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Olaparib for adjuvant treatment of high-risk HER2-negative, BRCA-positive early breast cancer after chemotherapy: A Single Technology Appraisal

Produced by Bristol Technology Assessment Group, University of Bristol

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Contributions of authors

Howard Thom, Elsa Marques and Nicky Welton critiqued the health economic analysis submitted by the company. Penny Whiting, Eve Tomlinson, Rachel James, and Chris Cooper summarised and critiqued the clinical effectiveness data reported within the company's submission. Hugo Pedder critiqued the statistical aspects of the submission. Chris Cooper critiqued the company's search strategy. All authors were involved in drafting and commenting on the final report. PW and HT take joint overall responsibility for the report.

Commercial in confidence (CiC) data are highlighted in blue throughout the report.

Academic in confidence (AiC) data are highlighted in yellow throughout the report.

Abbreviations

Abbreviation	Definition
AE	Adverse Events
AiC	Academic in confidence
AIC	Akaike Information Criteria
AML	Acute Myeloid Leukaemia
BC	Breast cancer
BIC	Bayesian Information Criterion
BNF	British National Formulary
BRCA	Breast cancer gene
BRCA-1	Breast cancer gene 1
BRCA-2	Breast cancer gene 2
BRCAm	Breast cancer susceptibility gene mutation
CAA	Comercial Access Agreement
CDK	Cycklin Dependent Kinase
CI	Confidence interval
CEAC	Cost-Effectiveness Acceptability Curve
CiC	Commercial in-confidence
CPS+EG score	Clinical and pathologic stage and oestrogen receptor status and histologic grade
CRD	Centre for Reviews and Dissemination
CS	Company Submission
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DC01	Data cut-off 1
DC02	Data cut-off 2
DF	Disease-free
dDFS	Distant disease-free survival
EAG	External Assessment Group
eBC	Early breast cancer
EBCTCG	Early Breast Cancer Trialists Collaborative Group
ECG	Echocardiogram
EMA	European Medicines Agency
eMIT	Electronic market information tool
ER	Oestrogen receptor
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire Core 30
EQ-5D	EuroQol 5 dimensions
EQ-5D-3L	EuroQol 5 dimensions 3 level
FDA	Food and Drug Administration
gBRCAm	Germline BRCA-mutated
HER2	Human Epidermal Growth Factor Receptor 2
HERC	Health Economics Research Centre
HR	Hormone Receptor

Abbreviation	Definition
HR	Hazard Ratio
HRQoL	Health-Related Quality of Life
ICER	Incremental Cost Effectiveness Ratio
iDFS	Invasive disease-free survival
IDMC	Independent Data Monitoring Committee
ITT	Intention to treat
KM	Kaplan-Meier
LYG	Life year gained
mBC	Metastatic breast cancer
MCID	Minimal clinically important difference
MDS	Myelodysplastic syndrome
MHRA	Medicine and Healthcare products Regulatory Agency
NGTD	National Genomic Test Directory
NHS	National Health Service
NIHR	National Institute for Health and Care Research
NICE	National Institute for Health and Care Excellence
NR	Not Reported
OLS	Ordinary Least Squares
OS	Overall Survival
OWSA	One way sensitivity analysis
PAS	Patient Access Scheme
PP	Per protocol
PR	Progesterone receptor
pCR	Polymerase chain reaction
PF	Progression-Free
PFS	Progression-Free Survival
PH	Proportional Hazards
PSA	Probabilistic Sensitivity Analysis
PSS	Person social services
PSSRU	Person social services research unit
PROM	Patient reported outcome measure
QALY	Quality-Adjusted Life Year
QoL	Quality of life
RCT	Randomised Controlled Trial
RFS	Recurrence free survival
RoB	Risk of bias
RWE	Real world evidence
SAE	Serious adverse event
SA	Sensitivity analysis
SAS	Safety analysis set
SMR	Standardised mortality rate
SR	Systematic review
STA	Single Technology Appraisal

Abbreviation	Definition
STEEP	Standardised terms for efficacy endpoints
TAG	Technology Assessment Group
TLR	Targeted Literature Review
TNBC	Triple Negative Breast Cancer
TP	Transition probability
UK	United Kingdom
VBA	Visual basic for applications
WGS	Whole genome sequencing

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ISSUES

1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the evidence 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.
- Sections 1.3 to 1.6 explain the key issues in more detail.

Background information on the condition, technology and evidence and information on non-key issues are in the main EAG report.

All issues identified represent the EAG's view, not the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the EAG's key issues

Table 1 provides an overview of the key issues identified by the EAG.

TABLE 1 SUMMARY OF KEY ISSUES

Issue	Summary of issue	Report sections
1	Clinical effectiveness data are immature	3.2.6 4.2.6
2	Potential risk of bias in estimates of HRQoL	3.2.1
3	HRQoL measures used in the economic model	3.2.4.2 **Error! Reference source not found.**
4	Access to BRCA testing in HR+/HER2-	3.2.2.3 4.2.8.1

HRQoL = Health-related quality of life, BRCA = Breast cancer gene, HR+/HER2- = Hormone receptor positive/ Human epidermal growth factor receptor 2 negative.

The key differences between the company's preferred assumptions and the EAG's preferred assumptions in triple negative breast cancer (TNBC) are the inclusion of long-term recurrence risks, parametric model for survival following early metastatic recurrence, and evidence source for HRQoL. Key differences in HR+/HER2- are the parametric model for

recurrence, parametric model for survival following early non-metastatic recurrence, evidence source for HRQoL, and inclusion of BRCA testing costs.

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:

- Reducing non-metastatic and metastatic recurrence
- Increasing overall survival through reduction in recurrence
- Increasing risk of side effects, namely anaemia and neutropenia
-

Overall, the technology is modelled to affect costs by:

- Its higher drug price than conservative "watch and wait" care
- Reducing the need for pharmacological, surgical, and radiotherapy costs through reduction in recurrence
- Increasing cost with side effects of treatment (anaemia and neutropenia).
- Requiring universal BRCA testing; not considered by the company as there is a case for it to be offered on the National Health Service (NHS) for all TNBC soon, but timelines for HR+/HER2- patients are more uncertain
-

The modelling assumptions that have the greatest effect on the ICER are:

- The source of evidence on HRQoL in TNBC and HR+/HER2-
- Inclusion or exclusion of BRCA universal testing costs in HR+/HER2-
- The parametric model for survival after early metastatic recurrence in TNBC and HR+/HER2-
- The long-term recurrence risk in TNBC
- The parametric model for recurrence in HR+/HER2-
-

1.3 The decision problem: summary of the EAG's key issues

The company's definition of the decision problem as defined in the company submission (CS) matches the final NICE scope.(1, 2) The EAG have no concerns regarding how the decision problem was defined by the company. Only one relevant trial exists of olaparib in the specified population – the OlympiA trial (NCT02032823).(3) This trial was directly relevant to the scope with only minor issues to note regarding the study population which the EAG do not consider likely to have had any impact on estimates of clinical effectiveness (section 2.2).

1.4 The clinical and cost effectiveness evidence: summary of the EAG's key issues

The four key issues identified by the EAG are issues of both clinical- and cost-effectiveness:

ISSUE 1 IMMATURITY OF DATA

Report section	Section 3.2.6 and Section 4.2.6
Description of issue and why the EAG has identified it as important	Clinical effectiveness data from the trial are immature to inform the model Although there is a median of 3.5 years follow-up in OlympiA, the median has not been met for any of the effectiveness time-to-event outcomes. This means there is uncertainty regarding the long-term risk of recurrence in TNBC, the appropriate distribution for recurrence in HR+/HER2-, and distribution for survival following early metastatic recurrence. HR+/HER2- patients were added at a later stage to the OlympiA trial in a protocol amendment, resulting in small numbers recruited and shorter follow-up for this subgroup. There is more uncertainty in HR+/HER2- estimates as the company relied on estimates from the intention to treat (ITT) trial population on both cancer subgroups (which are dominated by TNBC) as a proxy for HR+/HER2-.
What alternative approach has the EAG suggested?	The EAG have suggested using literature on non-zero long-term recurrence in TNBC and alternative distributions for recurrence in HR+/HER2- and survival following early metastatic recurrence in both populations. However, longer follow-up data are required to reduce the uncertainty.
What is the expected effect on the cost-effectiveness estimates?	Changing the assumptions on long-term recurrence and survival after early meta-static recurrence in TNBC changed the deterministic ICER from £35,855 to £39,157/QALY. Changing the assumptions on recurrence and survival after early meta-static recurrence in HR+/HER2- changed the deterministic ICER from £41,879 to £48,288. It is not possible to know how the results would change if using HR+/HER2- data only instead of ITT as a proxy.
What additional evidence or analyses might help to resolve this key issue?	This currently relates to unresolvable uncertainty. The company needs longer follow-up from OlympiA and/or other studies.

ISSUE 2 POTENTIAL RISK OF BIAS IN ESTIMATES OF HRQOL

Report section	Section 3.2.1
Description of issue and why the EAG has identified it as important	There are high concerns regarding missing data for HRQoL questionnaires throughout the OlympiA trial.
What alternative approach has the EAG suggested?	The missing data was caused by low completion rates of HRQoL questionnaires. See below for suggested additional analyses.
What is the expected effect on the cost-effectiveness estimates?	It is possible that the missing data have resulted in biased estimates of European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire Core 30 (EORTC QLQ-C30) which were then mapped to utility scores for the model. This is particularly concerning if data were not missing at random but related to the outcome i.e., if those with poor HRQoL were less likely to complete questionnaires.
What additional evidence or analyses might help to resolve this key issue?	Additional analyses based on multiple imputation methods of missing HRQoL data to include adjustment for other outcome variables proxying for the outcome of interest could be used to explore the potential impact of missing data on estimates of HRQoL that would then be mapped onto utility scores for the model. An alternative approach could be to use a threshold analysis that assumes different plausible HRQoL values for the missing data and demonstrates their impact on the ICER.

ISSUE 3 HRQOL MEASURES USED IN THE ECONOMIC MODEL

Report section	Section 3.2.4.2 and Section **Error! Reference source not found.**
Description of issue and why the EAG has identified it as important	HRQoL was measured using the EORTC QLQ-C30 in the OlympiA trial. This is a standard outcome measure for cancer trials but does not consider breast cancer specific quality of life (there are subscales available that do this that could have been used) and does not translate directly to utilities. Instead, a mapping exercise has to be carried out to map to EuroQol 5 dimensions (EQ-5D) utilities, which the company performed, but adopted an older mapping algorithm which has been shown to provide biased estimates and applied it to only data cut-off 1 (DCO1).
What alternative approach has the EAG suggested?	Ideally, patients in the OlympiA trial would have completed an additional generic HRQoL questionnaire like the EQ-5D. It is quick and easy to administer and would directly inform utilities for the cost-effectiveness analysis. In the absence of direct utility scores from the OlympiA trial, the EAG would recommend exploring different mapping algorithms for EORTC-QLQ-C30 scores (e.g., Gray 2021 (4) algorithm), which are designed to prevent potential biases from OLS-based mapping algorithms such as the one used by the company. As these newer mapping algorithms are not fully externally validated yet, the EAG suggests applying utility scores from the literature, derived from responses to the EQ-5D

	questionnaires in good quality UK studies in a similar patient group at the different health states of the model.
What is the expected effect on the cost-effectiveness estimates?	Changing the HRQoL source of evidence used to inform the model has a substantial impact on the ICER (Table 22), adding over£7,000/QALY and £9,000/QALY to the ICER in TNBC and HR+/HER2- respectively.
What additional evidence or analyses might help to resolve this key issue?	Using newer mapping algorithms such as the Gray 2021 algorithm for mapping EORTC QLQ C30 scores onto EQ-5D utilities for the DF state as additional sensitivity analysis to the ones already reported, and providing these mapped scores for data at DCO2.(4, 5)

ISSUE 4 ACCESS TO BRCA TESTING IN HR+/HER2-

Report section	Section 3.2.2.3 and Section 4.2.8.1.1
Description of issue and why the EAG has identified it as important	Treatment with olaparib requires patients to be tested for gene mutations on the BRCA gene, which is currently not offered routinely to all patients in the NHS. The National Genomic Test Directory (NGTD) indicates that all TNBC patients under 60 years of age are currently eligible for BRCA testing; furthermore, latest update to the online NGTD spreadsheet suggests that BRCA testing for all those with TNBC may start piloting. Testing for those with HR+/HER2- is limited to specific patient subgroups (Table 6). Although there is an indication that testing may become universally available for the HR+/HER2- subgroup, the timelines for this group are substantially more uncertain. Including BRCA testing in HR+/HER2- population has a substantial effect on the ICER.
What alternative approach has the EAG suggested?	Given clinical advice received, the EAG prefers to include the cost of BRCA testing in the model for HR+/HER2- patients.
What is the expected effect on the cost-effectiveness estimates?	Including BRCA testing increases the deterministic EAG base case ICER in HR+/HER2- from £57,443 to £64,773. This effect on the ICER will disappear when universal BRCA testing is available for HR+/HER2- patients.
What additional evidence or analyses might help to resolve this key issue?	The NGTD or other stakeholders could be engaged to provide further clarity on whether BRCA testing will soon take place in HR+/HER2-.

1.5 Other key issues: summary of the EAG's view

The EAG do not have any other key issues to highlight.

1.6 Summary of EAG's preferred assumptions and resulting ICER

The company produced separate models for TNBC and HR+/HER2- population. Table 2 and Table 3 provide a summary of the EAG's preferred assumptions and ICERs in TNBC and HR+/HER2-, respectively.

TABLE 2 SUMMARY OF EAG'S PREFERRED ASSUMPTIONS IN TNBC*

Scenario	Incremental cost	Incremental QALYs	ICER (change from company base case)
Company's base case Based on data cut-off 2 (DCO2) provided in Clarification Questions and following minor corrections to Excel code.	[redacted]	[redacted]	£35,855
Company's base case (Probabilistic based on 1000 samples)	[redacted]	[redacted]	£34,685
Introducing EAG's preferred assumptions			
Risk of recurrence after 5 years is 5% over following 10 years (company base case was 0%)	[redacted]	[redacted]	£37,961
Distribution for survival following early metastatic recurrence is Gompertz (company base case was exponential)	[redacted]	[redacted]	£39,157
Utility values follow Verill et al 2020 (company base case was mapping from OlympiA using Crott & Briggs (2010) for the DF and non-metastatic health states and using Lidgren (2007) utilities for the metastatic health states.)	[redacted]	[redacted]	£46,835
Utility values in non-metastatic recurrence set to mid-point of progression-free and metastatic recurrence (company base case assumed the same HSUV for the non-metastatic recurrence health state as the DF health state).	[redacted]	[redacted]	£46,549
EAG's preferred base case final ICER	[redacted]	[redacted]	**£46,549**
EAG's preferred base case final ICER (Probabilistic based on 10,000 samples)	[redacted]	[redacted]	**£46,142**

TABLE 3 SUMMARY OF EAG'S PREFERRED ASSUMPTIONS IN HR+/HER2-*

Scenario	Incremental cost	Incremental QALYs	ICER (change from company base case)
Company's base case	[redacted]	[redacted]	£41,879

Scenario	Incremental cost	Incremental QALYs	ICER (change from company base case)
Based on DCO2 provided in Clarification Questions and following minor corrections to Excel code.			
Company's base case (Probabilistic based on 1000 samples)	[redacted]	[redacted]	£40,293
Introducing EAG's preferred assumptions			
Distribution for recurrence is generalised gamma (company base case was lognormal)	[redacted]	[redacted]	£46,430
Distribution for survival following early metastatic recurrence in Gompertz (company base case was exponential)	[redacted]	[redacted]	£48,288
Utility values follow Verill 2020 (company base case was mapping from OlympiA using Crott & Briggs (2010) for the DF and non-metastatic health states and Lidgren (2007) for the metastatic health states.)	[redacted]	[redacted]	£57,787
Utility values in non-metastatic recurrence set to mid-point of progression-free and metastatic recurrence (company base case assumed the same HSUV for the non-metastatic recurrence health state as the DF health state).	[redacted]	[redacted]	£57,443
EAG's base case without BRCA testing costs ICER	[redacted]	[redacted]	**£57,443**
Include BRCA testing costs	[redacted]	[redacted]	£64,773
EAG's preferred base case final ICER	[redacted]	[redacted]	**£64,773**
EAG's preferred base case final ICER (Probabilistic based on 10,000 samples)	[redacted]	[redacted]	**£59,592**

Modelling errors identified and corrected by the EAG are described in Section 5.3.2. For further details of the exploratory and sensitivity analyses done by the EAG, see Section 6.1.

2 INTRODUCTION AND BACKGROUND

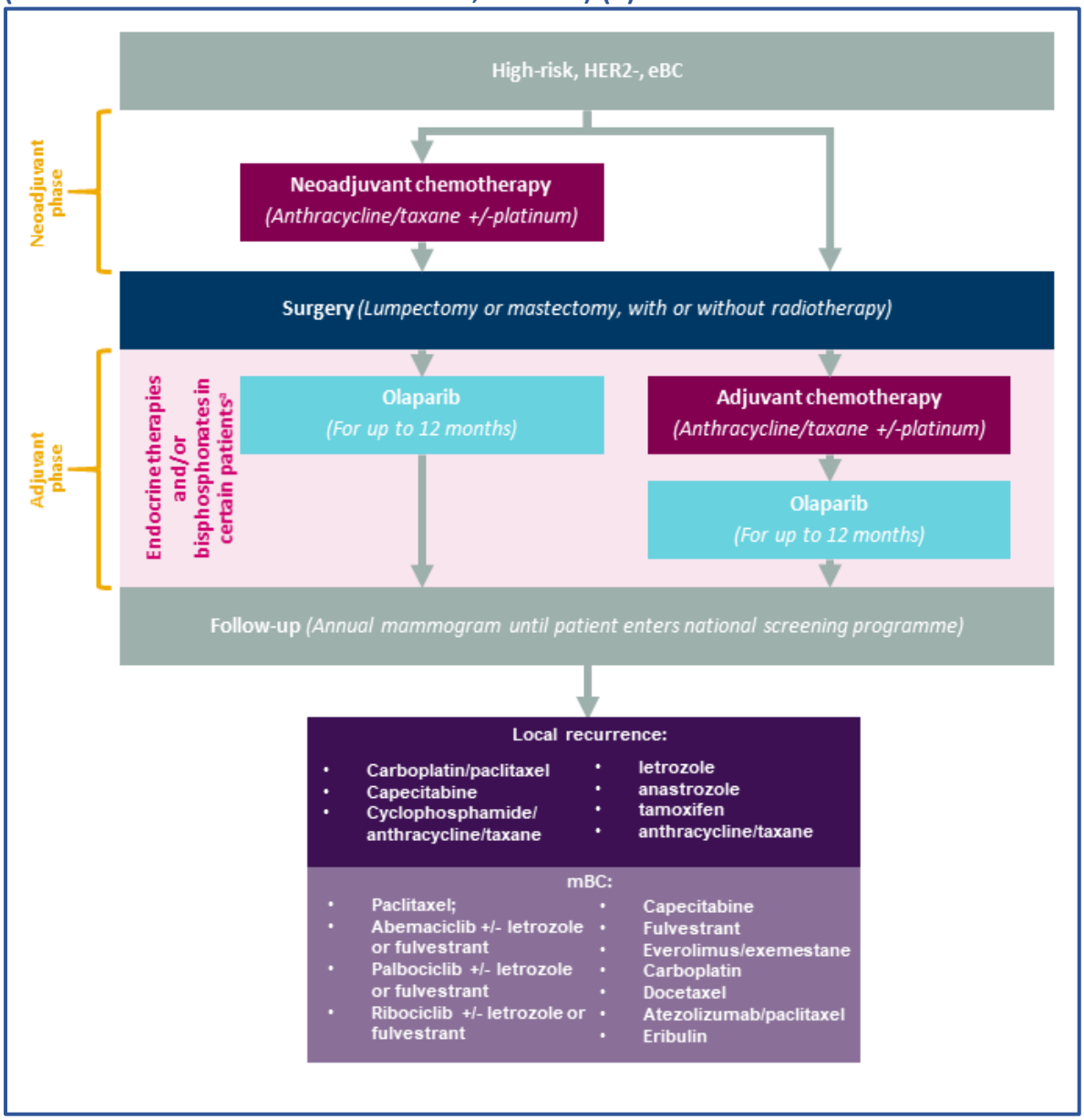
This report provides a critique of the evidence submitted by the company (AstraZeneca) in support of adjuvant treatment of high-risk Human Epidermal Growth Factor Receptor 2 (HER2)-negative, Breast Cancer Susceptibility Gene (BRCA)-positive early breast cancer after chemotherapy. It considers the company evidence submission and the company's executable model received on 26/2/2022.(1) It also considers the company's response to a request for clarification from the EAG received on 6/6/2022.(6) This included additional results for a new data cut-off (DC02) from 12/7/2021(clarification response, Appendix 1) and an updated economic model.(6)

2.1 Critique of the company's proposed place of the technology in the treatment pathway and intended positioning of the intervention.

