>EAG rationale for assuming similar or better PARPi efficacy in high-risk populations versus low-risk is misleading</u> On page 57 of the EAG report states that: <i>"The EAG's clinical experts asserted that the relative treatment benefit of PARPis was likely to be greater in those high-risk patients included in the PRIMA trial</i>	GSK requests that the EAG also consider the available evidence from PAOLA-1 when evaluating the plausibility of similar or better relative treatment efficacy of PARPi in high- and low-risk populations.	The EAG has not considered all available published evidence on differences in relative efficacy between low and high-risk advanced ovarian cancer patients (e.g., PAOLA-1 post-hoc analyses). These data demonstrate that differences in relative efficacy between high-risk and low-risk patients are at least inconclusive, with differences in results observed between	The EAG has been made aware that in PAOLA-1 there is an increased efficacy in lower-risk patients compared to higher-risk patients. The EAG notes that this in the combination therapy of olaparib and bevacizumab. As such, the PAOLA-1 trial considers patients that are bevacizumab

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<i>compared to those low-risk patients excluded from the PRIMA trial. The EAG's clinical experts' opinion was supported by data from the ATHENA-MONO and SOLO-1 trials."</i> The EAG also states the following on page 57 of the report: <i>"Accordingly, data from the ATHENA-MONO trial clearly supports the EAG's clinical expert in demonstrating that the relative treatment benefit of PARPis is greater in a high-risk population compared to a low-risk population. Overall, data from the SOLO-1 and ATHENA-MONO trials supports the views of the EAG's clinical experts with regards to the relative treatment benefit of PARPis being the same or greater in</i>		clinical trials of PARPi treatments.	responders and have initiated and continued treatment with bevacizumab. The EAG notes that the effects of combination treatment may not be the same as monotherapies. As such, we have included text stating the EAG's assumptions are based on a consideration of PARPi monotherapies following platinum-based chemotherapy.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<i>a high-risk population compared to a low-risk population.”</i> GSK believe that these statements omit important information from the CS that provide appropriate justification.			
<u>EAG statement on company consideration of available evidence for comparisons of niraparib and rucaparib is misleading</u> On page 145 of the report, the EAG states the following: <i>“In addition, the EAG considers the analysis provided for the BRCAwt population compared against rucaparib to ignore the specific populations and evidence available that should have been used to compare niraparib against</i>	Update text to the following: <i>“Whilst the company has asserted that comparing high-risk data from PRIMA to all-risk population data from ATHENA-MONO is not appropriate, the EAG considers the analysis provided for the BRCAwt versus rucaparib does not utilise all relevant populations and evidence available. Specifically, the cost-effectiveness analysis could have included comparisons of niraparib and rucaparib in the HRd/BRCAwt and HRp/BRCAwt subgroups”.</i>	ITC comparisons of high-risk patients in PRIMA to all-risk populations in SOLO-1 and ATHENA-MONO are not appropriate given the relevance of risk as an effect modifier. Cost-effectiveness analyses comparing niraparib and rucaparib in the HRd/BRCAwt and HRp/BRCAwt subgroups were not presented, considering UK clinical practice and the use of the same standard of care across BRCAwt populations.	The EAG has removed the use of the word “ignored” and amended the text on page 145 to the following: <i>“In addition, the EAG considers the analysis provided for the BRCAwt population compared against rucaparib does not utilise all relevant populations and evidence available. Specifically, the EAG considers that the cost-effectiveness analysis</i>

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<i>rucaparib in the HRd/BRCAwt and HRp/BRCAwt subgroups instead”.</i> EAG statement that the company “ignored” the specific populations and evidence available is misleading.		Additionally, indirect treatment comparisons based on PRIME and ATHENA-MONO trials suggested that the two treatments do not differ significantly. Therefore, it is inappropriate to suggest suitable evidence has been ignored.	<i>should have included comparisons of niraparib and rucaparib in the HRd/BRCAwt and HRp/BRCAwt subgroups.”</i>