The company have proposed that olaparib be used as adjuvant therapy in high risk patients with early breast cancer who are HER2-negative and have a germline BRCA mutation who have previously been treated with neoadjuvant or adjuvant chemotherapy. This would be as an alternative to watchful waiting. The EAG considers that the company's description of the proposed place of the technology in the treatment pathway is appropriate.

Limited details were provided on subsequent treatment options following olaparib in the original CS;(1) these are considered in the model and so are important to consider when first describing the patient pathway. Additional details on treatment options following olaparib treatment were provided in response to a request for clarification from the EAG (clarification response, question A9).(6) The proposed positioning in the treatment pathway, including the additional information provided in the clarification response, is shown in Figure 1. Clinical advice received by the EAG suggests that the proposed treatment pathway reflects treatments that would be used in practice and that olaparib is included at an appropriate point within the treatment pathway. Neoadjuvant and adjuvant chemotherapy treatments in the proposed treatment pathway are in line with NICE guidelines for the diagnosis and management of early breast cancer. (7) All treatments included in the pathway post-olaparib are available for routine commissioning in the NHS, all are listed in the BNF, and all but one treatment (carboplatin) includes breast cancer amongst the BNF-listed treatment indication. (8, 9)

FIGURE 1. PROPOSED POSITION OF OLAPARIB TREATMENT IN THE TREATMENT PATHWAY FOR PEOPLE WITH HIGH-RISK HER2-NEGATIVE, BRCA-POSITIVE EARLY BREAST CANCER AFTER CHEMOTHERAPY (REPRODUCED FROM CLARIFICATION RESPONSE, FIGURE 1).(6)



2.2 Critique of company's definition of decision problem

Table 4 summarises the decision problem as outlined in the NICE scope and provides a summary of how this was addressed in the CS.(2) The company's definition of the decision problem as defined in the CS matches the final NICE scope.(1)

TABLE 4 SUMMARY OF DECISION PROBLEM

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Population	Adults with BRCA1- or BRCA2-positive, HER2-negative, high risk early breast cancer that has been treated with surgery and neoadjuvant or adjuvant chemotherapy.	As per scope	NA	The EAG are content that the population assessed in the CS matches that defined in the scope. There is variation in how "high risk" can be defined. The EAG considers the approach taken to define patients at high risk in the CS to have been appropriate. Further details are provided in section 3.2.2 below. The population included in the trial of olaparib on which the clinical effectiveness data is based appears comparable to the United Kingdom (UK) population that would be eligible for olaparib treatment. Further details are provided in 3.2.2 below.
Intervention	Olaparib	As per scope	NA	The EAG have no concerns regarding the intervention. Further details are available in section 3.2.3.
Comparator(s)	Established clinical management without olaparib.	The company clarified that established clinical management without olaparib would involve a "watch and wait" approach.	NA	The EAG agree with the company's clarification that "watch and wait" is established clinical management. Further details are available in section 3.2.3.
Outcomes	The outcome measures to be considered include: distant disease-free survival (dDFS) invasive disease-free survival (iDFS) overall survival (OS) adverse effects (AEs) of treatment	As per scope	NA	The EAG are content that the outcomes reported in the CS match those as defined in the scope and were measured using standard criteria. Further details are available in section 3.2.4. The CS highlights iDFS as the primary outcome. This is the standard primary outcome for studies in this area.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	health-related quality of life (HRQoL)			
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 of any managed access arrangement for the intervention will be taken into account. The use of olaparib is conditional on the presence of mutations in the BRCA1 or BRCA2 genes. The economic modelling should include the costs associated with diagnostic testing for BRCA1 or BRCA2 mutations in people with high-risk early breast cancer who would not otherwise have been tested. A sensitivity analysis	Company excluded BRCA testing in both subgroups in base case	Company assumed BRCA testing will be universal for all BC types on the NHS soon	The CS expresses treatments in terms of QALYs. These were derived from a mapping exercise from disease-specific quality of life questionnaires to patients in the OlympiA trial. The EAG disagrees with the source of QALYs for the model and suggests a different one. Costs were considered from an NHS perspective only. Person social services (PSS) costs are likely to be relatively small but more pronounced at stages of recurrence, which the intervention would avoid. Including PSS costs would likely have a small effect on the ICER in favour of the intervention. The EAG considers the CS estimates to be conservative. The EAG included the cost of universal testing for the BRCA gene mutation 1 and 2 for patients in the HR+/HER2- type. The CS argues these costs should not be considered as universal testing is predicted in the national guidelines for both cancer types. The EAG agrees that they may be offered for TNBC, but it is less likely to happen for HR+/HER2- in the near future. An SA is provided without the cost of testing.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	(SA) should be provided without the cost of the diagnostic test.			
Subgroups	If the evidence allows, subgroups based on HR status will be considered.			Appropriate subgroups were considered in the CS with data reported separately for subgroups evaluated. Further details are available below in section 3.2.6.1.1.
Special considerations including issues related to equity or equality	The availability and cost of biosimilar and generic products should be taken into account. Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.			The CS highlights that Medicines and Healthcare products Regulatory Agency (MHRA) marketing authorisation for olaparib in the indication under evaluation is anticipated in [redacted]. Testing for BRCA mutations is not yet routinely available on the NHS for all patients potentially eligible for olaparib in this setting. This is discussed further in section 3.2.2.3. This has potential equity issues as those able to pay for testing would be more likely to know their tumour status and hence be eligible for olaparib treatment.

3 CLINICAL EFFECTIVENESS

The clinical effectiveness critique focuses on the following key questions:

- Is there evidence of clinical effectiveness?
- Are estimates that feed into the economic model reliable and appropriate to the scope?
- Have the most appropriate estimates been selected to feed into the economic model?

3.1 Critique of the methods of review(s)

The EAG have provided a detailed critique of the systematic review (SR) conducted for the company submission in Appendix 9.1. The company SR was summarised in the CS and reported in more detail in a separate confidential report.(1, 10) The SR addressed a much broader question than the question specified by the scope; it is unclear why the company did not focus the review to match the scope rather than reporting their much broader SR – this would have been more appropriate. The EAG's critique of the SR focuses on whether the clinical effectiveness inputs to the economic model could have been biased by the way that the systematic review was conducted. Despite limitations in how the review was conducted and reported, the EAG are confident that the OlympiA trial (NCT02032823) is the only trial relevant to the submission.(3, 11) A detailed critique of the trial is provided in section 3.2.

3.2 Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

Only one relevant trial exists of olaparib in the specified population – the OlympiA trial (NCT02032823). Full details of this trial, including the clinical trial report and journal publication were provided to the EAG as part of the CS and are considered in the critique below.(1, 11)

3.2.1 Study design

The OlympiA trial is a multicentre, international, phase III, parallel group trial that compared olaparib to placebo as adjuvant therapy for people with germline BRCA-mutated (gBRCAm), HER2-, high-risk early breast cancer (eBC), who had undergone surgery and adjuvant or neoadjuvant chemotherapy. The study commenced enrolment in April 2014 and the last patient was recruited in April 2019. The trial was initially restricted to patients with TNBC but a protocol amendment expanded the trial to include HR+/HER2- patients in 2015. The study characteristics of OlympiA are presented in the CS, Table 6, page 32.(1) Of the 600 study centres, 22 sites that recruited 106 patients were from the UK and Northern Ireland.(12) Patients were randomised on a 1:1 basis to olaparib or placebo. The EAG considers this an appropriate design to evaluate the efficacy of olaparib compared to established clinical management. The design is in line with European Medicines Agency (EMA) evaluation guidelines that recommend the use of double-blind phase III randomised

controlled trials (RCTs) to establish the benefit-risk profile of a medicinal anticancer product.(13)

As part of the company submission a quality assessment of the OlympiA trial using the tool from Centre for Reviews and Dissemination (CRD) guidance for conducting systematic reviews was provided.(14) This tool was previously recommended by NICE, but the latest NICE guidance does not recommend any specific tool. There are several limitations with this approach to assessing the quality of randomised controlled trials. The CRD tool is outdated and there are now more in depth, robust tools available that focus specifically on risk of bias.(15) The quality assessment was performed at the trial level rather than the outcome level. The full quality assessment is provided in Appendix D3 of the CS.(16) This did not identify any concerns regarding the risk of bias in the olaparib trial. The EAG have provided a detailed assessment of the risk of bias in the OlympiA trial using the updated Cochrane Risk of Bias (RoB) Tool carried out at the outcome rather than study level.(15) Detailed results are available in Appendix 9.2 and are summarised below in Table 5.

TABLE 5 RISK OF BIAS IN OLYMPIA TRIAL ASSESSED SEPARATELY FOR EACH OUTCOME

ROB 2.0 domain	Outcome				
	dDFS	**iDFS**	**OS**	**AE**	**HRQoL**
Randomization process	Low	Low	Low	Low	Low
Deviations from intended interventions	Low	Low	Low	Low for ITT/ High for PP	Low
Missing Outcome Data	Low	Low	Low	Low	Some concerns
Measurement of the outcome	Low	Low	Low	Low	Low
Selection of the reported result	Low	Low	Low	Low	Low
Overall	**Low**	**Low**	**Low**	**Low for ITT/ High for PP**	**Some concerns**

ITT=Intention to treat; PP=per-protocol

There were some concerns regarding missing outcome data for HRQoL. There was low risk of bias for all other outcomes for estimates of the intention to treat effect which was the appropriate analysis for the effectiveness and HRQoL outcomes. For adverse events, the effect of interest is adherence to the intervention – "if patients take olaparib, are they more likely to experience AEs than if they take placebo?". The safety analysis was therefore considered to be at high risk of bias as (i) the safety analysis was based on all those who took at least one dose of study treatment and (ii) a greater number of patients in the olaparib arm (97 patients) did not complete study treatment due to adverse events

compared to the placebo group (41 patients). This is considered likely to have resulted in bias in estimates of adverse effects. Adverse events modelled in the iDFS health state are directly informed by the trial and potentially underestimated.

KEY ISSUE: Potential risk of bias in estimates of HRQoL

3.2.2 Patients

The inclusion criteria for the OlympiA trial are summarised in Table 7, p33 of the CS.(1) Full inclusion criteria are provided in Table 52 in Appendix M of the CS and details of the included study population are provided in Tables 9 and 10.(1, 16) Initially only people with TNBC were included. A protocol amendment was made in 2015 following input from the Food and Drug Administration (FDA) to expand the trial inclusion criteria to include HR+/HER2- patients. Overall the EAG are content that the inclusion criteria are appropriate for the scope and decision problem.

Baseline demographic and cancer characteristics were well balanced across to the olaparib and placebo groups. The EAG does not have any concerns regarding the comparability of the treatment groups. Clinical advice received by the EAG suggested that the patient characteristics of OlympiA are broadly reflective of clinical practice in England.

There are a small number of issues to note with the study population, none of which are considered likely to have had a substantial impact on estimates of clinical effectiveness. These are outlined below in sections 3.2.2.1, 3.2.2.2, and 3.2.2.3.

3.2.2.1 Proportion of patients with TNBC and HR+HER2- disease

The CS highlights that the relative proportion of those with TNBC and HR+/HER2- disease differs to that seen in UK clinical practice, mainly due to the protocol amendment to expand the trial to include HR+/HER2- patients, which has resulted in the OlympiA population having a greater proportion of patients with TNBC patients with more mature data for this subpopulation.(1) The EAG do not consider this to be of concern as randomisation was stratified by HR receptor status and stratified results are available based on HR status. This means that we have data to determine whether there is a difference in the effectiveness of olaparib based on HR status. However, these data are limited as there are less data and less follow-up time for those with HR+/HER2- disease (see section 3.2.6.1.1).

3.2.2.2 Definition of high risk

Clinicians routinely assess whether patients have high-risk disease to determine the anticipated risk of recurrence and to inform treatment decisions, particularly whether to offer chemotherapy in addition to surgery-alone or surgery followed by endocrine therapy. Defining patients as being at "high risk" is not straightforward, and different approaches and definitions may be used. The patient organisation submission also highlights this as an important issue for patients - *"Definition of 'high-risk' early or locally advanced breast*

cancer: it is important that there is a discussion about who is defined as 'high-risk' so it is clear who may be eligible for this treatment option.(17) The definition of high risk used for the OlympiA trial is reported in the study eligibility criteria, Table 52, Appendix M as follows:(16)

"For patients who underwent initial surgery and received adjuvant chemotherapy:

- TNBC patients must have been axillary node-positive (≥pN1, any tumour size) or axillary node-negative (pN0) with invasive primary tumour pathological size >2 cm (≥pT2)
- ER and/or PR-positive/HER2-negative patients must have had ≥4 pathologically confirmed positive lymph nodes

For patients who underwent neoadjuvant chemotherapy followed by surgery:

- TNBC patients must have had residual invasive breast cancer in the breast and/or resected lymph nodes (non pCR)
- ER and/or PR-positive/HER 2 negative patients must have had residual invasive cancer in the breast and/or the resected lymph nodes (non pCR) and a CPS&EG score ≥3."

AstraZeneca conducted a validation process consisting of two rounds of interviews with UK clinicians to determine whether the definition of "high risk" used in the trial is considered generalisable to the UK population. In addition to the validation interviews, AstraZeneca is also [redacted] the results of which will be provided to NICE once available. These activities are detailed in section B.1.3.1.5 of the CS." .(1)

In response to a request for clarification from the EAG (clarification response, question A10), the company clarified that clinicians involved in this process were practicing UK oncologists who were considered experts in eBC and who were treating these patients in clinical practice; many had used olaparib before.(6) It was unclear how many, if any, were directly involved in the OlympiA trial. Clinical advice received by the EAG suggested that this process was appropriate and agrees with the conclusion that the olaparib results are generalisable to the UK population in terms of how a high risk population is defined.

3.2.2.3 BRCA-mutation testing

In order for breast cancer patients to be eligible for treatment with olaparib, they have to have a germline BRCA mutation. Testing is not currently routinely performed in the early breast cancer setting. The CS highlights that tumour BRCA1/2 testing has recently been included on the NGTD "desirables list"; the EAG were not able to find any reference to this. In their response to the factual accuracy check, the company did provide a copy of the NGTD desirables list that included BRCA1/2 testing for breast cancer patients. The latest update to the online NGTD spreadsheet suggests that BRCA testing for all those with TNBC

will shortly being whole genome sequencing (WGS) piloting, but this is not currently in routine use.(18) WGS piloting involves a number of trusts assessing the feasibility of running WGS for BRCA testing. As the company acknowledge in their description of the decision problem, current guidance only recommends testing in those with a high pre-test likelihood of carrying the mutation. Current NGTD criteria for BRCA testing are detailed in Table 50 of the Appendices to the CS and are reproduced in Table 6 NGTD BRCA testing eligibility criteria.(16) If olaparib is to be introduced into routine clinical use for those with HR+/HER- eBC, then BRCA testing would need to be extended to all those with HR+/HER- disease, not just those that fulfil the criteria in Table 6. The current piloting of testing all those with TNBC would also need to become routine practice so that those aged >60 years with TNBC would also be offered routine BRCA testing. Clinical advice received by the EAG suggests that routine BRCA testing for those with TNBC and HR+/HER2- is very likely to become routine in the near future, but no clear timeline is currently available for this.

TABLE 6 NGTD BRCA TESTING ELIGIBILITY CRITERIA

Testing criteria
Living affected individual (proband) with breast or ovarian cancer where the individual +/- family history meets one of the criteria. The proband has any of the following: a. Breast cancer (age < 30 years) b. Bilateral breast cancer (age < 50 years) c. Triple negative breast cancer (age < 60 years) d. Male breast cancer (any age) e. Breast cancer (age <45 years) and a first degree relative with breast cancer (age <45 years) f. Pathology-adjusted Manchester score ≥15 or BOADICEA score ≥10% g. Ashkenazi Jewish ancestry and breast cancer at any age

KEY ISSUE: Access to BRCA testing in HR+/HER2-

3.2.3 Interventions

The intervention consisted of olaparib tablets at a dose of 150mg twice daily (300 mg daily dose) with 100 mg tables (200 mg daily dose) used to manage dose reductions. Both olaparib and placebo tablet were green, film coated tablets that were matched in appearance and packed in identical containers. Table 7 in the clinical study report (CSR) provides a detailed overview of olaparib dosage and placebo.(19) Instructions regarding dose and mode of delivery were identical for the two interventions. Treatment was administered for a maximum of 12 months or until there was recurrence of disease, diagnosis of a second primary malignancy or treatment discontinuation. Reasons for treatment discontinuation included patient decision, adverse events, pregnancy, and severe non-compliance with the study protocol.

The list price of olaparib stated in the CS is £2,317.50 per 56 tablet (14 day) pack. This matches the list price reported in the online BNF.(20) The cost is the same for a 100mg

olaparib tablet as for a 150mg tablet. A confidential commercial access agreement ([redacted]) is in place for olaparib; the net price of olaparib for NHS hospitals in England is [redacted] per 14-day pack. A more detailed description of costings is provided in Table 39 of the CS. (1)

Concomitant medications were summarised in Table 8 of the CS. Investigators could prescribe medication that were considered necessary for the patient's welfare and that were not expected to impact the study results. Permitted medication included endocrine therapy, anti-emetics, anti-diarrhoeals, anti-coagulants, bisphosphonates or denosumab. Clinical advice to the EAG suggested that this was reasonable and likely to reflect how these patients would be treated in practice. Most patients were prescribed concomitant medications during the trial (olaparib arm: [redacted]%; placebo arm: [redacted]%).(1) A very small number of patients received medications that were not permitted during the trial ([redacted]) As the numbers were very low and reported to have been balanced between treatment groups, the EAG do not consider it likely that this will have influenced trial results.

3.2.4 Outcomes

Full details on how outcomes were defined and timepoints at which these were measured are available in Section 3 of the CSR.(19) Table 7 summarises the outcomes reported in the CS,(1) New England Journal of Medicine article(11) and CSR.(19) This highlights whether the outcomes are recommended by the EMA,(13) whether they were included in the NICE scope, and whether the outcome was used in the economic model. The only outcomes that input directly into the economic model are the adverse events – incidence of anaemia and neutropenia grade 3 or above. Other outcomes were used to estimate inputs for the economic model – see section 4.2.6 for a more detailed explanation of how trial results input into the model.

TABLE 7 SUMMARY OF OUTCOMES LISTED IN THE CS AND THEIR RELATIONSHIP TO EMA RESEARCH RECOMMENDATION, THE FINAL NICE SCOPE AND THE COMPANY'S ECONOMIC MODEL

Outcome	Recommended by EMA(13)	In NICE scope?	Used in Economic Model
Primary outcome			
iDFS	Yes	Yes	Indirectly – see section 4.2.6. Individual parametric curves for each arm rather than hazard ratio. Not as reported in the clinical effectiveness section.
Secondary outcomes			
dDFS	Yes	Yes	Indirectly – see section 4.2.6. Proportion with metastatic recurrence applied to iDFS.