Issue 3 Clinical plausibility of EAG preferred comparator survival extrapolations

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<u>Plausibility of EAG olaparib survival extrapolations for BRCAm population analysis</u> For the EAG preferred base case cost-effectiveness analysis for the BRCAm population, an OS HR of [REDACTED] and PFS HR of [REDACTED] for niraparib versus olaparib were applied to PRIMA-	GSK requests that the EAG specify that the PFS and OS landmark survival estimates presented in the report for SOLO-1 correspond to the all-risk population rather than the high-risk population.	The EAG used all-risk PFS and OS data from SOLO-1 to help validate olaparib extrapolations in the model. However, it is well established that the high-risk population are anticipated to have worse survival than an all-risk population, as	This is not a factual inaccuracy and therefore no change has been made.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
based survival extrapolations for niraparib to generate long-term survival extrapolations for olaparib. On pages 128 and 129, the EAG states the following: <i>“The EAG notes that the application of the HR results in landmark estimates of PFS for olaparib that are closely aligned with the evidence from SOLO-1, which showed 48.4% of patients progression-free at five years compared to ■% estimated in the economic model. This is in comparison to ■% in the company’s base case analysis, assuming clinical equivalence between niraparib and olaparib.”</i>		observed for olaparib in SOLO-1 for PFS(7) and highlighted in other studies discussed in the company submission illustrating differences in PFS and OS between low and high-risk populations (such as PAOLA-1 and AR1ZE).	

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 133 of the EAG report, the following is stated: <i>“As shown, OS at seven years for olaparib estimated using the EAG preferred approach is much closer aligned to the most recent data available from SOLO-1 (67%) than the estimates using the company’s approach (████), i.e. assuming clinical equivalence with niraparib.</i> <i>Although the estimates at 10 and 20 years for olaparib using the EAG preferred approach seem high, the EAG does not consider them to be unreasonable given the observed OS at 7 years. This was confirmed by clinical experts to the EAG who stated that the resulting estimates are clinically</i>			

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<i>plausible in light of the observed data.”</i>			
<u>Plausibility of EAG rucaparib survival extrapolations for BRCAwt population analysis</u> The EAG cost-effectiveness analysis for the BRCAwt population considered an HRd BRCAwt specific OS HR of [REDACTED] and a PFS HR of [REDACTED] (relative efficacy data from ITCs that compared PRIMA vs. ATHENA-MONO) to produce long-term survival extrapolations for rucaparib. This was then used to inform an expected ICER range for rucaparib versus niraparib. The EAG report states on page 138: <i>“As shown in Error! Reference source not found., the company’s approach of assuming</i>	GSK requests that the EAG specify that the PFS and OS landmark survival estimates presented in the report for ATHENA-MONO correspond to the all-risk population rather than the high-risk population.	The EAG used all-risk PFS and OS data from ATHENA-MONO to help validate long-term extrapolations in the model. However, it is well established that the high-risk population are anticipated to have worse survival than an all-risk population.	This is not a factual inaccuracy and therefore no change has been made.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<i>clinical equivalence for niraparib and rucaparib produces estimates of PFS for rucaparib that would not be in line with the observed data from ATHENA-MONO.”</i> The EAG also states the following on page 139 of the report: <i>“The latest published estimates of median PFS at four years from ATHENA-MONO, presented at the European Society for Medical Oncology (ESMO) 2024, are also shown below in Error! Reference source not found. compared to the EAG preferred model estimated value. The EAG notes that it is reassuring that the median estimates produced using their preferred approach to modelling rucaparib PFS lie in-between that reported for</i>			

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<i>the HRd/BRCAwt and HRp/BRCAwt populations. While the EAG is unable to estimate where the model-predicted value should lie within that range, it is noted that it would be expected to be closer to (but higher than) that of the HRp/BRCAwt population.”</i> On page 144 of the EAG report, the the following statement is provided: <i>“Based on the immature OS data available for rucaparib and the observed benefit for OS with niraparib in PRIMA being similar to placebo, a clinical expert to the EAG noted that the predicted OS outcomes for both rucaparib and niraparib at 10 and 20 years may be overly optimistic. However, the EAG considers the</i>			