Outcome	Recommended by EMA(13)	In NICE scope?	Used in Economic Model
			Not as reported in the clinical effectiveness section.
OS	Yes	Yes	Indirectly – see section 4.2.6. Parametric curves for survival following non-metastatic and metastatic recurrence, fit to combined treatment arms. Not as reported in the clinical effectiveness section.
Incidence of new primary breast/ovarian cancers	No	No	No
EORTC QLQ-C30	Patient reported outcome measure (PROM) recommended but do not specify which should be used (appendix with further details not yet available)	HRQoL included but specific measures not specified	Indirectly – EORTC QLQ-C30 mapped to EQ5D scores. FACIT-Fatigue is not used in the model.
FACIT-Fatigue score			
Safety and tolerability analyses: AEs, serious adverse events (SAEs), discontinuation due to AE(s), deaths, laboratory data, vital signs and echocardiograms (ECGs)	Yes	Yes	Only anaemia and neutropenia ≥grade 3

3.2.4.1 Efficacy outcomes

Efficacy outcomes were assessed at baseline, every 3 months for years 1-2, every 6 months for years 3 to 5 and annually after this. The choice of iDFS as the primary outpoint is justified in clinical trials of eBC where mortality is relatively low, particularly in the early stages of the trial. The EMA guidance on evaluation of anticancer medicinal products highlights that if DFS is the primary endpoint then OS should be reported as a secondary endpoint.(13) Efficacy outcomes were investigator assessed using the standardised terms for efficacy endpoints (STEEP) system definition.(21) The EAG considered that the efficacy outcomes reported in the trial were appropriate measures to assess the efficacy of olaparib in this population and were measured according to standard criteria.

The economic model used survival curve data on iDFS, dDFS and OS to estimate the proportion of patients in each of the following states and how this would change over time: iDFS (starting point), non-metastatic BC (locoregional recurrence), early and late onset metastatic BC (distant recurrence) and death (see section 4.2.6). However, the format of results was substantially different. Parametric models were fit to each trial arm for iDFS; rather than using dDFS directly the proportion with metastatic recurrence was estimated and applied to the iDFS curves; data on survival of disease free patients was not used; parametric curves were fit to a combined treatment population for survival following non-metastatic and metastatic. It would have been preferable to also report results of the clinical effectiveness analysis in this format so that the link between clinical- and cost-effectiveness data were clearer.

3.2.4.2 Health-related quality of life (HRQoL)

Data on HRQoL were collected at baseline and every 6 months post-treatment for a period of 2 years. HRQoL was assessed using two patient reported outcome measures (PROMs): EORTC QLQ-C30 and Functional Assessment of Chronic Illness Therapy -Fatigue (FACIT-F) tool.(22, 23) EORTC QLQ-C30 was developed specifically to assess quality of life in cancer patients. It includes 30 questions covering whether a patient is able to continue with certain activities, whether they are experiencing certain symptoms such as pain and nausea, how well they are sleeping, with two final questions asking them to rate their overall health and quality of life over the past week on a scale from 1 to 7. The analysis focused on overall EORTC QLQ-C30 scores and on the gastrointestinal symptoms' items from the tool as nausea, vomiting, and diarrhoea have been reported with olaparib. The EAG considers this is an accepted and appropriate to tool to assess quality of life in cancer trials such as OlympiA. In addition to the core questionnaire, there are additional modules available for specific cancer types, but these were not used in the OlympiA trial. The EORTC QLQ-BR23 module is designed specifically for breast cancer patients to provide a more accurate and comprehensive assessment of the impact of new treatments on quality of life.(24) An updated version of this module, the QLQ-BR45, is undergoing validation.(25) The use of either one of these modules in addition to the EORTC QLQ-C30 may have provided a more accurate assessment of HRQoL for the OlympiA trial.

The FACIT-F tool was developed to assess fatigue associated with anaemia in cancer patients. This a 40-item tool to assess self-reported fatigue and its impact on daily activities and function. It is estimated to take 10-15 minutes to complete.(23) The CSR highlight this tool was included to measure treatment related fatigue as fatigue had been previously reported with olaparib.(19) The EAG considers the choice of this tool as reasonable based on this rationale. These data are not used in the economic model.

A limitation of both these tools is that they do not directly provide HRQoL measures for the economic model, as per NICE reference case. The trial protocol could have included an additional EQ-5D questionnaire in the study to directly collect data on utilities from trial

patients. This is a brief, generic, HRQoL questionnaire and would not have placed much additional burden on participants to complete.(26) In Section 4.2.7.1 we discuss how patients' responses to the EORTC QLQ-C30 were instead mapped onto index scores for the EuroQoL (EQ-5D) questionnaire to provide HRQoL data for the economic model.

KEY ISSUE: HRQoL measures used in the economic model

3.2.4.3 Safety analyses

Data on adverse events were collected at all study visits. All patients who received at least one dose of the study drugs (olaparib or placebo) contributed to the safety analysis set (SAS). Full details on how AEs were defined and classified are provided in the study protocol; details were lacking in the CS and CSR.(1, 19) The protocol specified that adverse events were grouped and graded according to the common terminology criteria for adverse events (CTCAE) version 4.03.(27) **Error! Reference source not found.** provides an overview of the AE groupings and definitions for the OlympiA trial.

TABLE 8 OVERVIEW OF AE GROUPINGS AND DEFINITIONS

AE category	Details
All grade adverse events (AEs)	"An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g. laboratory findings, electrocardiogram).(28)
Grade ≥3 AEs(27)	Severe or medically significant where hospitalisation or prolongation of hospitalisation was indicated, and that were disabling, limiting self-care and activities of daily living.
Serious AEs	AE that fulfils the following criteria: • Results in death • Immediately life-threatening • Requires in-patient hospitalisation or prolongation of existing hospitalisation • Results in persistent or significant disability/incapacity or substantial disruption of ability to conduct normal life functions • Important medical event that may jeopardise the patient or may require medical intervention to prevent one of the outcomes listed above.
Treatment related AEs	AE considered by the investigators to be causally related to the study treatment

AE category	Details
AEs of special interest	AEs considered to be potential risks associated with olaparib treatment: • Myelodysplastic Syndrome and Acute Myeloid Leukaemia • New Primary cancers • Pneumonitis
Deaths due to AEs	Death that is not clearly due to breast cancer recurrence or progression.
Dose interruptions due to AEs	Missing doses due to AEs.
Dose reductions due to AEs	Reduce study drug dosage because of an adverse event. Therapy was withheld until AE returns to grade ≤1 unless specified otherwise in dose modification instructions. Once a dose was reduced, dose escalation was not permitted.
Discontinuations due to AEs	Stopping study drug because of an adverse event

3.2.5 Protocol deviations

Data were collected regarding 18 "important protocol deviations", defined as "pre-defined protocol deviations which have a very high likelihood of influencing the primary efficacy and/or the secondary safety results", for the OlympiA trial. These are shown in Table S18 in the supplementary appendix of the OlympiA CSR.(19) Overall, 252/1836 (13.7%) patients had important protocol deviations: 130 (14.1%) in the olaparib group and 122 (13.3%) in the placebo group.

The trial protocol specified that a sensitivity analysis would be conducted excluding patients with important protocol deviations if at least 10% of patients in either intervention group had a protocol deviation that meant they did not have the intended disease or indication or did not receive any treatment.(1) Thirty out of 1836 patients (1.6%), 16 (1.7%) in the olaparib group and 14 (1.5%) in the placebo group met these criteria. Three patients, all in the olaparib arm, did not have histologically confirmed non-metastatic primary invasive breast cancer, six did not have the BRCA mutation (3 in the olaparib arm and 3 in the placebo arm) and 21 (10 in the olaparib arm and 11 in the placebo arm) did receive study treatment. As the threshold for sensitivity analysis was not met, this was not conducted.

The EAG consider it unlikely that protocol deviations would have impacted trial result as the number of protocol deviations was low and similar across intervention groups.

3.2.6 Trial results

Results in the CS were for data cut-off 1 (DCO1; 27/3/2020), the interim analysis. This had been protocoled to occur when 165 events of events of invasive disease or death had been observed from the first 50% of patients recruited (i.e. from the first 900 patients – the "mature cohort"). DC01 data reported 284 events of invasive disease or death in the ITT

population. In a response to a request for clarification from the EAG, the company highlighted that at this timepoint 169 events had occurred in the mature cohort, very close to the 165 events at which this analysis had been scheduled to take place. They also highlighted that, as stated in section 9.8.1 the CSR, "upon review of the interim analysis, the IDMC concluded that the pre-defined statistical threshold for superiority of olaparib versus placebo for iDFS was met in the ITT population (2-sided, 0.005 significance level). Therefore, upon the IDMC's declaration of superiority, the interim analysis became the primary analysis of iDFS for this study."

The company response to our request for clarification included results for a new data cut-off (DC02) from 12/7/2021. The additional data provided DC02 show 341 events of invasive disease or death in the intention to treat population. The CSR highlights that the independent data monitoring committee (IDMC) unblinded the OlympiA trial earlier than expected on 17 February 2021 due to the observed efficacy. This means that a small proportion of data that contributed to DC02 were unblinded. The EAG do not consider this likely to have had a substantial effect on results due to the short time period involved.

3.2.6.1 Efficacy Results

Table 9, reproduced from Table 17 in the company's response to clarification questions summarises the key results for DC01 and DC02.(6) There was strong evidence ($p<0.01$) that olaparib was superior to placebo for all primary and secondary endpoints.

TABLE 9 SUMMARY OF OLYMPIA PRIMARY AND KEY SECONDARY ENDPOINTS, DCO1 AND DCO2 (FAS), REPRODUCED FROM COMPANY'S RESPONSE TO CLARIFICATION QUESTIONS.(6)

	DCO1 (27 March 2020)		DCO2 (12 July 2021)	
	Olaparib (N=921)	Placebo (N=915)	Olaparib (N=921)	Placebo (N=915)
Primary endpoint: iDFS				
Number of events, n (%)	106 (11.5)	178 (19.5)	134 (14.5)	207 (22.6)
Hazard ratio (95% CI)	0.58 [redacted]		0.63 (0.50–0.78)	
Hazard ratio (99.5% CI)	0.58 [redacted]		NA	
Log-rank test: p-value	0.0000073		[redacted]	
% (95% CI) of patients free of invasive disease at 1 year	93.3 [redacted]	88.4 [redacted]	93.4 [redacted]	88.4 [redacted]
Percentage (95% CI) of patients free of invasive disease at 2 years	89.2 [redacted]	81.5 [redacted]	89.7 [redacted]	81.4 [redacted]
Percentage (95% CI) of patients free of invasive disease at 3 years	85.9 [redacted]	77.1 [redacted]	86.1 [redacted]	77.3 [redacted]
Percentage (95% CI) of patients free of invasive disease at 4 years	NA	NA	82.7 [redacted]	75.4 [redacted]

	DCO1 (27 March 2020)		DCO2 (12 July 2021)	
	Olaparib (N=921)	Placebo (N=915)	Olaparib (N=921)	Placebo (N=915)
Median clinical follow-up time (years) (minimum- maximum)	[redacted]	[redacted]	[redacted]	[redacted]
Type of iDFS event				
Distant CNS recurrence	22 (2.4)	36 (3.9)	24 (2.6)	38 (4.2)
Distant excluding CNS recurrence	50 (5.4)	84 (9.2)	64 (6.9)	98 (10.7)
Regional (ipsilateral) recurrence	6 (0.7)	14 (1.5)	9 (1.0)	18 (2.0)
Local (ipsilateral) recurrence	7 (0.8)	11 (1.2)	9 (1.0)	12 (1.3)
Contralateral invasive breast cancer	8 (0.9)	12 (1.3)	15 (1.6)	18 (2.0)
New primary cancers (non-breast)	11 (1.2)	21 (2.3)	11 (1.2)	23 (2.5)
dDFS				
Number of events, n (%)	89 (9.7)	152 (16.6)	107 (11.6)	172 (18.8)
Hazard ratio (95% CI)	0.57 [redacted]		0.61 (0.48–0.77)	
Hazard ratio (99.5% CI)	0.57 [redacted]		NA	
Log-rank test: p-value[d]	0.0000257		[redacted]	
Percentage (95% CI) of patients free of distant disease at 1 year	94.3 [redacted]	90.2 [redacted]	94.4 [redacted]	90.3 [redacted]
Percentage (95% CI) of patients free of distant disease at 2 years	90.0 [redacted]	83.9 [redacted]	90.6 [redacted]	84.0 [redacted]
Percentage (95% CI) of patients free of distant disease at 3 years	87.5 [redacted]	80.4 [redacted]	88.0 [redacted]	81.0 [redacted]
Percentage (95% CI) of patients free of distant disease at 4 years	NA	NA	86.5 [redacted]	79.1 [redacted]
Median clinical follow-up time (years) (minimum- maximum)	[redacted]	[redacted]	[redacted]	[redacted]
OS				
Number of events, n (%)	59 (6.4)	86 (9.4)	75 (8.1)	109 (11.9)
Hazard ratio (95% CI)	0.68 [redacted]		0.68 [redacted]	
Hazard ratio (98.5% CI)	NA		0.68 (0.47–0.97)	
Hazard ratio (99% CI)	0.68 [redacted]		NA	
Log-rank test: p-value[d]	0.0236		0.009	
Percentage (95% CI) of patients alive at 1 year	98.1 [redacted]	96.9 [redacted]	98.0 [redacted]	96.9 [redacted]
Percentage (95% CI) of patients alive at 2 years	94.8 [redacted]	92.3 [redacted]	95.0 [redacted]	92.8 [redacted]
Percentage (95% CI) of patients alive at 3 years	92.0 [redacted]	88.3 [redacted]	92.8 [redacted]	89.1 [redacted]
Percentage (95% CI) of patients alive at 4 years	NA	NA	89.8 [redacted]	86.4 [redacted]
Median clinical follow-up time (years) (minimum- maximum)	[redacted]	[redacted]	[redacted]	[redacted]

The EAG are concerned that the test for proportional hazards (PH) does not hold for any of the primary or secondary endpoint summarised above in Table 9, so hazard ratios (HRs) should be interpreted with caution and should not be applied to extrapolate curves for the economic model. Kaplan-Meier plots are shown in Figure 2 to Figure 4 for DCO2, reproduced from the company's response to a request for clarification from the EAG.(6) These plots show that although there is a median of 3.5 years follow-up the estimated median time, where 50% of patients experience an event, has not been met for any of the effectiveness time-to-event outcomes. This means that we remain uncertain regarding the long-term benefits of olaparib treatment**.**

KEY ISSUE: Clinical effectiveness data are immature

FIGURE 2 KAPLAN–MEIER PLOT OF IDFS IN OLYMPIA, DCO2 (FAS) REPRODUCED FROM FIGURE 7 IN THE COMPANY RESPONSE TO REQUEST FOR CLARIFICATION.(6)

FIGURE 3 KAPLAN–MEIER PLOT OF DDFS IN OLYMPIA, DCO2 (FAS) REPRODUCED FROM FIGURE 8 IN THE COMPANY RESPONSE TO REQUEST FOR CLARIFICATION.(6)

FIGURE 4: KAPLAN–MEIER PLOT OF OS IN OLYMPIA, DCO2 (FAS) REPRODUCED FROM FIGURE 9 IN THE COMPANY RESPONSE TO REQUEST FOR CLARIFICATION.(6)

3.2.6.1.1 Subgroups

Subgroup analysis stratified on the following variables was reported for both DC01 and DC02 (clarification response, section 1.2.1) for the outcome iDFS:

- Prior chemotherapy: adjuvant vs neoadjuvant

- Prior Platinum therapy: yes vs no
- HR status: HR+/HER2- vs TNBC
- BRCA mutation type: BRCA1 vs BRCA2
- BRCA status by prior platinum therapy setting: BRCA1/2/both with and without platinum therapy for current breast cancer
- HR status by prior chemotherapy setting: HR+/HER2- or TNBC with adjuvant or neoadjuvant chemotherapy
- Type of prior chemotherapy: anthracycline alone, taxane alone, both combined
- Type of breast cancer surgery prior to radiotherapy: breast conservation, unilateral mastectomy, bilateral mastectomy

Additional stratified analyses were available for the following variables for DC01 only (CSR, Figure 5):(19)

- No bilateral vs bilateral oophorectomy
- Axillary nodal status at surgery prior to randomisation: node negative vs node positive
- CPS+EG score at baseline: 2-4 vs 5 or 6
- Age at randomisation: <50 years vs 50-64 years
- Race: White vs Asian
- Ethnicity: Hispanic or latino vs other
- Ashkenazi Jewish descent: yes vs no
- Sponsor: Astrazeneca vs NRG
- Geographic Region: North America vs Europe vs Asia Pacific and South Africa

These analyses showed that effects were generally consistent across subgroups. There was evidence that olaparib was effective in all subgroups considered. The EAG consider subgroup analyses to have been appropriate and have no concerns that relevant subgroups have not been considered.

The main subgroup analysis of interest was the analyses stratified by HR status as two separate economic models were constructed for these two subgroups. Results for these subgroups are summarised in Table 10. Although results were similar across subgroups, there were fewer patients in the HR+/HER2- group than in the TNBC group, partly as this group was only included after a protocol modification in 2015 (see section 3.2.2.1).

TABLE 10 iDFS RESULTS STRATIFIED ACCORDING TO HR STATUS

Outcome	Result	TNBC	HR+/HER2-
iDFS	Olaparib: Events/N	109/751	25/168
	Placebo: Events/N	173/758	34/157
	HR (95% CI)	0.62 (0.49, 0.79)	0.68 (0.40, 1.13)

3.2.6.2 HRQoL

Full details of the HRQoL assessment for DC01 were reported in section B.2.6.3 and Appendix M of the company submission.(1) More limited details for DC02 were reported in the company's response to the request for clarification from the EAG.(6) A limitation with the HRQoL data is that completion of these questionnaires was poor. Although completion rate was high at baseline ([redacted] for olaparib; [redacted] for placebo) this [redacted] to [redacted] at 6 and 12 months, [redacted] at 18 months, and [redacted] at 24 months; rates were similar in the olaparib and placebo arms for both DC01 and DC02.

Both EORTC QLQ-C30 global health status and the FACIT-F scores showed small improvements over the trial with no evidence of a clinically meaningful difference between arms (Figures 11 to 14 from the company response to clarification).(6) The EAG agrees that there is not enough evidence to confirm whether olaparib negatively affects HRQoL but some caution should be applied to interpreting these results due to low response rates.

Results were stratified according to whether patients received prior adjuvant or neoadjuvant treatment. The EAG requested that the company provide stratified data on EORTC QLQ-C30 by recurrence type – metastatic cancer, non-mentalistic recurrence and disease free as these data were of greater relevance to the economic model. In response to the request for clarification from the EAG, the company provided data stratified on whether patients were recurrence free or had a recurrence. These data are available in Table 1 of the company's response to the EAG's request for clarification.(6) The CS highlighted that numbers were very low post-recurrence (with only [redacted] records available for those in the olaparib arm and [redacted] for those in the placebo arm), as HRQoL data were only collected up to two years post-baseline. These data are therefore of limited value and the EAG agree that it was appropriate not to have reported these or included these data in the economic model.

3.2.6.3 Safety Analyses

The Safety Analysis Set (SAS) was based on 1815 patients who received treatment - ten patients (1.1%) in the olaparib arm and 11 patients (1.2%) in the placebo arm did not receive treatment. Median treatment duration was [redacted] in the olaparib arm and [redacted] in the placebo arm for DCO1.

The CS highlighted that "the safety profile of olaparib was consistent with that observed in previous trials". They referenced following four studies in support of this (29-32)Table 11. Olaparib was associated with greater numbers of AEs, grade≥3 AEs, dose interruptions due to AEs, dose reductions due to AEs, and discontinuations due to AEs compared to placebo group. It was not clear at what time point following treatment AEs occurred. However, serious AEs and deaths due to AEs were similar between groups. Full details of AEs are reported in Table 17 of the CS for DC01; a detailed breakdown on individual AEs was not provided by the company for DC02. AEs that occurred more frequently with olaparib

compared to placebo included anaemia, gastrointestinal disorders, fatigue, decreased appetite, nervous system disorders, and neutropenia.

AEs that were included in the economic model were those that were grades 3 to 4 and occurred in at least 2% of patients.(6) The only AEs that met these criteria and that were included in the economic model were anaemia and neutropenia. Data were not reported (NR) on the number of patients with neutropenia for DCO1 and were only available in response to the EAG's request for clarification (question B1) for DC02.(6) Of the 223 adverse events in the olaparib arm of grade ≥3, less than half were due to the AEs of anaemia and neutropenia that were included in the model. Other AEs of grade ≥3 that were more frequent in the olaparib arm than the placebo arm for DC01 included fatigue, nausea, vomiting. Full details of AE of grade ≥3 are provided in Table 19 of the CS.(1) A detailed breakdown of AEs was not provided for DC02, although there were only an additional 2 AEs of grade ≥3 compared to DC01 in the olaparib arm and no new AEs in the placebo arm.

Myelodysplastic syndrome (MDS), acute myeloid leukaemia (AML), new primary malignancies and pneumonitis were highlighted by the company as AEs of special interest as they are considered to be potential risks associated with olaparib treatment.(1) There was no evidence of a greater risk of any of these conditions with olaparib treatment in the OlympiA trial, but these are rare conditions and numbers of patients experiencing these events were very small (Table 11). Data for these AEs were not reported for DC02. It would have been helpful to have provided pooled safety data across all known studies of olaparib to provided more robust evidence on the risk of these rare but serious AEs.

TABLE 11 RESULTS OF SAFETY ANALYSES FOR DC01 AND DC02

	DCO1 (27 March 2020)		DCO2 (12 July 2021)	
AEs	**Olaparib (N=911) n (%)**	**Placebo (N=904) n (%)**	**Olaparib (N=911) n (%)**	**Placebo (N=904) n (%)**
Any AE	835 (91.7)	753 (83.3)	836 (91.8)	758 (83.8)
Grade ≥3 AEs: Any	221 (24.3)	102 (11.3)	223 (24.5)	102 (11.3)
Anaemia	79 (8.7)	3(0.3)	79(8.7)	3(0.3)
Neutropenia	NR	NR	[redacted] (4.9)	7(0.8)
Serious AEs	79 (8.7)	76 (8.4)	79 (8.7)	78 (8.6)
AEs of special interest:				
MDS/AML	2(0.2)	3(0.3)	[redacted]	
Anaemia	216(23.7)	35 (3.9)		
New primary malignancies	[redacted]	[redacted]		
Pneumonitis/ILD	9(1.0)	11 (1.2)		
Deaths due to AEs	1 (0.1)	2 (0.2)	1 (0.1)	2 (0.2)
Dose interruptions due to AEs	[redacted]	[redacted]	286 (31.4)	99 (11.0)
Dose reductions due to AEs	[redacted]	[redacted]	213 (23.4)	33 (3.7)
Discontinuations due to AEs	90 (9.9)	38 (4.2)	98 (10.8)	42 (4.6)

*Incorrect value for the number of dose interruptions due to AEs is reported in Table 21 of the CS (236 rather than 286). The correct value was reported in the response to clarification questions.

**Only proportion of patients with AEs reported and this does not equate to a whole number of participants

3.3 Conclusions of the clinical effectiveness section

3.3.1 Is there evidence of clinical effectiveness?

The EAG support the company's conclusions that there is strong evidence of clinical effectiveness of olaparib, but the data is immature with the median time at which 50% of patient experience an event, not yet met for any of the iDFS, dDFS, or OS outcomes. The short-term benefits have been established, but there is uncertainty as to the long-term benefits of olaparib.

3.3.1 Are estimates that feed into the economic model reliable and appropriate to the scope?

The EAG are content that there is only one trial of relevance to the scope – the OlympiA trial and this was directly relevant to the NICE scope. The EAG has no concerns regarding the reliability of the clinical effectiveness data. Although a small number of issues were identified with the CS and OlympiA trial, none are considered likely to have impacted on estimates of effectiveness.

HRQoL was measured using the EORTC-QLQ C30 which was be mapped to the EQ-5D scores to give data on utilities that can be used in the model. The EAG also have concerns regarding the low completion rate of HRQoL questionnaires and the potential for this to have resulted in missing data that could have impacted on the trial estimates of HRQoL.

The EAG have some concerns that the relatively small sample size and limited follow-up for the OlpymiA trial mean that potentially serious but rare AEs may not have been identified in the OlympiA trial. It would have been helpful to have provided pooled safety data across all known studies of olaparib to provided more robust evidence on the risk of these rare but serious AEs.

3.3.2 Have the most appropriate estimates been selected to feed into the economic model?

The only data presented in the clinical effectiveness section that directly informed the economic model were data on adverse events. Although standard measures were used to measure clinical effectiveness and HRQoL, these did not feed directly into the economic model. Effectiveness was assessed using appropriate measures and assessed using standard criteria. Results data were presented as hazard ratios which assumes PHs but there was evidence that the proportional hazards were violated. Estimates used for the model were based on survival curves which was appropriate. The EAG are content that appropriate estimates were selected to feed into the economic model.

4 COST EFFECTIVENESS

4.1 EAG comment on company's review of cost-effectiveness evidence

Searches of the key biomedical databases, trials registry resources, websites and relevant conferences were undertaken in December 2020 and updated in January 2022. Reference checking of eligible study reports and systematic reviews was also undertaken. The company modified their search strategy in response to Clarification Question B23, which adjusted the search to records with economic evaluation terms or outcome terms in the title, rather than both such terms. Additional records were rescreened by the company and no additional relevant economic evaluations were included. Following this correction, the EAG regard the search approach for studies reporting cost analyses and data appropriate to the task. For the HRQoL review, searches of the key biomedical databases, trials registry resources, websites and relevant conferences were undertaken in December 2020 and updated in January 2022. Reference checking of eligible study reports and systematic reviews was also undertaken. The search strategies directly align with the decision problem and the search approach is suitable to identify studies and study data for the submission.

4.2 Summary and critique of the company's submitted economic evaluation by the EAG

We provide a summary and critique of the cost-effectiveness models submitted by the company for the TNBC and the HR+/HER2- populations. These are high-quality cost-effectiveness models largely aligned with NICE recommendations on methods for economic evaluation. The use of a semi-Markov model structure to reflect changing probabilities over time is particularly admirable. The models are based on the population from the OlympiA trial, which represents the target populations in TNBC and HR+/HER2-, as discussed in Section 3.2.2.

4.2.1 NICE reference case checklist

The company's cost-effectiveness analysis is largely aligned with the NICE reference case (Table 12).

The company took an NHS perspective only and did not provide a justification for the exclusion of PSS costs; for example, social-care costs for patients with metastatic recurrence. These are likely to be small, and their impact on the results is likely negligible as we found that results are insensitive to costs on metastatic health states.

EQ-5D utilities and QALYs were valued using UK population tariffs but obtained indirectly as only the EORTC QLQ-C30 questionnaire was completed by OlympiA patients. The source of HRQoL estimates is discussed in greater detail in Section **Error! Reference source not found.**.

TABLE 12 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	Aligned with reference case
Perspective on costs	NHS and PSS	NHS perspective only. No justification for exclusion of PSS costs but assumption has no impact on results.
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Aligned with reference case
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Aligned with reference case.
Synthesis of evidence on health effects	Based on systematic review	Aligned with 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.	Aligned with reference case. Health benefits expressed in QALYs as per reference case. EQ-5D utility values were indirectly obtained using mapping algorithms for the trial population.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Aligned with reference case. Patient reported disease-specific quality of life measured by the EORTC QLQ-C30 questionnaire.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Aligned with reference case. Mapped OlympiA patients EORTC QLQ-C30 responses to the UK population tariffs for the EQ-5D.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Aligned with 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	Aligned with reference case
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Aligned with reference case (3.5%)

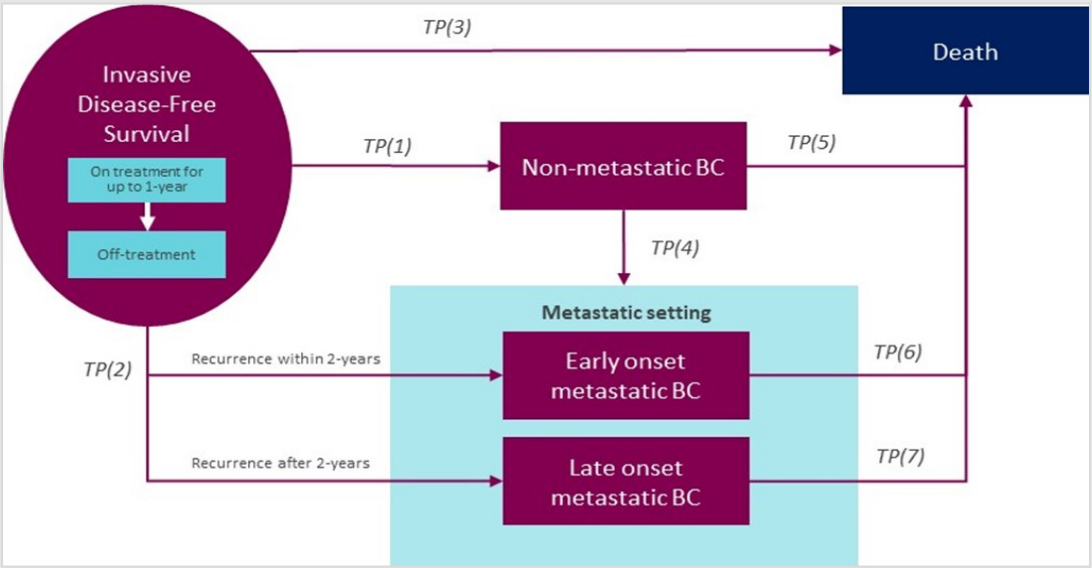
Element of health technology assessment	Reference case	EAG comment on company's submission
PSS, personal social services; QALYs, quality-adjusted life years; EQ-5D, EuroQol questionnaire, NICE recommended instrument to measure generic health-related quality of life, valued using UK societal preference weights, designed to derive QALYs.		

4.2.2 Model structure

The company submitted a fully executable health economic model in Excel®. The model adopts a semi-Markov model structure with monthly cycles and 57 years' time-horizon and is reproduced in Figure 5. Each of 5 states of the semi-Markov model was represented by 720 (maximum implemented time horizon was 60 years of 12 month cycles, giving 720) 'tunnel' states of an underlying Markov model; the underlying Markov model thus had 3600 states. The advantage of this semi-Markov model is that it allows for "memory" to be introduced in the Markov chain, by which transition probabilities depend on time spent in the current state rather than only depending on time in the model. The same model structure is applied to produce cost-effectiveness results for TNBC and HR+/HER2- patient populations separately.

Patients enter the model in the 'invasive disease-free survival' (iDFS) state with or without treatment up to 1-year and can transition to 'non-metastatic BC' (i.e., locoregional recurrence), 'metastatic BC' (i.e., distant recurrence), and 'death'. From the 'non-metastatic BC' state patients can transition to 'metastatic BC'. 'Metastatic BC' is divided into 'early-onset metastatic BC' (<2 years from being eligible for olaparib treatment) and 'late-onset metastatic BC'(2+ years from treatment eligibility) depending on whether metastases occur from treatment initiation. Patients can transition from all health states to 'death'.

FIGURE 5 COST-EFFECTIVENESS MODEL STRUCTURE REPRODUCED FROM FIGURE 15 OF CS DOCUMENT B(1)



This model structure is similar to others that have been used in early breast cancer. The model for appraisal TA632 "Trastuzumab emtansine for adjuvant treatment of HER2-positive early breast cancer" included a 'Remission' state, separated iDFS into on and off treatment, and modelled 1st and 2nd line treatment in the metastatic state.(29) These extra states were justified by the Markov structure, where the tunnel state for remission introduced some dependence on time, but is no longer required in the full semi-Markov structure used for olaparib. Unlike the olaparib model, 'early' and 'late' recurrence were split by an 18-month cut-off in TA632. The choice of an 18-month cut-off was justified by a comparison of post-progression survival in patients who recurred before and after 18 months in the trastuzumab HERA study(30), and the EAG for TA632 noted that an 18 month cut-off is consistent with previous breast cancer assessments TA107, TA424 and TA569.(29, 31, 32). Other cut-offs were not explored so it is unknown if 18 months had statistical justification over cut-offs at, say, 12 or 24 months (as used in the CS for olaparib).

The evaluation for TA612 "Neratinib for extended adjuvant treatment of hormone receptor-positive, HER2-positive early stage breast cancer after adjuvant trastuzumab" explicitly named local and distant recurrence states modelled in an equivalent way to this model for olaparib.(33) As in TA632, a remission state was included, which is no longer required in this semi-Markov structure. Early and late distant recurrence were not modelled in TA612.(33, 34)

In CS B.3.2.2.2 the company's justification for the 2-year cut-off between "early" and "late metastatic BC" was the POSH study (McKenzie 2020) which showed lower post-recurrence survival in patients who recur within 2 years.(35) This study was in a population 67% TNBC and 33% HER2+ and did not report by cancer type, although a regression analysis found

HER2+ status to be associated with longer post-recurrence survival (HR 0.66; 0.51-0.86; p=0.002). The 2 year timepoint in the POSH study was arbitrary; the authors did not explore alternative timepoints to find the point with greatest impact on post-recurrence survival. Although the EAG considers there is little justification for choosing a 2-year cut-off for this model, scenario analyses using cut-offs of 1 and 3 years found almost no impact on the ICER (Table 21) so the EAG accepts this assumption is reasonable.

4.2.3 Population

The population used for the cost-effectiveness analysis is consistent with the NICE scope and evaluates olaparib within its targeted marketing authorisation (Section Patients3.2.2).

4.2.4 Interventions and comparators

As per the NICE scope and as described in Section 3.2.3, the intervention is oral olaparib at 300mg (as two 150mg tablets) twice per day.

The comparator in the economic analysis is "watch and wait" which consists of follow-up with screening for recurrence. This was aligned with the NICE scope and our clinical advice received by the EAG agreed with this as most relevant comparator. Both treatment groups include endocrine therapy for the HR+/HER- population.

4.2.5 Perspective, time horizon and discounting

The perspective adopted was that of the NHS. The use of PSS was not discussed or elicited from patients in the trial or clinical experts for inclusion in the model.

The economic evaluation adopted a lifetime horizon. Patients entered the model at age 43 with a time horizon of 57 years, giving a maximum life expectancy of 100 years. No justification for the 100-years life expectancy was given except to note in CS B.1.3.1.3 that for the ~2300 new cases of breast cancer detected in the UK in women aged under 39 years (36), indicating that a 57 year time horizon is conservative. Time horizons were varied in scenario analyses in Table 21 (40 and 50 years) and but these only marginally increased the ICER. The EAG disagrees that 57 years is a conservative time horizon, but accepts this time horizon for the analysis.

Discounting of both costs and QALYs was at 3.5% per year, in line with NICE reference case. Given the potential of olaparib to reduce long-term recurrence and increase survival, the company presented a scenario analysis with a 1.5% discount rate. NICE guidance specifies that 1.5% can be considered for costs and outcomes when treatment confers substantial quality of life or life expectancy gains; this could be applicable to olaparib as patients who avoid locoregional or distant recurrence may have better overall survival. However, NICE also specifies that there must be confidence about the gains, which is not true for olaparib given the immaturity of trial data. Discounting of 3.5% is therefore most appropriate.

4.2.6 Treatment effectiveness and extrapolation

The data and assumptions used for transition probabilities (i.e., treatment effects and extrapolations) are summarised in Table 13**Error! Reference source not found.**. We next critique key points of these assumptions.

KEY ISSUE: Clinical effectiveness data are immature

TABLE 13 DATA AND ASSUMPTIONS USED FOR COST-EFFECTIVENESS MODEL TRANSITION PROBABILITIES

Transition probability	Data/assumptions	EAG Comment
TP1/TP2 (Disease-free survival to non-metastatic recurrence/metastatic recurrence)	Lognormal distribution fit to Olympia iDFS data on basis of fit statistics Hazard of olaparib set to that of placebo after point at which parametric curves cross. Conditional probability of recurrence from OlympiA is used to estimate split between TP1 and TP2; this conditional probability is assumed the same in TNBC and HR+/HER2- and in olaparib and placebo. In TNBC TP1/TP2 are set to zero after 5 years. Validated with UK medical oncologist opinion and against UK Prospective study of Outcomes in Sporadic versus Hereditary breast cancer (POSH) study iDFS at 10 years.(35, 37, 38) In HR+/HER2- the OlympiA ITT data (i.e., the full population, where TNBC dominated) were used as a proxy. iDFS at 2, 5, 10 and 20 years were validated against empirical data (EBCTCG (2005), Pan et al. (2017)). (39) (40)UK medical oncologists also validated the extrapolations.	In HR+/HER2- lognormal and generalised Gamma models have very similar AIC and extrapolations up to 20 years. The lognormal model assumes the treatment benefit is maintained over a longer period of time. Due to uncertainty in the long-term estimates, the EAG considers the generalised Gamma distribution is the most plausible choice (Table 14).
TP3 (Disease-free survival to death)	Background mortality elevated by published standardised morality rate (SMR) of 1.46 (0.5, 2.82) for gBRCAm patients.(41) Company supported assumption with literature review which	Evidence on the SMR is weak with a very wide 95% CI. Levi et al. (2002) provides an alternative source for SMR of 2.0 which the EAG will also use. (42)

Transition probability	Data/assumptions	EAG Comment
	identified only older or smaller studies, or studies in non-relevant populations.	
TP4 (Non-metastatic BC to metastatic BC)	Estimated using 81 patients in OlympiA who had non-metastatic recurrence. Assumed the same in both subgroups and both treatment groups. AIC/BIC similar across distributions but lognormal selected as had lowest AIC.	EAG agrees the lognormal is reasonable.
TP5 (Non-metastatic BC to death)	Estimated using 81 patients in OlympiA who had non-metastatic recurrence. Assumed the same in both subgroups and both treatment groups. AIC/BIC similar across distributions but exponential selected as had lowest AIC.	Scenario analysis indicates limited impact on ICER so EAG agrees it is a reasonable assumption.
TP6 (Early onset metastatic BC to Death)	OlympiA ITT data in patients with early onset metastatic recurrence. Evidence provided for non-proportional hazards so placebo and olaparib modelled independently. Exponential curves selected as had lowest AIC and conservative long-term survival on both arms.	Exponential curves are not appropriate if proportional hazards are violated because these single hazard rate models implicitly assume proportional hazards. EAG prefers the Gompertz as, excluding the exponential, has lowest AIC/BIC and gives a plausible difference in survival between arms in the long term.
TP7 (Late onset metastatic BC to Death)	Weighted average of survival probabilities for first-line treatments of BRCAm mBC.	

TP = transition probability, AIC = Akaike information criteria, BIC = Bayesian information criterion, mBC = metastatic breast cancer

4.2.6.1 Treatment discontinuation

Discontinuation before 1-year follows Kaplan-Meier (KM) data from the OlympiA trial (CS Document B Figure 28), with almost 80% of patients remaining on treatment up to about 11 months.(1) Given that the treatment should be offered for a maximum of 12 months, the EAG agrees data from OlympiA is the best source of data.

4.2.6.2 Recurrence rate (TP1/TP2)

The risk of recurrence in both TNBC and HR+/HER2- was modelled as a lognormal distribution fit to OlympiA data. The TNBC subgroup in OlympiA was used to model TNBC type, while the full ITT group in OlympiA was used as a proxy for the HR+/HER2- model due to limited sample size of the HR+/HER2- subgroup (iDFS events were n=25 for olaparib and n=34 for placebo in DCO2). Whilst the EAG recognises that data are limited for HR+/HER2-

and an assumption is necessary, the ITT results are dominated by the TNBC group which will may over or underestimate the true risk in the HR+ population; the company did not provide extrapolations fit to the HR+/HER2- group so it is not possible to tell the direction of the bias.