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<i>difference in benefit is still clinically plausible.”</i>			
<u>Use of PFS HR value of [REDACTED] from EAG ITC in the economic model based on reconstructed BRCAwt curves from ATHENA-MONO</u> On page 124, the EAG states “<i>Therefore, the EAG did not have access to all of the survival data available for the subgroups of interest from PRIMA (HRd/BRCAwt and HRp/BRCAwt) in order to implement these in the economic model.</i>” As a consequence, the EAG derived an HR PFS value of [REDACTED] from an ITC, based on a reconstructed ATHENA-MONO curve for BRCAwt (page 137 and Section 3.4.4).	GSK requests that the EAG update the statement on page 124 to accurately reflect that the PRIMA PFS/OS KM data for BRCAwt patients are available in the published domain (Monk et al. 2024(1))	The EAG approach was taken due to the absence of specific data that would allow for separate comparisons for HRd/BRCAwt and HRp/BRCAwt. However, these data are publicly available (Monk et al. 2024(1)), and based on this, the EAG could have conducted economic analysis for the HRd/BRCAwt and HRp/BRCAwt subgroups.	Thank you for highlighting this. The following text has been added to the paragraph described by the company (page 137) to add further explain the EAG approach. <i>“During factual accuracy it was brought the EAG's attention that these data were available in the supplementary material of Monk et al. 2024. However, during the time of the EAG report, this was not known to the EAG, and the company had not provided these data in their CS or response to clarification. Therefore, the EAG</i>

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
GSK believes that PFS/OS PRIMA data were available to conduct HRd/BRCAwt and HRp/BRCAwt specific analyses. GSK also believes that it would have been more appropriate for the EAG to use the PFS HR values for each subgroup separately, which are available in Table 37 of the EAG PRIMA analysis.			<i>considers that this would be the most appropriate data to include for comparisons against rucaparib in the model for the most robust assessment. The EAG notes the preference for the company to implement this analysis in the economic model using available IPD, rather than requiring the EAG to digitise published KM curves. In addition, the company should also include additional data on file, not available to the EAG, related to each subgroup. For example, time to treatment discontinuation, niraparib dosage data (per cycle), proportion receiving subsequent treatment and corresponding</i>

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
			<i>distribution of patients receiving each type of subsequent treatment ”.</i>

Issue 4 Clarity of EAG ICER results presentation

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
In addition to the incremental NMB, the EAG displays the ICER for some of the base case and scenario analyses in a number of places throughout the report (table 6, table 7, table 9, table 10, table 11, table 12, table 13, text in p. 113, table 44, table 45, text in p.141, and throughout Section 5 Cost-Effectiveness Results: text in p.163, table 73, table 74, table 76, table 77, table 78, table 79, text in p. 176, table 80, text in p.177, p.178, table 81, table 82, table 84, p.182, table 85). Although it is noted by the EAG that ICER results correspond to the southwest quadrant of the cost-effectiveness plane, it may not be immediately clear to the reader that the ICERs presented by the EAG correspond to the comparator versus niraparib, rather than niraparib versus the comparator.	Update the relevant sections of the text and tables to explicitly highlight that ICERs in the southwest quadrant represent comparing the comparator (i.e. olaparib or rucaparib) versus niraparib.	This amendment will help the reader to correctly interpret the presented results and avoid any potential confusion.	This is not a factual accuracy; no change is required.

Issue 5 Misleading statements regarding company presentation of supporting evidence, rationale and analyses conducted

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<u>EAG statements on BGI genomics test (pp. 37, 44, 62, 66, 68, 76, 84, 87):</u> The EAG report indicates that the PRIME trial is unreliable because the test used to determine HRD status (BGI Genomics) has not been validated, relying only on one source (advisory board meeting minutes). GSK believe that this does not accurately reflect the status of the BGI Genomics test.	Update the report to remove all references stating that the BGI Genomics test used to determine HRD status has not been validated.	The BGI Genomics Homologous Recombination Deficiency Detection Kit has been validated in a recent study (Feng et al. 2023(8)) and has had CE-IVDD certification since 2022(9), allowing its use in the European Union and the United Kingdom, which recognises the CE-IVDD mark for in vitro diagnostic products up to 30 June 2026.(10)	The EAG acknowledges that the BGI Genomics Homologous Recombination Deficiency Detection Kit is certified for use in the UK. However, this does not alleviate the EAG's concern that the results of the test are likely to be dissimilar to the test used in the PRIMA trial. These concerns were raised by the company's own clinical advisory board and the previous NICE TA1055.
<u>EAG statement on SLR conduct (p. 53):</u> On page 53, the EAG report states, "<i>No information is provided in the CS regarding the quality</i>	GSK requests that the EAG review this statement in light of the clarification provided	The company submission states, "<i>The data was extracted by one reviewer and a second reviewer assessed the entries to ensure</i>	The EAG has amended the text in Table 15 to state that the data extraction was appropriate and that a

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<i>assessment of the extracted data. For instance, it is unclear whether the quality assessment comprised a review of the entire dataset or a check of 25% of the extracted data”.</i> This is a misinterpretation of the company submission that GSK are happy to correct.	regarding the SLR quality assessment methods.	<i>consistency and accuracy,”</i> we intended this to convey that the quality assessment by the second reviewer covered all extracted data.	second reviewer assessed all entries entered by the first reviewer.
<u>EAG statement on PRIMA trial conduct (p. 60):</u> On page 60, the EAG report notes that in the PRIMA trial, five patients who did not receive either niraparib or placebo after randomisation were excluded from the safety analysis, which is considered a minor concern. GSK feel that this assessment misses important context.	GSK requests that the EAG review this statement considering the clarification provided regarding the patients included in the safety analysis.	In clinical trials, it is standard practice to exclude patients who did not receive any dose of the assigned treatment from the safety analysis (i.e., safety analysis population). In the PRIMA trial, safety was assessed in all patients included in the safety analysis set, which was protocol-specified, so the lack of data for these patients should not be considered missing data.	The EAG has updated the wording of this text to reflect that the population corresponds to the All-Patients Treated definition of the ITT population.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<u>EAG statement on rucaparib status (p. 79):</u> On page 79, the EAG report states, "<i>Olaparib has been approved in patients with BRCAm, while rucaparib has been approved in patients with BRCAwt,</i>" which is misleading.	Specify that rucaparib is "recommended" for patients with BRCAwt.	Rucaparib is indicated/approved for use regardless of BRCA status, whereas it is recommended by NICE for use in BRCAwt patients. This amendment ensures the report accurately reflects the registration and reimbursement status of rucaparib.(11)	The EAG has updated the wording to clarify that rucaparib is recommended in the BRCAwt population.
<u>EAG statement on company evidence provided to support equivalence assumption</u> On page 108, the EAG report states that: <i>"Within the economic modelling, the company made the assumption that PARPis are equivalent in their effectiveness. However, the company did not provide any evidence to support this assertion in the CS".</i>	Update the relevant text on page 108 to more clearly outline the company's rationale for assuming equivalence, e.g. as follows: <i>"Within the economic modelling, the company made the assumption that PARPis are equivalent in their effectiveness, based on the results of the Bucher ITC analysis, available published real world evidence (SACT, Kim 2024(12)) and clinical expert feedback. However, the EAG believes</i>	The current text states that the company provided no evidence to support this in the CS. However, this is not accurate and misleading as the company outlined their supporting evidence in Section 3.4.6 of the CS.	The EAG has amended the text to the following to explicitly state the EAG's position: <i>"Within the economic modelling, the company made the assumption that PARPis are equivalent in their effectiveness. The EAG does not consider the company to have provided sufficient</i>