The hazard on olaparib is constrained to be less than or equal to that on the watch & wait control group; this was necessary as the parametric curves cross. In TNBC, the EAG agrees that a lognormal distribution is an acceptable choice; the AIC and BIC of the lognormal, Gompertz, generalised Gamma and loglogistic were all similar (Clarification responses: Table 22). Extrapolated iDFS at 2, 5 and 10 years were compared to the POSH study (Clarification responses: Table 25) and all four give similar extrapolations and degree of agreement.(35) The company argue that the POSH study does not include high risk patients so is likely an overestimate of survival and the higher iDFS of Gompertz is less plausible. Beyond this, there is little justification for choosing between lognormal, generalised Gamma and loglogistic. Scenario analyses (Table 21) indicate they each have similar ICERs. The EAG therefore considers a lognormal distribution for TP1/TP2 in TNBC to be reasonable.

The conditional probability of recurrence being non-metastatic (TP1) or metastatic (TP2) was estimated using OlympiA data. The company merged across olaparib and placebo groups, giving a conditional probability of 23.8% (81 divided by 341). Splitting by treatment group would give slightly lower probability on placebo (23.2% or 48 divided by 207) than on olaparib (24.6% or 33 out of 134). The EAG conducted a 2-sample test for equality of proportions, with no continuity correction, to test the equality assumption. This gave a Chi-squared score of 0.093 on 1 degree of freedom, and a p-value of 0.761, which failed to pick up evidence of a difference in the ratios. The EAG is therefore more confident that the assumption of a common conditional probability across treatments may be reasonable.

The company assumed that long-term risk of recurrence in TNBC was zero after 5 years and that it remained elevated for HR+/HER2- throughout the lifetime horizon of the model (CS B.3.3.3.1). Their justification for these assumptions were interviews with clinicians. (43)The company conducted scenario analyses using 3, 7 and 10 years as the cut-off for zero risk of recurrence in TNBC, and a scenario setting 10 year recurrence risk to 5% after the initial 5 years post initiation of treatment (Table 21).(44) The latter was justified by reference to the Reddy 2017 database study, which indicated recurrence-free survival (RFS) at 10 years after the initial 5-year period was 91%.(44) Meanwhile, the Pan 2017 meta-analysis of 88 trials found that, for TNBC patients disease free at 5 years, the risk of distant recurrence is 10-41% over the following 15 years.(40) Based on these studies and clinical advice received by the EAG, the 0% risk beyond 5 years was deemed implausible, and the EAG adopted a 10-year recurrence risk of 5% risk after the initial 5 years.

In HR+/HER2-, the company assumed the risk of recurrence would continue indefinitely. The selection of parametric curve for TP1/TP2 has therefore a greater impact on the ICER (Table

21). The AIC/BIC in the ITT population were the lowest (i.e., indicating best model fit) and very similar for the Gompertz, lognormal, log-logistic, and generalised Gamma models, while Weibull and Gamma had worse fit. The exponential had a reasonable fit but long-term iDFS was implausibly low (Clarification response: Figure 17). Empirical data were used to validate long-term extrapolations at 2, 5, 10 and 20 years, and the Gompertz was found to significantly overestimate long-term iDFS at 10 years and 20 years, while loglogistic somewhat underestimates it (Clarification responses: Table 26). (39, 40) The company therefore selected a lognormal but did not justify this choice over a generalised gamma, especially given the very similar AIC/BIC and extrapolations.(39, 40)

The EAG compared iDFS from lognormal and generalised Gamma curves up to 57 years (the time horizon for the model). These comparisons, along with the AIC, BIC, time at which the olaparib and placebo arms cross, and estimates from empirical literature, are presented in Table 14. Due to uncertainty about long-term treatment effects, and clinical advice received by the EAG, the EAG recommends using the generalised Gamma which provides the most plausible long-term estimates. Generalised gamma extrapolated Olaparib and placaebo hazard curves also cross at an earlier timepoint (5.4 vs 14.5 years). which the model assumes the hazards are the same, and thus represent a more conservative assumption.

FIGURE 6: FIT OF THE PARAMETRIC SURVIVAL MODELS TO THE KAPLAN-MEIER DATA FOR IDFS IN OLYMPIA (TNBC, LEFT; HR+/HER2*, RIGHT; FIGURE 17 FROM COMPANY CLARIFICATION RESPONSES APPENDIX 2)(6)

*ITT population used as a proxy for HR+/HER2- population

Footnotes: Olaparib and placebo arms adjusted for crossing hazards over time; for TNBC, the iDFS extrapolations incorporate no long-term risk of recurrence after 5 years; for HR+/HER2, the iDFS extrapolations assume a lifetime risk of recurrence.

Abbreviations: HER2: human epidermal growth factor receptor-2; HR: hormone receptor; iDFS: invasive disease-free survival; ITT: intent-to-treat; TNBC: triple-negative breast cancer

TABLE 14 EXTRAPOLATED IDFS PROBABILITIES IN HR+/HER2- USING PARAMETRIC MODELS EQUALLY SUPPORTED BY AIC/BIC AND COMPARISON WITH EMPIRICAL DATA UP TO 20 YEARS.

		AIC	BIC	Timepoint (years)										
				1	2	3	4	5	10	20	30	40	50	57
Lognormal. Crossing year 14.5*	Olaparib	1748.18	1757.83	[redacted]										
	Placebo	2461.37	2471.01	[redacted]										
	Abs diff	-	-	[redacted]										
Generalised Gamma. Crossing year 5.4*	Olaparib	1749.98	1764.45	[redacted]										
	Placebo	2463.04	2477.5	[redacted]										
	Abs diff	-	-	[redacted]										
Loglogistic. Crossing year 7.75*	Olaparib	1749.86	1759.51	[redacted]										
	Placebo	2468.38	2478.02	[redacted]										
	Abs diff	-	-	[redacted]										
Empirical data	EBCTCG (2005)(39)	-	-	-	88.50%	-	-	73.30%	59.50%	52.7% (15 yrs)	-	-	-	-
	Pan et al. (2017) (40)	-	-	-	-	-	-	78.00%	64.00%	48.00%	-	-	-	-

*Timepoint at which instantaneous hazard of olaparib becomes higher than that on placebo, after which the model uses the placebo instantaneous hazards

4.2.6.3 Disease-free survival to death (TP3)

The company used background mortality inflated by a published standardized mortality ratio of 1.46 (0.5, 2.82) for females <50 years old carrying BRCA mutation relative to non-carriers from Mai 2009, to inform the probability of death from disease-free survival (TP3).(41) This study was based on 5,287 genotyped patients of whom 120 were BRCA carriers, although the number in the female <50 years old subgroup was not specified. However, this SMR is for BRCAm vs non-BRCAm for females in the absence of breast, ovary, pancreas or prostate cancer. It is not specific to BRCAm patients with early breast cancer after surgery and/or (neo)adjuvant therapy. The background mortality is also general and not specific to the patient population. Furthermore, the 95% CI ranges from 0.5 to 2.82, indicating substantial uncertainty. The company justified this choice (Clarification response B9) through a targeted literature review (TLR) which identified 11 studies on excess mortality in the target population. Significantly, the Clèries 2022 study showed no excess mortality in patients disease-free over time, while other studies included excess mortality due to non-metastatic or metastatic recurrence, which are already included in the model.(45) Only two studies reported the excess mortality risk from other causes after breast cancer treatment.(42, 46) However, both were earlier (2001 and 2002 compared to 2009) and had smaller sample sizes than the Mai 2009 study. For example, Levi et al. (2002) was a Swiss-based study in 1095 women diagnosed with breast cancer between 1974 and 1984. It estimated the SMR associated with non-cancer related causes (e.g., cardiovascular, digestive and respiratory disease or other external causes) in breast cancer patients to be 2.0 in any of the different follow-up periods after diagnosis (10–14 years, 15–19 years and 10–19 years). The EAG considers the Mai 2009 SMR to be the best estimate available. However, due to our concerns about the reliability of Mai 2009, we include new scenario analyses assuming an SMR of 1.00 as indicated by Clèries 2022 and 2.00 as reported by Levi et al. (2002).

4.2.6.4 Metastatic recurrence (TP4) and death (TP5) from non-metastatic recurrence

The OympiA trial data on the 81 patients who had non-metastatic recurrence was used to estimate the probability of metastatic recurrence (TP4) and death (TP5) in such patients. The same probabilities were used for both TNBC and HR+/HER2- and for olaparib and placebo. This was justified by the small sample size available for both probabilities; Clarification Responses Table 5 reported [redacted] events from non-mBC to mBC (TP4) and [redacted] from non-mBC to death (TP5). The EAG requested that these assumptions be relaxed in a scenario analysis (Clarification question B3) and a formal statistical test to confirm no evidence of a difference between TNBC and HR+/HER2- and between olaparib and placebo (Clarification question B8) but the company did not conduct either. However, scenario analyses indicate model selection has a very limited impact on the ICER (Table 21). The EAG therefore considers that the company base case assumption is adequate.

The AIC and BIC for all parametric distributions for TP4 and TP5 were very similar (Clarification responses: Table 27).(6) The lognormal had lowest AIC on TP4 and exponential

had lowest AIC on TP5, which were the final selections by the company. Extrapolations presented by the company (Figure 7) differed to a moderate extent after 10 years but again scenario analyses indicate model selection has a very limited impact on the ICER (Table 21). The EAG therefore considers the company assumed distributions reasonable.

FIGURE 7 EXTRAPOLATION OF PARAMETRIC SURVIVAL MODELS FIT TO ITT OLYMPIA KAPLAN-MEIER DATA FOR NON-METASTATIC TO METASTATIC RECURRENCE (LEFT, TP4) AND FOR NON-METASTATIC TO DEATH (RIGHT, TP5) IN OLYMPIA, POOLED ARMS (FROM CLARIFICATION RESPONSES FIGURE 20)

4.2.6.5 Early onset metastatic BC to Death (TP6)

The probability of transition from early onset metastatic BC to death (TP6) was fit to Kaplan-Meier survival data of the ITT population in OlympiA, separated by treatment arms. The company selected independent exponential curves. This data for early metastatic patients in OlympiA were relatively mature, with [redacted] deaths in [redacted] patients on olaparib and [redacted] in [redacted] patients on placebo; this data were sufficient to reliably estimate risks of death separately by treatment arm. The AIC/BIC were lowest for exponential curves on olaparib and BIC was lowest for exponential on placebo, with AIC of exponential on placebo being very close to that of other distributions (Table 15Table 15). The exponential curve gave relatively low extrapolated survival for both olaparib and placebo (Figure 8) but differed from other placebo curves by <10% and from other olaparib curves by <5%.

However, the company presented evidence that hazards between arms were non-proportional; both Kaplan-Meier curves and log-cumulative hazards indicated violation of proportional hazards (Clarification Responses: Figure 21 and Figure 22).(6) Independent exponential curves with a single hazard rate parameter implicitly assume proportional

hazards. Excluding exponential, the Gompertz has lowest AIC and BIC for both olaparib and placebo (Table 15). Extrapolations for the Gompertz were considered plausible by our clinical advisors and, given the long-term uncertainty, give a more conservative long-term difference between arms (Figure 8). The EAG therefore prefers Gompertz curves for both olaparib and placebo on TP6.

TABLE 15 AIC AND BIC VALUES FOR THE PARAMETRIC SURVIVAL MODELS FITTED TO DATA ON THE TIME FROM METASTATIC RECURRENCE TO DEATH (PLACEBO ARM) (FROM CLARIFICATION RESPONSES TABLE 28)(6)

Model	Olaparib (N=[redacted])		Placebo (N=[redacted])	
	AIC	BIC	AIC	BIC
Exponential	521.45 [1]	524.10 [1]	857.49 [2]	860.62 [1]
Weibull	523.23 [4]	528.54 [4]	857.69 [4]	863.95 [4]
Loglogistic	522.39 [3]	527.70 [3]	857.62 [3]	863.88 [3]
Lognormal	530.99 [6]	536.29 [6]	859.17 [6]	865.43 [5]
Gompertz	522.06 [2]	527.37 [2]	857.19 [1]	863.45 [2]
Generalized gamma	524.53 [5]	532.49 [5]	858.05 [5]	867.44 [6]

Footnotes: [X]: rank on lowest AIC/BIC by arm.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion.

FIGURE 8 EXTRAPOLATION OF PARAMETRIC SURVIVAL CURVES FIT TO ITT OLYMPIA KAPLAN-MEIER DATA FOR EARLY METASTATIC RECURRENCE TO DEATH (TP6). (FROM CLARIFICATION RESPONSES FIGURE 23)(6)

4.2.6.6 Late onset metastatic BC to Death (TP7)

Transitions to death from late onset metastatic BC patients were based on an average of survival probabilities for first-line treatments of BRCAm metastatic BC, using data external to OlympiA. UK medical oncologists and national guidelines informed the selection of three first-line treatments for late onset metastatic BC TNBC and HR+/HER2- patients (Table 16). Our clinical advisors also agreed with this selection. A published SR and clinical guidelines were used to identify studies on long-term survival on each of these options (Table 16).(47, 48) Baseline characteristics were only available for the full study population of Flatiron and IMpassion 130 studies. Merged TNBC and HR+/HER2- data were used from OlympiAD as there were only 28 patients on the capecitabine, vinorelbine, Eribulin (TPC) arm. Sample sizes for the relevant subgroups were also small for Flatiron (n=36) and IMpassion 130 (n=45).

Parametric survival curves were fit to the OlympiAD and Flatiron data with AIC and BIC reported in Company Submission B.3.3.5 Table 33. Fit was similar for most models but worse for exponential and Gompertz. The Company selected the models with lowest AIC/BIC for both data, which was lognormal for OlympiAD and loglogistic for Flatiron. The EAG notes that alternative distributions have little impact on the ICER, which is likely due to these being applied to both the olaparib and Watch-and-Wait options.

Weights were assigned to these distributions based on UK oncologist opinions and, in TNBC, the proportion of BRCAm patients that would be eligible for atezolizumab having tested PD-L1 positive. These weights are provided in Table 16. Alternative weights were explored by the EAG in sensitivity analyses.

TABLE 16 DATA AND ASSUMPTIONS USED FOR SURVIVAL ON FIRST-LINE TREATMENTS FOR LATE-ONSET MBC, WEIGHTED AVERAGE OF WHICH IS USED FOR TP7 (LATE ONSET METASTATIC BC TO DEATH)

Treatment	Evidence	Data and assumptions	Weight in TNBC*	Weight in HR+/HER2-*
Single chemotherapy	TPC (capecitabine, vinorelbine, Eribulin) subgroup who had not previously received chemotherapy for mBC of OlympiAD.(49, 50)	Individual patient data with Lognormal survival curve.	70%	10%
CDK4/6 inhibitor plus endocrine therapy	Collins et al. (2021) (Flatiron Health RWE study).	Individual patient data with Loglogistic survival curve.	0% (Not approved in TNBC)	90%
Atezolizumab plus paclitaxel	BRCAm biomarker subgroup of IMpassion 130 study (clinical trial).(7)	Only hazard ratio atezolizumab plus nab-paclitaxel versus nab-paclitaxel alone available. This was combined with	30%	0% (Not recommended for HR+/HER2- patients in the UK)

Treatment	Evidence	Data and assumptions	Weight in TNBC*	Weight in HR+/HER2-*
		survival on TPC arm of OlympiAD to give survival probability.		

*Same weight used for olaparib and placebo arms

4.2.6.7 Adverse events

As outlined in Section 3.2.4.3, the only adverse events included in the model were anaemia and neutropenia. The impact of adverse events on the economic model are discussed in the Sections 4.2.7.4 in relation to HRQoL decrements (or disutilities), and 4.2.8.2 in relation to costs.

4.2.7 HRQoL

Utilities to inform HRQoL in the health states of iDFs and non-metastatic recurrence were informed by mapping responses to the EORTC QLQ-C30 disease-specific HRQoL questionnaires for patients in the Olympia trial to utility scores in the EQ-5D-3L generic HRQoL tool health states.(26) As highlighted in section 3.2.4.2, the OlympiA trial did not administer generic HRQoL questionnaires with societal preference-based valuations, such as the EQ-5D. As quality of life measurements for the OlympiA trial were were collected routinely every 6 months only up to recurrence or for a maximum of 2 years, and completion rates were low, HRQoL in the health states of metastatic BC were informed by published utilities in the literature. The description of the CS base case and sensitivity analysis scenarios for utility values used in the different health states of the model are summarized in Table 37 of the CS Document B.

KEY ISSUE: HRQoL measures used in the economic model

4.2.7.1 Mapping utilities from the EORTC QLQ-C30 for iDFS and non-metastatic recurrence health states

The company reviewed the Oxford Population Health, Health Economics Research Centre (HERC) database of mapping studies to discuss the best algorithm to apply for mapping responses to the EORTC QLQ-C30 to the EQ-5D utilities,(51) and focus on using two algorithms Crott & Briggs 2010(52) in their base case analysis, and Longworth (2014) (53) algorithm in sensitivity analysis.

Crott & Briggs 2010(52) is the first and oldest mapping algorithm for the EORTC QLQ-C30 responses into EQ-5D-3L utilities for patients with locally advanced breast cancer. It uses a sample of over 800 observations and ordinary least squares (OLS) regression analysis, providing an intuitive and easy to use algorithm. This algorithm produces the highest estimated utilities from all sources of utilities considered for this economic model. Due to the skewed nature of quality of life scores, OLS-based mapping algorithms, and Crott & Briggs 2010 in particular, have been shown to produce biased estimates and have poor

external validity.(54, 55) Furthermore, Crott & Briggs 2010 algorithm was developed from a population with advanced localized breast cancer but does not differentiate between type of cancer.(52)

Longworth and colleagues in 2014 and 2015 (53, 56) have produced mapping algorithms from the EORTC QLQ-C30 to EQ-5D-3L utilities using several estimation methods, including OLS, and found that 'response mapping' was the most appropriate method for mapping utilities from the EORTC QLQ-C30. Longworth 2014 algorithms were derived from an international population of patients with a mixture of cancers, including breast cancer (n=771, mean age 68 years).

Gray and colleagues developed the most recent algorithm for mapping from the EORTC QLQ-C30 onto EQ-5D utilities for patients with advanced localized breast cancer, using an 'adjusted limited dependent variable mixture model' (which can be applied in Stata using the 'aldvmm' command) to overcome the issues with skew in prior algorithms.(4, 5) Although this was published in November 2021, prior to company submission in April 2022, this algorithm was not considered for mapping of the OlympiA trial patients data.

The company argues that Crott & Briggs 2010 algorithm is more appropriate to derive utilities in the base case analysis because it is derived from a breast cancer population, as opposed to a mixture of cancers (including breast) as in Longworth, and it has been used in a previous NICE appraisal (TA423). It is established that Crott & Briggs produces biased estimates and the EAG argues that precedent of TA423 may not be appropriate as it is an older appraisal (in 2016) prior to external validation of Longworth's and Gray's algorithm, and on locally advanced or metastatic breast cancer patients after failure of two or more chemotherapy regimens, a more advanced state of the disease than olaparib. The EAG therefore considers that the Crott & Briggs 2010 mapping algorithm is not the most suitable form to portray the quality of life of patients in the disease-free and non-metastatic recurrence health states for olaparib for the economic model.

4.2.7.2 Alternatives to mapping algorithms: obtaining EQ-5D utility scores directly from the literature

Lidgren et al (2007) published utility estimates for breast cancer patients attending a Swedish breast cancer outpatient clinic at different states of their disease and applied UK societal preferences valuations to derive utility scores.(57) It provides estimates for four patient subgroups: i) first year after primary breast cancer diagnosis, ii) first year after recurrence, iii) second and following years after primary/recurrence, iv) metastatic disease, most of them between the ages of 50 and 64 years.