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	<i>that the company did not provide sufficient evidence to support this assertion in the CS".</i>		<i>evidence to support this assertion within the CS."</i>
<u>Company exploration of alternative efficacy assumptions for comparators</u> On page 24 table 5, the EAG report states the following: <i>"The EAG notes that based on this assumption, the company did not vary the relative treatment effectiveness against either olaparib or rucaparib in the probabilistic sensitivity analyses, i.e. applied a fixed hazard ratio of 1 for both OS and PFS."</i> Similarly on page 185, the EAG report states: <i>"Furthermore, the company did not vary any differences in treatment effectiveness between niraparib and the included comparators in the probabilistic sensitivity analysis (PSA)."</i>	Update text in table 5, page 24 of the EAG report to: <i>"The EAG notes that based on this assumption, the company did not vary the relative treatment effectiveness against either olaparib or rucaparib in the probabilistic sensitivity analyses, i.e. applied a fixed hazard ratio of 1 for both OS and PFS. Treatment effectiveness parameters were instead varied in scenario analysis."</i> Update text in table 5, page 24 of the EAG report to: <i>"Furthermore, the company did not vary any differences in treatment effectiveness between niraparib and the included comparators in the probabilistic</i>	This statement may give the reader the impression that the company did not explore any differences in treatment effectiveness between niraparib and the included comparators. However, the company did conduct a scenario analysis using the PFS Bucher ITC result for niraparib versus olaparib in the CS (Section 3.11.3) as well as several additional scenarios varying OS and PFS HRs for both comparators in response to clarification questions (Table 22 and Table 23). This amendment will help the reader to understand that while efficacy assumptions were not varied in the PSA, different efficacy assumptions	This is not a factual inaccuracy; no change is required. These statements are referring solely to the probabilistic sensitivity analysis as probabilistic results are used for decision making.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	<i>sensitivity analysis (PSA). The company instead varied treatment effectiveness parameters through scenario analysis.</i>	were explored in scenario analysis by the company to explore uncertainty around the equivalence assumption.	
<u>EAG statements on company evidence provided to support SACT niraparib dose distribution</u> On p.155, the EAG notes that: <i>“The SACT data were considered the most appropriate source to inform the dose distribution by the company as the data aligned with dosing in the MONITOR-UK study, which the company considers reflects clinical practice.”</i> On p. 161 the EAG report states that: <i>“While more patients received a higher starting dose in PRIMA than in the SACT dataset, which the company considers more reflective of clinical practice, not using the</i>	Update the sentence on p.155 as follows: <i>“The SACT data were considered the most appropriate source to inform the dose distribution by the company as the data aligned with dosing in the MONITOR-UK study, which clinical experts consulted by the company stated was a more accurate reflection of niraparib use in UK clinical practice.”</i> Update text on p.161 to include the following: <i>“Although the company has presented evidence suggesting similar efficacy of</i>	The EAG does not clearly state GSK’s rationale to support use of the niraparib SACT dose distribution in the company base case analysis provided in Section 3.6.1 of the CS. The company also noted in Section 2.11 of the CS that evidence from PRIMA and a real-world study (Bruno 2024) showed similar efficacy between ISD and FSD dosing for niraparib which would support similarity in efficacy between niraparib doses.	The comments highlighted by the company are not factual inaccuracies. However, the EAG has amended the text on page 155 to that suggested by the company, as this is the first time at which the EAG discusses the company’s use of SACT data to inform dosage.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<i>PRIMA dose distribution ignores the intrinsic link between dose and treatment effect.”</i> On p. 186 of the EAG report, the following statement is included: <i>“The company informed starting dose distribution of niraparib using SACT data. As the treatment effectiveness and discontinuation used in the model is informed by the PRIMA trial, in the EAG base case the dose distribution of niraparib at baseline has been informed using PRIMA and each cycle is informed by the observed proportion of patients receiving each of the three niraparib doses (100 mg, 200 mg, 300 mg) for either the BRCAm or BRCAwt population.”</i>	<i>ISD and FSD, the EAG believes that using PRIMA data represents a more conservative approach and maintains the integrity of the intrinsic connection between dose and treatment effect.”</i> Update text on p.186 to include the following: <i>“The company informed starting dose distribution of niraparib using SACT data, which the company considered more reflective of clinical practice based on the MONITOR-UK study and clinical expert feedback. As the treatment effectiveness and discontinuation used in the model is informed by the PRIMA trial, in the EAG base case the dose distribution of niraparib at baseline has been informed using PRIMA and each cycle is informed by the observed proportion of patients receiving</i>		