Utilities from the Lidgren study are derived from EQ-5D directly, a preference-based generic HRQoL tool, to inform utilities in the model; the study used the UK population valuation tariffs and does not require mapping between different types of measures. The patient

subgroups mimic the patients' health state at the different states of this model; with estimates from groups ii), iii), and iv) used to inform utilities in the iDFS, non-metastatic BC and the two metastatic BC health states in the model, respectively. They provide the lowest utility values for the DF and non-metastatic recurrence states that the company considered in sensitivity analysis. Lidgren and colleagues have set all negative EQ-5D values to zero for analysis, overestimating the mean values in subgroups ii) and iii) which informed the utilities of the DF and non-metastatic recurrence health states; Lidgren's estimatesfor these health states, may therefore be overestimated.

The company further identified additional sources of utilities from studies reporting EQ-5D scores, of which the EAG considers one to be relevant. Verrill et al 2020 is an industry-sponsored, UK cross-sectional study of 299 patients with HER2+ early or metastatic BC.(58) Patients completed the EQ-5D-5L questionnaire, a superior measure to the 3L version and crosswalk utility values to the 3L questionnaire as recommended by NICE are reported. Results were reported by patient group: i) early BC on treatment post-surgery; ii) early BC after completion of adjuvant treatment ; and iii) during metastatic BC treatment. Mean ages are 55 years in groups i) and iii) and 57 years in group ii), which are closer to the OlympiA trial population than other sources.

The company considers that these estimates are not suitable because they are derived from a HER+ population and does not have information on the BRCA mutation status. Lidgren estimates, used in the company's sensitivity analysis, are based on all types of breast cancer, of which HER2+ is the most common (70% vs 30% HER2-), and Crott & Briggs mapping algorithm, which is used as the company's base case, is developed on a population of more advance BC regardless of HER2 type or gene mutation, and are both in international populations. Verrill 2020 is a more recent study than Lidgren or Crott & Briggs, in a UK population, and uses the EQ-5D-5L, more sensitive generic quality of life tool which does not require mapping from disease-specific questionnaires. In the absence of an unbiased mapping algorithm to allow us to use quality of life data estimates from the OlympiA trial, the EAG considers that the utility estimates from Verrill 2020 are the most likely to represent the true quality of life of patients in the different health states of this model.

4.2.7.3 Using the same utility values for the DF and non-metastatic recurrence

Results from the regression analysis of the mapped utility scores at DC01 showed a difference between health states of recurrence and recurrence free of [redacted] (95% CI [redacted]. The company argues that this difference is not important, not significant, and past TA632 and TA569 NICE evaluations have also assumed no difference. Assuming no difference based on precedent or p-value slightly above the 0.05 threshold is inappropriate. An average decrement of [redacted] in utility equates to patients without recurrence having on average 10 additional days or "perfect health" in a year (95% CI 0 - 20 days), which is not small nor insignificant. This difference could have been different at DCO2, but additional mapped scores were not provided. Clinical advice received by the EAG suggested that the

utility value for this state lies somewhere between the utility in the iDFS and the mBC health states. The EAG considers the midpoint between these two utilities which is 0.777 (SE=0.015) to be more plausible.

4.2.7.4 Using the same utility estimates for the Olaparib and Control groups

Patients in the olaparib arm have an average decrease in mapped utility scores of [redacted] ([redacted] CB.3.4.5 Table 36) compared with the placebo group. The company argues that this difference is below the minimal clinically important difference (MCID) of 0.03 and not statistically significant. Establishing a MCID for the EQ-5D utility values has been highly contentious and non-consensual. The new DCO2 from July 2021, Figure 11 of the Clarification Question Response document shows that the quality of life scores had not converged after 2 years, with increasingly lower QoL scores in the QLQ-C30 for the olaparib arm compared with control at 2 years from baseline, albeit with confidence intervals (CIs) still slightly overlapping. There is the possibility that the detrimental effects in quality of life of olaparib continue for a period beyond administration of the treatment. The company has not produced updated mapped utilities using this additional data, which could have shown a bigger difference in mapped utility scores between arms at DCO2. Applying the estimated differences between arms in mapped utility scores at DCO1 produces minimal changes in the ICER.

The company includes instead decrements in utility due adverse events (anaemia and neutropenia, as discussed in Section 4.2.6.7). Disutility values were taken from the TA563 for anaemia and the literature for neutropenia, and durations are estimated using OlympiA data.(59, 60) However, it has ignored decrements in utility due to other side effects in the intervention arm, which could be responsible for the lower quality of life scores observed in the EORTC QLQ-C30 questionnaires and mapped utility scores. In response to Clarification Question B18 the company argued that the incidences of other grade ≥3 AEs were so low that incorporating disutilities for these would not materially change conclusions.(6) The EAG considered whether disutilities from adverse events spill over beyond the year of treatment, but accepts that the impact on the ICER would be low and accepts not to include them. Given its severity and published findings of a link with olaparib, the EAG raised a concern about not accounting for leukaemia in the model in Clarification Questions B19 and B20.(61) The company replied with evidence from DCO2, with median follow-up 3.5 years, that there was 1 leukaemia event in each of the two OlympiA arms. This incidence rate is low, so the EAG agrees with the company that inclusion of this leukaemia is unlikely to impact on the ICER.

Quality of life measurements for the OlympiA trial were collected routinely every 6 months up to recurrence for a maximum of 2 years. More patients in the control arm reported EORTC QLQ C30 scores than in the intervention arm ([redacted] vs [redacted] patients reported), corresponding to higher mapped utility scores (mean [redacted] [SD=[redacted]] vs mean [redacted] [SD=[redacted]]). This raw difference equates to 28 additional days in “perfect health” for

patients in the control arm after recurrence. Those data were not missing completely at random, but it would be possible to use multiple imputation methods controlling for known confounders and other outcome measures to impute missing values.(62) The differences observed between groups could have been higher in a complete dataset. Given that the potential side effects of olaparib would take place in the relatively short-term during the period of drug administration, the EAG agrees that the evidence that the differences in quality of life from taking olaparib will be persistent after recurrence are not strong, and both arms should have the same utility scores at the health states of metastatic and non-metastatic recurrence.

4.2.8 Resources and costs

4.2.8.1 Identification of resources

Resources identified by the company include:

i) Treatment-related costs
ii) Drug acquisition costs (including endocrine and subsequent therapies)
iii) Drug administration and monitoring costs
iv) Disease management costs
v) AE costs
vi) End of life care costs

All resources identified are NHS resources. The use of PSS was not discussed during the company's submission nor elicited from patients in the OlympiA trial or their clinical expert panel. It is unclear whether the source of end-of-life care costs includes PSS costs. It is likely that patients recovering from cancer, particularly in the more advanced stages of the disease, would have access to personal social services and specialist equipment. For example, in a recent trial of exercise to prevent shoulder problems after breast cancer surgery, the authors report on average £122 and £93 PSS costs with equipment per arm and other 'wider' costs of £148 and £262 in the year after surgery for the primary breast cancer tumour, for patients at high-risk of developing shoulder problems.(63) In the olaparib model, the additional PSS costs are likely to be relatively small and the impact on the ICER low, but by reducing recurrence, the EAG agrees that the estimates from the company are conservative on this aspect.

4.2.8.1.1 BRCA Testing

The company base case assumes that all patients in the TNBC and HR+/HER2- populations will receive routine BRCA testing and thus no costs of testing are included. The justification for this is given in Company Submission B 1.3.1.3 and in clarification response B.13. This refers to the NGTD criteria that are reproduced in Table 6, and which were discussed in Section 3.2.2.3. These indicate that TNBC patients aged less than 60 years would be eligible for BRCA testing, although the latest update to the online NGTD spreadsheet suggests that BRCA testing for all those with TNBC may start piloting.

The company also references i) a published multi-country (including UK) cost-effectiveness analyses that found population-based BRCA testing to be highly cost-effective; and ii) a stated ambition by the NHS to have one of the most advanced genomic healthcare ecosytems in the world.(1, 64-67) In the Clarification Response B.13, the company also referred to published evidence that the numbers receiving BRCA testing have increased in the UK each year.(6)

The EAG agrees that BRCA testing can be widely available in the NHS usual care pathway for TNBC in the near future.

However, none of the company's claims references and responses provide evidence that BRCA testing will become standard practice on the NHS for HR+/HER2-, and clinical advice received by the EAG was sceptical that the NHS would introduce population level BRCA testing as routine care in the near future. The observed increased uptake in BRCA testing is currently at patients' expense, rather than funded by the NHS, which could impose inequities in the access to olaparib if testing is not offered on the NHS for all HER2- patients. BRCA testing may not be needed only for Olaparib, and may allow tailoring of surgical approach for the patient and informing prophylactic management for the affected relative, but this would be additional value of BRCA testing rather than a justification for it not being needed in Olaparib prescribing.

The EAG therefore considers that the model for HR+/HER2- patients should include the cost of BRCA testing since olaparib is a BRCA targeting therapy. Results without BRCA testing costs are also presented, since the impact of the ICER would disappear once testing become widely available on the NHS for HR+/HER2-

KEY ISSUE: Access to BRCA testing in HR+/HER2-

4.2.8.2 Measurement of resource use

The company performed a review of the literature to retrieve relevant treatment costs, but all studies were excluded as they did not provide UK-specific cost or resource use.

Olaparib treatment resource use was informed by the OlympiA trial. Treatment for both TNBC and HR+/HER2- patients include 1 year adjuvant treatment with olaparib tablets at a dose of 300 mg twice daily administered until recurrence of disease, tolerability, or adverse events, or until completion of the 1 year treatment. In OlympiA, [redacted] patients had a slightly longer treatment duration (ranging from [redacted] days), which were attributed to interruptions in the treatment course. The model assumes that duration of treatment is limited to 1 year.

Time on treatment was measured in Kaplan Meier curves from the OlympiA trial patients and, as discussed in Section 4.2.6.1, applied for discontinuation of treatment in the model

(Figure 28 in CB.3.5.1.1 of the company's submission). The model has monthly cycles and assumes all tablets were used on months of discontinuation, to capture wastage. Clinical advice received by the EAG suggested that, if the patients appear well during the first 6 months, they could receive three-monthly prescriptions. If clinicians prescribe more than 4 weeks of treatment at any one time, the NHS could incur much higher costs of wastage than those estimated in the model; up to 6 full packs ([redacted]) wasted, for patients who discontinue in the latter 6-months. There is no good quality evidence on clinical prescribing practices that would better inform the costs of wastage, so the EAG accepts this limitation of the model and the company's assumption on wastage.

After discontinuation or completion of treatment, patients are assumed to undergo watch and wait until recurrence. 'Watch and wait' comprises of monitoring and surveillance for disease recurrence. No drug costs were assigned to patients on 'watch and wait'. The resource utilisation for 'watch and wait' were captured in the costs of disease management and monitoring assigned to the iDFS health state. These costs were applied to both arms of the model. Community care resources with surveillance and monitoring were elicited from the clinical expert panels. Resources related to managing side effects of the olaparib drug in the community in the iDFS state were not discussed and are not included. We expect the impact of this omission would be very minor.

HR+/HER2- patients receive additional adjuvant endocrine therapy until disease recurrence, death, or a maximum number of years. The model assumes that 90% of the HR+/HER2- patients receive adjuvant endocrine therapy, split equally between letrozole and anastrozole for a maximum duration of 10 years, and 10% receive tamoxifen. Clinical advice received by the EAG deemed reasonable to assume that some patients will not be able to tolerate endocrine therapy; and the choice between these treatments is likely to be informed by menopausal status, and that split is sensible.

Use of additional drugs and chemotherapy in health states of non-metastatic and metastatic BC recurrence were obtained from protocols and clinical guidelines or elicited from a panel of experts, with some of the duration and number of lines of treatment informed by the OlympiAD study.(1) Treatments available are numerous and dependent on whether patients have failed previous treatment lines. Sourcing resource use from protocols and guidelines rather than evidence for duration and intensity of treatments may over-estimate health care costs in these health states and thus the costs of BC recurrence, biasing the results in favour of the intervention. Clinical expert evidence for "market shares"(the proportion of patients who receive these treatments) is not strong, with a large uncertainty associated to estimates proposed.

The use of radiotherapy and surgery for non-metastatic BC were informed by the proportion of patients who went on to have these treatments in the OlympiA trial. These resources as well as surgery for metastatic BC were informed by clinical experts' opinion for the

metastatic BC health states, most likely due to too few patients achieving these health states in the OlympiA trial.

4.2.8.3 Valuation of resources

Unit costs were sourced from NHS reference costs, the Person Social Services Research Unit (PSSRU), the BNF and the pharmaceutical electronic market information tool (eMIT) as appropriate and in line with the NICE reference case.

Olaparib drug costs were supplied by the company, including confidential discounted prices. Prices for other drugs were obtained from the BNF, which report full drug costs. For the purposes of this appraisal, the EAG obtained discounted PAS and Comercial Access Agreement (CAA) access scheme costs for the additional drugs used in the model.

One-off costs due to the adverse events anaemia and neutropenia were included and sourced from the NHS reference costs.

Radiotherapy and further surgery costs for non-metastatic BC were informed by estimates reported in Sun et al 2020, an English observational study on women aged 50 years or older (mean age 67 years) between Jan 2014 and Dec 2015,(68) inflated to 2021 prices. Sun 2020 collected resource use and costs for one year after breast cancer diagnosis but explicitly excluded patients with metastatic breast cancer and costs of recurrence; this is therefore not an adequate source for resource use in the recurrence health states of the model. The EAG explored the possibility of using different sources of costs for the metastatic BC health states, including updating estimates from the literature from UK studies in breast cancer such as eRAPID and PERSEPHONE.(69, 70) The costs for metastatic health states are based on an older study, the OPTIMA prelim trial, which did not include treatments with the new CDK4/6 inhibitors.(71) These costs are therefore also unsuitable to inform the model. These costs, however, have a small impact on the ICER and in the absence of a better source of costs, the EAG accepts the company's cost estimates.

Further surgery for metastatic BC were valued using NHS 2019/20 reference costs for the "Stereotactic Intracranial Radiosurgery, for Neoplasms or Other" health care resource group code. There was no justification for using health care resource groups related to brain surgery alone. Clinical advice received by the EAG included treatment for bone metastases, whereby patients might undergo prophylactic operations to stabilise bone. Given that a small proportion of patients undergo further surgeries in the more advanced stages of cancer, it is likely that a change in costs due to different assumptions regarding which health care resource groups costs are applied would have minimal impact on the ICER, and EAG did not consider this a key issue.

End-of-life costs were obtained from previous NICE submissions and the source was not clear. These include costs in the last year of life in hospital and social hospice, hospice, and

home. The EAG considers these costs reasonable and in line with other sources of costs for end-of-life care for cancer. (72, 73)

5 COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

The company's base case deterministic results in TNBC are reproduced in Table 17 and for HR+/HER2- in Table 18. The probabilistic results are in TNBC are reproduced in Table 19 and for HR+/HER2- in Table 20. These are from the DCO2 results provided as part of Company Clarification Response Appendix 2.(6) The incremental QALYs and incremental costs were higher on olaparib than on the placebo ("watch and wait") comparator in both TNBC and HR+/HER2- and under both deterministic and probabilistic analyses. In TNBC the deterministic ICER was £35,855/QALY and in HR+/HER2- the ICER was £41,879/QALY. The probabilistic ICERs were marginally lower, with £34,685/QALY in TNBC and £40,293/QALY in HR+/HER2-.

TABLE 17 COMPANY DETERMINISTIC BASE CASE RESULTS (TNBC, OLAPARIB PAS PRICE) (FROM COMPANY CLARIFICATION RESPONSES TABLE 30)(6)

Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY gained)
Placebo ("watch & wait")	[redacted]	[redacted]	[redacted]				
Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£35,855

TABLE 18 COMPANY DETERMINISTIC BASE CASE RESULTS (HR+/HER2-, OLAPARIB PAS PRICE) (FROM COMPANY CLARIFICATION RESPONSES TABLE 31)(6)

Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY gained)
Placebo ("watch & wait")	[redacted]	[redacted]	[redacted]				
Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£41,879

TABLE 19 COMPANY PROBABILISTIC BASE CASE RESULTS USING 1000 SAMPLES (TNBC) (FROM COMPANY CLARIFICATION RESPONSES TABLE 32)(6)

Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY gained)
Placebo ("watch & wait")	[redacted]	[redacted]	[redacted]				

Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£34,685**

TABLE 20 COMPANY PROBABILISTIC BASE CASE RESULTS USING 1000 SAMPLES (HR+/HER2-) (FROM COMPANY CLARIFICATION RESPONSES TABLE 33)(6)

Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY gained)
Placebo ("watch & wait")	[redacted]	[redacted]	[redacted]				
Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£40,293**

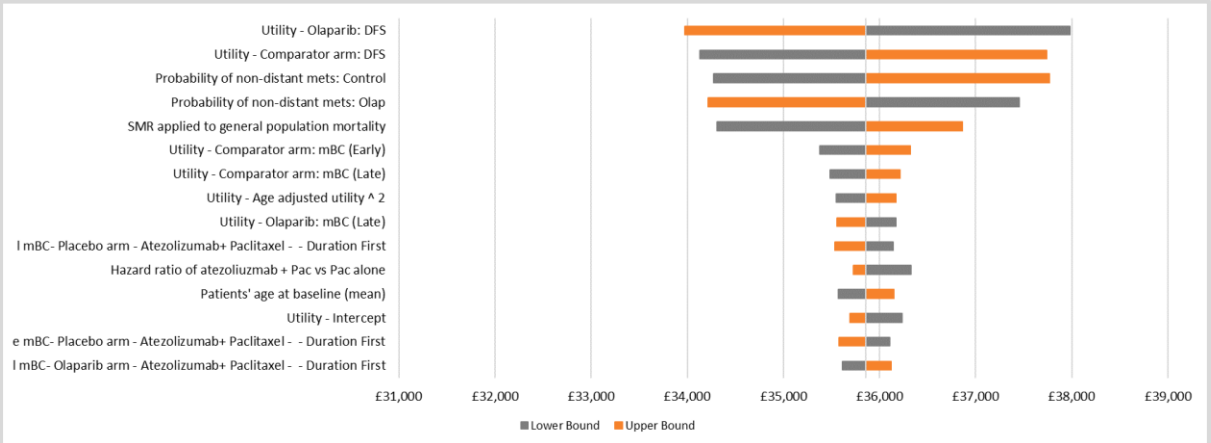
5.2 Company's sensitivity analyses

5.2.1 Company's deterministic sensitivity analysis

The company presented deterministic one way sensitivity analyses (OWSA) in both populations where each uncertain parameter was set to its lower and upper bounds and the ICER reported. Results are reproduced for TNBC in Figure 9 and for HR+/HER2- in Figure 10.

In TNBC the most influential parameters are the DFS utilities on olaparib and placebo, the probabilities of non-distant metastasis on both treatments (i.e., TP1), and the SMR applied to the general population mortality (i.e., TP3). In absolute terms these only shift the ICER down by approximately £1,000/QALY and up by £2,000/QALY.