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
	<i>each of the three niraparib doses (100 mg, 200 mg, 300 mg) for either the BRCAm or BRCAwt population.”</i>		
<u>Discussion of prognosis and treatment effect modification of HRd status (p. 67, 70, 76, 83 and 87):</u> In several instances, the EAG stated that HRd patients have a better “prognosis” than HRp patients and suggested that the difference in the prevalence of HRd patients between the PRIME and PRIMA trials may explain the difference in the relative improvement in PFS-INV for niraparib, compared to placebo, between the trials. For example, on page 67 the EAG states that: <i>“The EAG notes that there was substantially more HRd patients in the PRIMA ITT population compared to the PRIME ITT population. As HRd patients have</i>	The term “better prognosis” should be amended to state that HRd status has been shown to be a key treatment effect modifier. For example, the text on page 67 could be amended to say: <i>“As HRd status has been shown to be a key treatment effect modifier, the EAG notes that this difference in the prevalence of HRd patients between trials may explain the difference in the relative improvement in PFS-INV for niraparib, compared to placebo, between the trials.”</i>	The term “prognosis” implies that survival outcomes for both the intervention and control arms would be impacted, without necessarily impacting relative efficacy. Rephrasing it as “treatment effect modifier” would better reflect the EAG’s point and provide clarity to the reader. Similar updates should also be made to the text on pages 70, 76, 83, and 87.	The EAG has adjusted the text as requested by the company.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<i>been shown to have a better prognosis than HRp patients, the EAG notes that this difference in the prevalence of HRd patients between trials may explain the difference in the relative improvement in PFS-INV for niraparib, compared to placebo, between the trials.”</i> Use of the term "prognosis" appears potentially incorrect in this context, as the EAG appears to then discuss the impact on results in terms of relative efficacy.			
<u>EAG interpretation of fixed margin analysis:</u> On page 103 of the report, the EAG states that: <i>“The EAG notes that different values have been derived based on the lower 95% confidence intervals for different population subgroups. However, the EAG is concerned that this disparity</i>	Remove the following statement: <i>“As such, the EAG is concerned that assessments of non-inferiority using this method are more likely to establish non-inferiority when the lower 95% confidence intervals are derived from trials with high levels of uncertainty.”</i>	GSK believe that the EAG have misinterpreted the impact of uncertainty on fixed margin analyses. According to the methodology proposed by Kaul and Diamond (2007), “dmax” is the threshold below which the entire 95%CI from the Bucher ITC for NIRA vs RUCA should be below for NI vs RUCA to be	The EAG has removed the text as requested by the company.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
<i>indicates that these non-inferiority margins are not necessarily clinically meaningful. As such, the EAG is concerned that assessments of non-inferiority using this method are more likely to establish non-inferiority when the lower 95% confidence intervals are derived from trials with high levels of uncertainty.”</i>		established. The dmax is practically 1/U95 where “U95” is the upper 95%CI limit reported for the treatment effect of rucaparib versus placebo in the ATHENA-MONO study. If the uncertainty in the comparator trial population was higher, the U95 would be a larger value, and consequently dmax would decrease, setting a stricter threshold for NI. At the same time, the confidence interval of the Bucher ITC estimate would be wider since the variance in the comparator trial population would be higher. Therefore, contrary to the concern raised by the EAG, both of these points would decrease the chance of establishing NI when the 95%CI are derived from trials with high levels of uncertainty.	

Issue 6 Check of confidential marking

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response																																			
Page 155, Table 61 Dosing distribution at baseline and relative dose intensities	Relative dose intensity should be confidential	Update table to <table><tr><th></th><th colspan="2">Niraparib</th><th>Rucaparib</th><th>Olaparib</th></tr><tr><td>Dosing type</td><td>Fixed</td><td>Fixed</td><td>Fixed</td><td>Fixed</td></tr><tr><td>Route</td><td>Oral</td><td>Oral</td><td>Oral</td><td>Oral</td></tr><tr><td>Dose</td><td>200 mg</td><td>300 mg</td><td>600mg</td><td>300mg</td></tr><tr><td>% of patients at baseline</td><td>87% BRCAm 83% BRCAwt</td><td>13% BRCAm 17% BRCAwt</td><td>-</td><td>-</td></tr><tr><td>Relative dose intensity</td><td> </td><td> </td><td> </td><td> </td></tr><tr><td colspan="5">Abbreviations: BRCAm, breast cancer gene mutation; breast cancer gene wildtype.</td></tr></table>		Niraparib		Rucaparib	Olaparib	Dosing type	Fixed	Fixed	Fixed	Fixed	Route	Oral	Oral	Oral	Oral	Dose	200 mg	300 mg	600mg	300mg	% of patients at baseline	87% BRCAm 83% BRCAwt	13% BRCAm 17% BRCAwt	-	-	Relative dose intensity					Abbreviations: BRCAm, breast cancer gene mutation; breast cancer gene wildtype.					Thank you for highlighting the incorrect marking. This has been marked as confidential in the EAG’s updated report.
	Niraparib		Rucaparib	Olaparib																																		
Dosing type	Fixed	Fixed	Fixed	Fixed																																		
Route	Oral	Oral	Oral	Oral																																		
Dose	200 mg	300 mg	600mg	300mg																																		
% of patients at baseline	87% BRCAm 83% BRCAwt	13% BRCAm 17% BRCAwt	-	-																																		
Relative dose intensity																																						
Abbreviations: BRCAm, breast cancer gene mutation; breast cancer gene wildtype.																																						
Page 158	Average niraparib dose received in the PRIMA trial	Applying the average niraparib dose received in the PRIMA3 trial (mg for BRCAm, mg for BRCAwt)	Thank you for highlighting the incorrect marking. This has been marked as confidential in the EAG’s updated report.																																			

References

1. Monk BJ, Barretina-Ginesta MP, Pothuri B, Vergote I, Graybill W, Mirza MR, et al. Niraparib first-line maintenance therapy in patients with newly diagnosed advanced ovarian cancer: final overall survival results from the PRIMA/ENGOT-OV26/GOG-3012 trial. *Ann Oncol*. 2024;35(11):981-92.
2. GlaxoSmithKline. Final Overall Survival Analysis Clinical Study Report. A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study of Niraparib Maintenance Treatment in Patients with Advanced Ovarian Cancer Following Response on Front-Line Platinum-Based Chemotherapy. 2024.
3. Li N, Zhu J, Yin R, Wang J, Pan L, Kong B, et al. Treatment With Niraparib Maintenance Therapy in Patients With Newly Diagnosed Advanced Ovarian Cancer: A Phase 3 Randomized Clinical Trial. *JAMA Oncol*. 2023;9(9):1230-7.
4. González-Martín A, Pothuri B, Vergote I, DePont Christensen R, Graybill W, Mirza MR, et al. Niraparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. *N Engl J Med*. 2019;381(25):2391-402.
5. National Institute for Health and Care Excellence. Niraparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy. Technology appraisal guidance [TA673]. 2021 17 February 2021.
6. Moore K, Colombo N, Scambia G, Kim BG, Oaknin A, Friedlander M, et al. Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. *N Engl J Med*. 2018;379(26):2495-505.
7. .
<https://www.bgi.com/global/news/bgi%E2%80%99s-homologous-recombination-deficiency-detection-kit-receives-ce-ivdd-certification>.
<https://www.gov.uk/guidance/regulating-medical-devices-in-the-uk>.