FIGURE 9 DETERMINISTIC ONE-WAY SENSITIVITY ANALYSES FOR COMPANY BASE CASE (TNBC) (REPRODUCED FROM COMPANY CLARIFICATION RESPONSES FIGURE 28)(6)

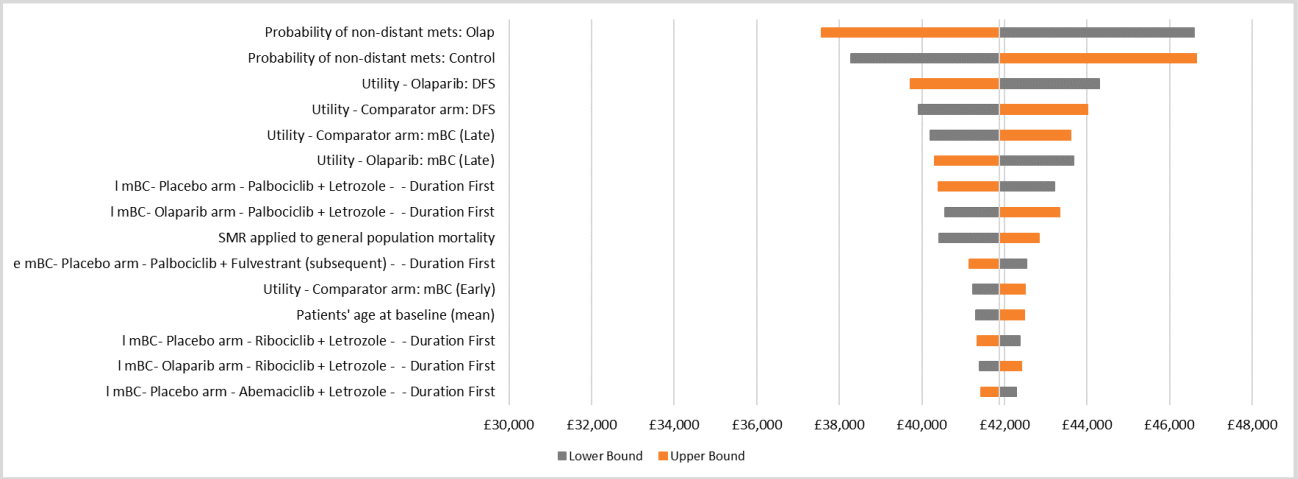


Abbreviations: DFS: disease-free survival; e-mBC: 'early onset' metastatic breast cancer; l-mBC: 'late onset' metastatic breast cancer; SMR: standardised mortality ratio; TNBC: triple negative breast cancer

In HR+/HER2- the most influential parameters are the probabilities of non-distant metastasis on olaparib and placebo (i.e., TP1). These increase and decrease the ICER by approximately £4,000/QALY. Of secondary, but still substantial, importance are the utilities in DFS and late mBC on both treatments, the duration of first-line therapy with

Palbociclib+letrozole in mBC, and the SMR applied to general mortality (i.e., TP3). These increase and decrease the ICER by £1,000-2,000/QALY.

FIGURE 10 DETERMINISTIC ONE-WAY SENSITIVITY ANALYSES FOR COMPANY BASE CASE (HR+/HER2-) (REPRODUCED FROM COMPANY CLARIFICATION RESPONSES FIGURE 29)(6)



Abbreviations: DFS: disease-free survival; e-mBC: 'early onset' metastatic breast cancer; l-mBC: 'late onset' metastatic breast cancer; SMR: standardised mortality ratio; HER2: human epidermal growth factor 2; HR: hormone receptor

5.2.2 Company's probabilistic sensitivity analysis

The ICERs for the probabilistic sensitivity analysis using 1000 samples were presented for TNBC in Table 19 and for HR+/HER2- in Table 20. The cost-effectiveness acceptability curve (CEAC) for TNBC is reproduced in Figure 11. This indicates that olaparib has a lower probability than placebo of having the greatest monetary net benefit up to about £[redacted]QALY. In the range £30-40,000/QALY there is at least [redacted] that each treatment has greatest monetary net benefit, again indicating high parameter uncertainty.

FIGURE 11 COMPANY COST-EFFECTIVENESS ACCEPTABILITY CURVE, OLAPARIB VS. PLACEBO SAMPLES ("WATCH & WAIT") USING 1000 (TNBC) (FROM COMPANY CLARIFICATION RESPONSES FIGURE 25)(6)

The cost-effectiveness acceptability curve for HR+/HER2- is reproduced in Figure 12. This indicates that olaparib has a lower probability than placebo of having the greatest monetary net benefit up to about £ QALY. In the range £40-50,000/QALY there is at least chance that each treatment has greatest monetary net benefit, indicating high parameter uncertainty.

FIGURE 12 COMPANY COST-EFFECTIVENESS ACCEPTABILITY CURVE, OLAPARIB VS. PLACEBO ("WATCH & WAIT") USING 1000 SAMPLES (HR+/HER2-) (FROM COMPANY CLARIFICATION RESPONSES FIGURE 27)(6)

5.2.3 Company's scenario analyses

The company ran the scenario analyses summarised in Table 21. Using a 1.5% discount rate (Section 4.2.5) had a substantial impact on the ICER in both populations.

In the TNBC population, the scenarios that had greatest impact on the ICER were the selection of parametric survival distribution for transitions from early onset mBC to death (i.e., TP6) and the choice of utility values for the three health states (Table 21).

There was greater sensitivity to scenario analyses in the HR+/HER2- population Table 21. The scenarios that had greatest impact on the ICER were the inclusion of BRCA testing costs, the selection of parametric survival distribution for iDFS (i.e., TP1 and TP2), the selection of parametric survival distribution for transitions from early onset mBC to death (i.e., TP6), and the choice utility values for the three health states.

TABLE 21 COMPANY SCENARIO ANALYSIS RESULTS (DISCOUNTED, TNBC & HR+/HER2- ANALYSES) (FROM COMPANY CLARIFICATION RESPONSES TABLE 34)(6)

Scenario	Base case value	Scenario analysis value	ICER (£/QALY) (TNBC)	ICER (£/QALY) (HR+/HER2-)
Base case	**–**	**–**	**£35,855**	**£41,879**
Discount rate	*3.5%*	*1.5%*	*£25,287*	*£30,564*
Time horizon	*57 years*	*40 years*	*£37,052*	*£42,883*
		50 years	*£35,916*	*£41,928*

Scenario	Base case value	Scenario analysis value	ICER (£/QALY) (TNBC)	ICER (£/QALY) (HR+/HER2-)
Time point for determining early vs. late recurrence	*2 years*	*1 year*	*£35,395*	*£41,571*
		3 years	*£36,220*	*£42,227*
Include wastage for IV and SC treatments	*Yes*	*No*	*£35,869*	*£41,878*
Include BRCA testing costs	*No*	*Yes*	*£37,010*	*£47,249*
TNBC: time point at which patients are no longer at a risk of recurrence	*5 years*	*3 years*	*£37,885*	*–*
		7 years	*£35,599*	*–*
		10 years	*£36,074*	*–*
TNBC: risk of recurrence after 5 years	*0%*	*10-year probability of recurrence of 5%*	*£37,961*	*–*
Age-adjusted utilities	*Yes*	*No*	*£32,996*	*£38,828*
Apply end-of-life costs to all deaths	*No*	*Yes*	*£35,981*	*£41,980*
TP1/TP2: conditional prob. Recurrence	*Combined treatment arms*	*By individual treatment arms*	*£35,524*	*£41,030*
TP1/TP2 distribution	*Lognormal*	*Loglogistic*	*£35,306*	*£45,817*
		Gompertz	*£36,562*	*£36,981*
		Generalised gamma	*£37,153*	*£46,430*
TP4 distribution	*Lognormal*	*Loglogistic*	*£35,728*	*£41,738*
		Exponential	*£35,700*	*£41,700*
TP5 distribution	*Exponential*	*Lognormal*	*£36,006*	*£42,063*
		Loglogistic	*£35,972*	*£42,020*
TP6 distribution	*Exponential*	*Loglogistic*	*£37,488*	*£44,149*
		Gompertz	*£36,917*	*£43,352*
		Lognormal	*£37,341*	*£43,942*
TP6: assume the same risk of death across arms	*No*	*Yes*	*£34,944*	*£40,624*
TP7 distribution: chemotherapy	*Lognormal*	*Loglogistic*	*£35,907*	*£41,879*
		Weibull	*£35,780*	*£41,877*
		Generalised gamma	*£35,852*	*£41,879*
TP7 distribution: CDK4/6 inhibitor	*Loglogistic*	*Lognormal*	*–*	*£41,889*
		Weibull	*–*	*£41,850*
		Generalised gamma	*–*	*£41,876*
Utility values		*Scenario 1:*	*£39,238*	*£45,840*

Scenario	Base case value	Scenario analysis value	ICER (£/QALY) (TNBC)	ICER (£/QALY) (HR+/HER2-)
	PF: 0.869 (Crott & Briggs 2010) Non-mBC: 0.869 (same as DF) mBC: 0.685 (Lidgren 2007)	*PF: 0.802 (Longworth 2014 algorithm) Non-mBC: 0.802 (same as DF) mBC: 0.685 (Lidgren 2007)*		
		Scenario 2: (same as base case) PF: 0.869 Non-mBC: 0.869 (same as base case) mBC: 0.521 (Lloyd 2006)	*£34,883*	*£40,723*
		Scenario 3: (Lidgren 2007 for all) PF: 0.779 Non-mBC: 0.779 mBC: 0.685	*£40,552*	*£47,379*
HR+/HER2-: Duration of adjuvant endocrine therapy	*10 years*	*5 years*	*–*	*£41,871*
		7 years	*–*	*£41,874*

5.3 Model validation and face validity check

5.3.1 Company validation and face validity check

The company's approach is described in CS B.3.10.

The company sought validation of their overall approach by three UK health economists. This could perhaps have been supplemented by input from clinicians with subject matter expertise.

Extensive quality control was conducted by the Company using four internal health economic modellers and a third-party vendor.
The external vendor review assessed face validity, model settings, sensitivity analyses, formulae, macros, and data sources. Extreme value and logic tests were conducted.

Model inputs were based, where possible, on OlympiA trial data and on UK empirical literature if none was available. In cases where UK empirical literature was used, it was informed and/or validated by external clinical expert opinion through two rounds of interviews.

External validity of model inputs and outputs was assessed where data were available, in particular as a criteria for model selection. Although the EAG disagreed with their selected distribution (Section 4.2.6.2), the company should be commended for using empirical data to validate the long-term recurrence rate model for HR+/HER2-.

5.3.2 EAG validation and face validity check

The EAG checked the model Excel file to ensure results matched those in the report, that all settings worked and modified results as expected, and checked for hidden sheets, rows, columns and dependencies on other files required to run the analyses. The Probabilistic Senstivity Analysis (PSA) calculations would only generate a CEAC if the "PSA Calcs" tab was unhidden. Furthermore, the probabilistic ICER was found to vary by roughly £[redacted] QALY when 1000 samples were used. We therefore used 10,000 samples for our final base case analyses. No other issues identified.

Face validity was assessed by changing time horizons, discount rates, survival models and checking the estimated costs and QALYs changed as expected. The EAG also received clinical advice on the model structure; advisers agreed it had face validity.

The EAG checked cell formula and Visual Basic for Applications (VBA) code to ensure they matched those described in the company submission. Particular attention was paid to the Markov trace calculations in tabs Trace1, Trace2, "TP Matrix1", and "TP Matrix2", as the 5-state semi-Markov model was implemented as Markov model with 720 Markov states for each of the 5 semi-Markov states (3600 Markov states in total). Two issues were identified and addressed during clarification questions.

Clarification question B6 identified that rates for TP6 and TP7 were reversed in "TP Matrix1" and "TP Matrix2" but that this was again reversed by a later labelling issue. The company corrected this error in the updated model based on DCO2.

In Clarification Question B6 the EAG raised that formulae in "TP Matrix1" and "TP Matrix2", and described in Company Submission Appendix N.1, incorrectly multiplies instantaneous hazards of recurrence by probability that the recurrence is non-metastatic. The correct formula should multiply probabilities only with other probabilities. The company responded that the two formulae give the same answer. The EAG agrees but notes it is due to the hazards being very small and thus matching probabilities, rather than the company's formula being correct.

In the final base case model, the EAG also corrected the Scenario Analyses in 'SA' tab to reflect settings in the 'Settings' and 'Efficacy' tabs. This required a macro that updated scenario values (columns 3, 6, and 9) and the defaults (13, 14, 15) in the 'SA' tab.

6 EVIDENCE ASSESSMENT GROUP'S ADDITIONAL ANALYSES

6.1 Exploratory and sensitivity analyses undertaken by the EAG

The EAG has performed additional work to explore the main drivers of cost-effectiveness and the uncertainties around the economic model. In this section we describe which areas of uncertainty were explored, describe the EAGs preferred assumptions, and additional sensitivity analyses. Results are presented in Sections 6.3 and 6.4.

6.1.1 Increasing the number of PSA samples for base case results

The model was found to produce a highly variable ICER under probabilistic analysis when only 1,000 samples are used, with the ICER changing by up to £[redacted]/QALY between runs. We therefore used 10,000 samples for the base case probabilistic analyses. Each analysis (e.g., EAG base case for TNBC) took more than 5 hours to run on an up-to-date computer.

6.1.2 Varying the transition probabilities assumptions:

- Changing the parametric distributions for TP1/2 and TP6 using the scenario explored by the company (Section 5.2.3) and the option implemented in the model.
- On the transition from mBC state to death (TP7) in TNBC and HR+/HER2- changed the case mixes (% weights) of patients assigned to single chemotherapy (OlympiAD), CDK4/6 plus endocrine (Collins 2021/Flatiron) in HR+/HER2-, and atezolizumab + paclitaxel (Impassion 130) in TNBC. Extreme scenarios were presented switching proportions to 100% and 0% on each option in TNBC and HR+/HER2-.
- Added scenarios using SMR of 1.00 from Clèries 2022 and 2.00 from Levi et al. (2002) for non-cancer related mortality from iDFS due to BRCA status.(42) (45)

6.1.3 Varying the cost assumptions:

- Including BRCA testing using a scenario explored by the company (Section 5.2.3) and the option implemented in the model.
- Apply PAS and CAA discounted costs on drugs used as different treatment alternatives in the recurrence states
- To represent the sensitivity to different market allocations on drug treatments on the recurrence states, we increased and decreased the drug acquisition and administration costs in early and late mBC by 20%.

6.1.4 Varying the utility assumptions:

- We modified the model to allow the non-mBC utility to be set to the midpoint level between PF and mBC. For the PSA, the standard error was calculated using the formula

$$SE_{non-mBC} = \sqrt{SE_{PF}^2 + SE_{mBC}^2}$$

Where zero correlation is assumed between the PF and mBC estimates. This may be violated but has little impact on the probabilistic ICER.

- We applied Verrill 2020 utility estimates the PF and mBC states (58)
- In sensitivity analysis, use Longworth 2014 algorithm used on OlympiA patients for iDFS, and Lidgren 2007 for mBC and set non-mBC health state to a midpoint level between the two other health states.(53, 57)
- In sensitivity analysis, use Lidgren 2007 for all health states, as per company's SA3.(57)

6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the EAG

The impact of additional cost-effectiveness analyses undertaken by the EAG on the ICER are incorporated in the EAG's preferred assumptions and described in detail in Section 6.3 below.

6.3 EAG's preferred assumptions

The EAG's preferred assumptions and, where they differ from the company base case, their cumulative effects on the ICER are presented for both populations in Table 22.

In both populations, the greatest driver of the ICER change was the adoption of Verrill 2020 utilities to inform the disease-free (DF) and mBC health states HRQoL utilities.(58) This increased the ICER by >£7,000/QALY in TNBC and and >£9,000 in HR+/HER2-.

Otherwise, the greatest driver for TNBC was the inclusion of a risk of recurrence after 5 years of 5% over the following 10 years. This was followed by the impact of changing the distribution for early onset mBC to death (i.e., TP6) from exponential to Gompertz, and using a different utility score in non-mBC to DF. The last of these had almost no impact on the ICER.

In HR+/HER2- the greatest drivers, other than changing the source for utilities, were the inclusion of BRCA testing costs (increased the ICER by ~£7,000/QALY) and changing the risk of recurrence distribution (i.e., TP1/2) to generalised Gamma (increased ICER by ~£4,500/QALY). As in TNBC, changing the distribution for early onset mBC to death (i.e., TP6) from exponential to Gompertz and using a different utility score in non-mBC to DF had less impact on the ICER.

TABLE 22 EAG'S PREFERRED MODEL ASSUMPTIONS.

Preferred assumption	Company base-case	Section in EAG report (Relevant section of CS)	Cumulative ICER (£/QALY) TNBC	Cumulative ICER (£/QALY) HR+/HER2-
Company base-case			***£35,855*** ***PSA: £34,685***	***£41,879*** ***PSA: £40,293***
EAG varying transition probabilities				
Time point for determining early vs. late recurrence is at 2 years	Same	Section 4.2.2 (CS B.3.2.2.2)	NA	NA
TNBC: time point at which patients are no longer at a risk of recurrence at 5 years	Same	Section 4.2.6.1 (CS B.3.3.3.1)	NA	NA
TNBC: risk of recurrence after 5 years is 5% over following 10 years	0%	Section 4.2.6.1	£37,961	NA
TP1/TP2: conditional prob. Recurrence by combined arms (i.e. not depend on treatment arms)	Same	Section 4.2.6.1	NA	NA
TP1/TP2 distribution is lognormal in TNBC and generalised gamma in HR+/HER2-	Lognormal in TNBC and HR+/HER2-	Section 4.2.6.1	NA	£46,430
TP4 distribution is lognormal	Same	Section 4.2.6.4	NA	NA
TP5 distribution is lognormal	Same	Section 4.2.6.4	NA	NA
TP6 distribution is Gompertz	Exponential	Section 4.2.6.5	£39,157	£48,288
TP6: assume different risk of death across arms	Same	Section 4.2.6.5	NA	NA
TP7 distribution: chemotherapy is lognormal	Same	Section 4.2.6.6	NA	NA
HR+/HER2- only. TP7 distribution: CDK4/6 inhibitor is loglogistic	Same	Section 4.2.6.6	NA	NA

Preferred assumption	Company base-case	Section in EAG report (Relevant section of CS)	Cumulative ICER (£/QALY) TNBC	Cumulative ICER (£/QALY) HR+/HER2-
HR+/HER2-: Duration of adjuvant endocrine therapy is 10 years	Same	NA	NA	NA
EAG varying utilities				
Utility values follow Verrill 2020 DF: 0.732 (SE=0.021) Non-mBC: same as DF mBC: 0.603 (SE=0.03)	PF: 0.869 (SE=0.002) Non-mBC: 0.869 (SE=0.002) mBC: 0.685 (SE=0.03) (Crott&Briggs 2010 and Lidgren 2007)	Section 4.2.7.1 and Section 4.2.7.2	£46,835	£57,787
Utilities the same in both olaparib and placebo arms but with disutilities due to AEs	Same	Section 4.2.7.4	NA	NA
Utility values are different across DF and non-mBC. Set to mid-point of DF and mBC, which is 0.6675 (SE=0.0345)	Assumed utilities in PF and non-mBC were the same	Section 4.2.7.3	£46,549	£57,443
EAG varying costs				
TNBC: Don't include BRCA testing costs	Same	Section 4.2.8.1.1Resources and costs	NA	NA
HR+/HER2-: Include BRCA testing costs	Didn't include testing costs	Section Resources and costs4.2.8.1.1	NA	£64,773
EAG Preferred base case			**£46,549** **PSA: £46,142**	**£64,773** **PSA: £59,592**

PSA=Probabilistic Sensitivity Analysis results. Used 10,000 samples for final EAG preferred base case. Company used 1,000 samples for their base case.

6.4 EAG's cost-effectiveness results

The EAG deterministic base case results for TNBC are presented in Table 23 and for HR+/HER2- in Table 24. Probabilistic results based on 10,000 samples are presented for

TNBC in Table 25 and for HR+/HER2- in Table 26. In both populations, and under both deterministic and probabilistic analysis, the life year gained (LYG), QALYs, and costs are all higher on olaparib than on placebo. In TNBC the deterministic ICER is £46,549/QALY and in HR+/HER2- is £64,773/QALY. In TNBC the probabilistic ICER is £46,142/QALY and in HR+/HER2- is £59,592/QALY.

TABLE 23 EAG DETERMINISTIC BASE CASE RESULTS (TNBC, OLAPARIB PAS PRICE)

Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY gained)
Placebo ("watch & wait")	[redacted]	[redacted]	[redacted]				
Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£46,549

TABLE 24 EAG DETERMINISTIC BASE CASE RESULTS (HR+/HER2-, OLAPARIB PAS PRICE)

Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY gained)
Placebo ("watch & wait")	[redacted]	[redacted]	[redacted]				
Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£64,773

TABLE 25 EAG PROBABILISTIC BASE CASE RESULTS (TNBC, OLAPARIB PAS PRICE). USING 10,000 SAMPLES.

Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY gained)
Placebo ("watch & wait")	[redacted]	[redacted]	[redacted]				
Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£46,142

TABLE 26 EAG PROBABILISTIC BASE CASE RESULTS (HR+/HER2-, OLAPARIB PAS PRICE). USING 10,000 SAMPLES.

Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY gained)
Placebo ("watch & wait")	[redacted]	[redacted]	[redacted]				
Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£59,592

6.4.1 EAG base case deterministic and probabilistic sensitivity analyses

The CEAC based on 10,000 samples for the EAG base case in TNBC is presented in Figure 13. If the NHS is willing to pay between £20,000 and 30,000 per additional QALY, the probability that olaparib is cost-effective is below [redacted]. The cost-effectiveness plane in Figure 14 indicates although olaparib produces higher health benefits on average, there is a relatively small probability that it could be a dominated treatment option (i.e., more costly and less effective than the "watch and wait" treatment option). In all simulations the costs on olaparib were more than [redacted] greater than on Placebo ("watch & wait").

The deterministic one-way sensitivity analyses in Figure 15 indicate that the utilities in DFS have by far the greatest impact on the ICER of the EAG base case, aligning with the impact indicated by changing the source for these utilities from the company base case in Table 22. Varying the utility on olaparib can decrease the ICER to £25,000/QALY but can also increase it to over £160,000/QALY.

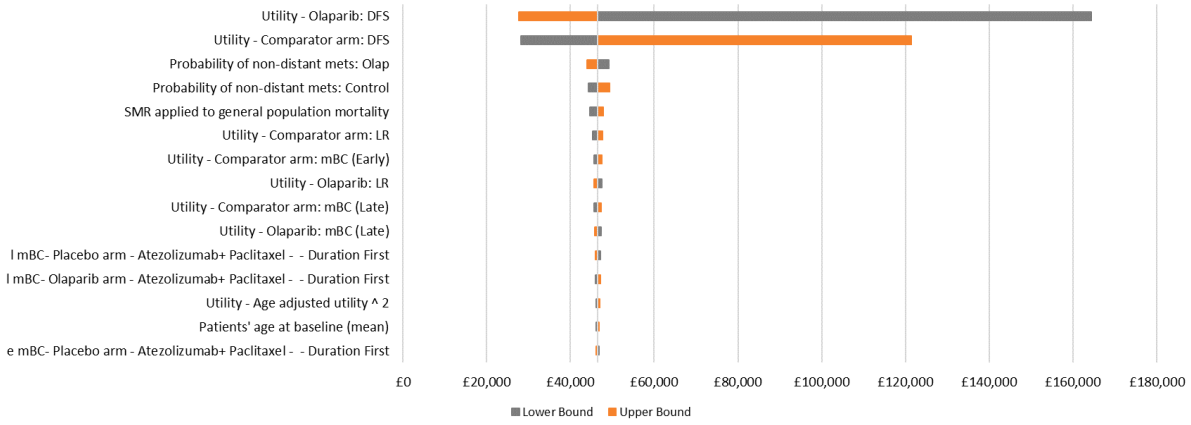
FIGURE 13 EAG BASE CASE COST-EFFECTIVENESS ACCEPTABILITY CURVE, OLAPARIB VS. PLACEBO ("WATCH & WAIT") (TNBC). USING 10,000 SAMPLES.

[redacted]

FIGURE 14 EAG BASE CASE COST-EFFECTIVENESS PLANE (TNBC). USING 10,000 SAMPLES.

[redacted]

FIGURE 15 DETERMINISTIC ONE-WAY SENSITIVITY ANALYSES FOR EAG BASE CASE. (TNBC).



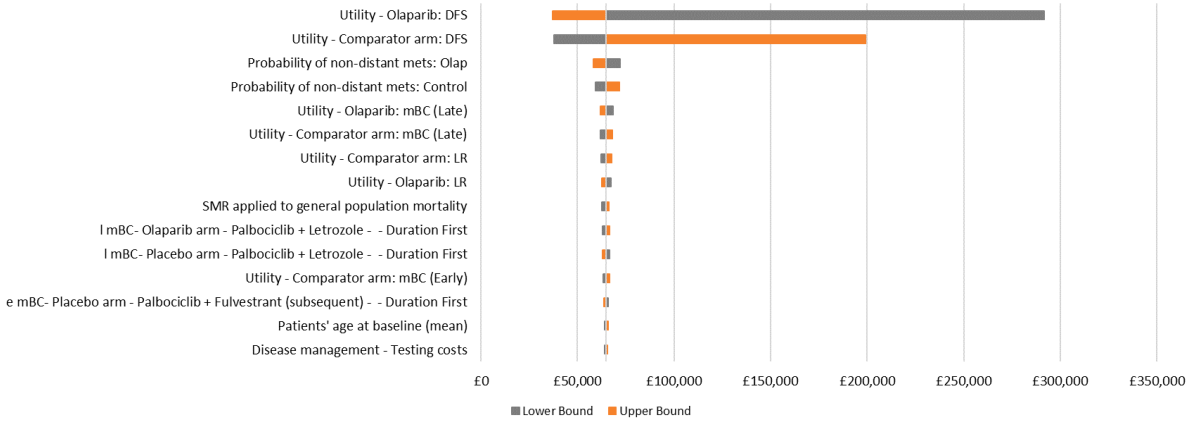
The cost-effectiveness results for the HR+/HER2- population reflect the additional uncertainty around this population. The CEAC using 10,000 samples for the EAG base case in HR+/HER2- is presented in Figure 16. If the NHS is willing to pay between £20,000 and £30,000 per additional QALY, the probability that olaparib is cost-effective is up to [redacted]. The cost-effectiveness plane in Figure 17 indicates that, although a majority of incremental effects are positive for olaparib, there is a probability that the health benefits are lower for the olaparib group, resulting it being a dominated treatment option. In all simulations the costs on olaparib were more than [redacted] greater than on "watch & wait".

The deterministic one-way sensitivity analyses in Figure 18 indicate that the utilities in DFS have by far the greatest impact on the ICER of the EAG base case. As in TNCB this aligns with the impact indicated by changing the source for these utilities from the company base case in Table 22. Varying the utility on olaparib can decrease the ICER to £30,000/QALY but can increase it to nearly £300,000/QAY.

FIGURE 16 EAG BASE CASE COST-EFFECTIVENESS ACCEPTABILITY CURVE, OLAPARIB VS. PLACEBO ("WATCH & WAIT") (HR+/HER2-). USING 10,000 SAMPLES.

FIGURE 17 EAG BASE CASE COST-EFFECTIVENESS PLANE (HR+/HER2-). USING 10,000 SAMPLES.

FIGURE 18 DETERMINISTIC ONE-WAY SENSITIVITY ANALYSES FOR EAG BASE CASE (HR+/HER2-)



Additional sources of uncertainty for the HR+/HER2- population include whether it is appropriate to use estimates for the full TNBC and HR+/HER2- population combined from the OlympiA trial, when these estimates are dominated by the TNBC population, and whether BRCA testing will be widely available on the NHS soon. If we assume BRCA testing would be available for this population, the deterministic ICER is £57,443/QALY (Table 22 of this report), considerably lower than the EAG base case.

6.4.2 EAG base case with company scenario analyses

The EAG reproduced the (deterministic) scenario analyses presented by the company and summarised in Section 5.2.3.

TABLE 27 EAG BASE CASE WITH COMPANY SCENARIO ANALYSIS RESULTS (DISCOUNTED, TNBC & HR+/HER2- ANALYSES) (BASED ON COMPANY CLARIFICATION RESPONSES TABLE 34)

Scenario	Base case value	Scenario analysis value	ICER (£/QALY) (TNBC)	ICER (£/QALY) (HR+/HER2-)
Base case	–	–	***£46,549***	***£64,773***
Discount rate	*3.5%*	*1.5%*	£33,210	£47,595
Time horizon	*57 years*	*40 years*	£47,906	£66,299
		50 years	£46,616	£64,849
Time point for determining early vs. late recurrence	*2 years*	*1 year*	£45,411	£63,347
		3 years	£47,432	£66,107
Include wastage for IV and SC treatments	*Yes*	*No*	£46,566	£64,772
Include BRCA testing costs	*TNBC: No* HR+/HER2-: Yes	*TNBC: Yes* HR+/HER2-: No	£48,047	£57,443

Scenario	Base case value	Scenario analysis value	ICER (£/QALY) (TNBC)	ICER (£/QALY) (HR+/HER2-)
TNBC: time point at which patients are no longer at a risk of recurrence	*5 years*	*3 years*	£49,727	-
		7 years	£45,814	-
		10 years	£45,920	-
TNBC: risk of recurrence after 5 years	*10-year probability of recurrence of 5%*	0%	£45,086	£45,086
Age-adjusted utilities	*Yes*	*No*	£42,970	£60,201
Apply end-of-life costs to all deaths	*No*	*Yes*	£46,692	£64,896
TP1/TP2: conditional prob. recurrence	*Combined treatment arms*	*By individual treatment arms*	£46,047	£63,486
TP1/TP2 distribution	*TNBC: Lognormal HR+/HER2-: Generalized gamma*	*Loglogistic*	£45,782	£63,770
		Gompertz	£47,569	£51,388
		Generalised gamma	£48,284	-
		Lognormal	-	£58,204
TP4 distribution	*Lognormal*	*Loglogistic*	£46,394	£64,570
		Exponential	£46,364	£64,524
TP5 distribution	*Exponential*	*Lognormal*	£46,740	£65,057
		Loglogistic	£46,697	£64,992
TP6 distribution	*Gompertz*	*Loglogistic*	£47,358	£66,230
		Exponential	£45,053	£62,122
		Lognormal	£47,150	£65,862
TP6: assume the same risk of death across arms	*No*	*Yes*	£44,578	£61,379
TP7 distribution: chemotherapy	*Lognormal*	*Loglogistic*	£46,606	£64,772
		Weibull	£46,469	£64,774
		Generalised gamma	£46,546	£64,773
TP7 distribution: CDK4/6 inhibitor	*Loglogistic*	*Lognormal*	-	£64,754
		Weibull	-	£64,818
		Generalised gamma	-	£64,776
*Utility values (Company base case and scenarios)**	*PF: 0.703 Non-mBC: 0.653 mBC: 0.603*	*Company base case: PF: 0.869 Non-mBC: 0.869 mBC: 0.685*	£39,157	***£54,449***
		Scenario 1: Using Longworth 2014 mapping algorithm PF: 0.802	£42,131	***£58,563***

Scenario	Base case value	Scenario analysis value	ICER (£/QALY) (TNBC)	ICER (£/QALY) (HR+/HER2-)
		Non-mBC: 0.802 *mBC: 0.603*		
		Scenario 2: Using Crott & Briggs 2010 mapping algorithm *PF: 0.869* *Non-mBC: 0.869* *mBC: 0.521*	£37,743	***£52,369***
		Scenario 3: Using Lidgren 2007 published utilities *PF: 0.779* *Non-mBC: 0.779* *mBC: 0.685*	£44,496	***£61,947***
HR+/HER2-: Duration of adjuvant endocrine therapy	*10 years*	*5 years*	–	£64,764
		7 years	–	£64,768

* Scenario 1: DF based on OlympiA patients EORTC responses mapped to EQ-5D utilities using Longworth 2014 mapping algorithm, non-mBC set to DF, mBC based on Verrill 2020 as in EAG base case; Scenario 2: DF based on OlympiA patients EORTC responses mapped to EQ-5D utilities using Crott & Briggs 2010 mapping algorithm, non-mBC set to DF, mBC based on Lloyd et al; Scenario 3: All utilities based on published EQ-5D utilities from Lidgren 2007.

6.4.3 EAGs additional scenario analyses

Results of the EAG additional exploratory deterministic scenario analyses described in Section 6.1, and not covered by the company scenario analyses of Table 27, are provided in Table 28. Again, the utilities are found to have greatest impact on the ICER. Changing the mortality SMR for DF, the TP7 case mixes, and the drug acquisition and administration costs had little impact on the ICER.

TABLE 28 EAG DETERMINISTIC SCENARIO ANALYSIS RESULTS MODIFYING FROM EAG PREFERRED BASE CASE (DISCOUNTED, TNBC & HR+/HER2- ANALYSES)

Scenario (Relevant section of EAG report)	Base case value	Scenario analysis value	ICER (£/QALY) (TNBC)	ICER (£/QALY) (HR+/HER2-)
Base case	–	–	***£46,549***	***£64,773***
Transition probabilities				
Base SMR on Clèries 2022 (45) (Section 4.2.6.3)	1.46	1.00	***£44,473***	£62,285
Base SMR on Levi 2002(42)	1.46	2.00	£48,725	£67,383

Scenario (Relevant section of EAG report)	Base case value	Scenario analysis value	ICER (£/QALY) (TNBC)	ICER (£/QALY) (HR+/HER2-)
(Section 4.2.6.3)				
TNBC: TP7 case mixes	Single Chemotherapy: 70% Atezolizumab+Paclitaxel: 30%	Single Chemotherapy: 100% Atezolizumab+Paclitaxel: 0%	£46,444	-
TNBC: TP7 case mixes	Single Chemotherapy: 70% Atezolizumab+Paclitaxel: 30%	Single Chemotherapy: 0% Atezolizumab+Paclitaxel: 100%	£46,796	-
HR+/HER2-: TP7 case mixes	Single Chemotherapy: 10% CDK4/6+endocrine: 90%	Single Chemotherapy: 0% CDK4/6+endocrine: 100%	-	***£64,751***
HR+/HER2-: TP7 case mixes	Single Chemotherapy: 10% CDK4/6+endocrine: 90%	Single Chemotherapy: 100% CDK4/6+endocrine: 0%	-	***£64,980***
Utilities				
Health state utility values used Verrill 2020(58) (Section 4.2.7.2)	*DF: 0.732* *Non-mBC: 0.667* mBC: 0.6*03* *(Verill 2020 with non-mBC set to mid-point)(58)*	*DF: 0.802* *(0.797, 0.807)* *Longworth et al 2014(53)* *Non-mBC: (mid-point)* *mBC: 0.685 (Lidgren 2007)(57)*	[redacted]	[redacted]
Resource use and costs				
Increase drug acquisition and administration costs by 20% in mBC *(Section 4.2.8.2)*	-	-	£46,334	***£64,082***
Decrease drug acquisition and administration	-	-	£46,764	***£65,464***

Scenario (Relevant section of EAG report)	Base case value	Scenario analysis value	ICER (£/QALY) (TNBC)	ICER (£/QALY) (HR+/HER2-)
costs by 20% in mBC *(Section 4.2.8.2)*				

6.5 Conclusions of the cost effectiveness section

The company have submitted a cost-effectiveness model that addresses the decision problem defined in the final scope. The mode structure has face validity and is largely aligned with prior NICE submissions in early breast cancer. Separate models, with different parameters and assumptions but the same structure, were submitted in HR+/HER2- and TNBC. The EAG has some concerns about the data and assumptions underlying both models, as described in the Key Issues noted in Section 1.4.

The immaturity of data (Key Issue 1) meant there is uncertainty regarding the long-term risk of recurrence in TNBC, the appropriate distribution for recurrence in HR+/HER2-, and distribution for survival following early metastatic recurrence. More generally, there is uncertainty in HR+/HER2- as the company have needed to use the ITT population as a proxy for HR+/HER2- for the recurrence rates. The EAG recommend more conservative assumptions around the long-term risk of recurrence and extrapolations from the OlympiA trial.

The potential risk of bias in estimates of HRQoL (Key Issue 2) and the selected mapping algorithm used to inform HRQoL for the health states of the model (Key Issue 3) were a limitation with high impact on the ICER. A preference-based HRQoL tool such as the EQ-5D was not administered in the OlympiA trial. Patients completed the EORTC-QLQ-C30 but the company used an older mapping algorithm, based on OLS estimates, that has been shown to provide biased estimates and the EAG does not recommend.(4) The EAG would recommend using utility data from Verrill 2020, a UK study reporting EQ-5D utility scores in 299 patients HER2+ early and metastatic BC and further explore in sensitivity analyses the mapped EQ-5D utilities from the OlympiA data (DCO2) using newer algorithms such as the Gray et al. 2021 (4) and others.

Olaparib treatment requires patients to know their BRCA status. The company assumed universal access to BRCA testing for both TNBC and HR+/HER2- populations on the NHS. Clinical advice received by the EAG, and in consulting NGTD recommendations, the EAG agrees that all TNBC patients aged under 60 years of age could be offered BRCA testing in the future, and that a scheme of universal testing for TNBC patients is being piloted. There is no indication, however, that universal testing on the NHS would be available for the

HR+/HER2- population in the foreseeable future. The EAG therefore recommend including BRCA testing costs in the HR+/HER2- population (Key Issue 4).

The company ICER in both cancer types was assessed to be biased downwards, and the EAG have recommended preferred assumptions for a base case. In TNBC these changed the deterministic ICER from £35,855 to £46,549/QALY, and the probabilistic ICER from £34,685/QALY to £46,142/QALY. In HR+/HER2- these changed the deterministic ICER from £41,897/QALY to £64,773/QALY, and the probabilistic ICER from £40,293/QALY to £59,592/QALY. In sensitivity analyses the EAG relaxes some of these assumptions. A notable sensitivity analysis result is the one excluding BRCA testing costs for the HR+/HER2- population, which reduces the ICER by about £7,000/QALY.

7 Severity and Innovation

The company is not making a case for severity or innovation.

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9 APPENDICES

9.1 Appendix 1: Risk of bias in the systematic review (SR)(10) conducted for the company submission assessed using a modified version of the ROBIS tool.(74)

Phase 1: Relevance to the Scope

Category	Scope	Company systematic review
Patients/Population(s):	eBC; Adults with BRCA1- or BRCA2-positive; HER2-; high-risk; treated with surgery and neoadjuvant or adjuvant chemotherapy.	Adult patients (≥18 years) with non-metastatic primary invasive HER2-negative adenocarcinoma of the breast receiving treatment in the post-surgical adjuvant setting
Intervention(s):	Olaparib	Immune-oncology drugs (atezolizumab and pembrolizumab), cyclin-dependent kinase (CDK) 4/6 inhibitors (abemaciclib, palbociclib, and ribociclib), olaparib, capecitabine, and endocrine therapy
Comparator(s):	Established clinical management without olaparib.	Not specified
Outcome(s):	• iDFS • dDFS • OS • Adverse effects of treatment • HRQoL	• Efficacy, tolerability, and safety (restricted to RCTs) • Economic evaluations • HRQoL/health state utility values (HSUVs) • Cost/resource use

Does the question addressed by the review match the target question?	**NO**
Summary: The review question was much broader than the scope with a broader population, greater number of eligible interventions and wider range of outcomes.	

Phase 2: Concerns with the review process

The purpose of this assessment is to determine whether the evidence identified and synthesized by the systematic review can reliably be used to inform the economic model. Below we critique only those aspects of the review that impact on the studies that are relevant to this appraisal i.e., studies of olaparib for adjuvant treatment of people with high-risk HER2-negative, BRCA-positive early breast cancer after chemotherapy. This critique is based on the full company SR report provided in addition to the CS.(10)

DOMAIN 1: STUDY ELIGIBILITY CRITERIA	
Objectives: *"The current SLR was conducted to identify RCTs reporting the efficacy and safety of interventions of interest, including targeted therapies, endocrine therapy, immune-oncology drugs, and capecitabine, for patients with non-metastatic, primary, invasive HER2-negative breast cancer."* This is much broader than the question of interest – we are only interested in studies of olaparib in: patients with eBC; BRCA1- or BRCA2-positive; HER2-; high-risk; treated with surgery and neoadjuvant or adjuvant chemotherapy. Eligibility criteria initially matched our population of interest but were broadened to included *"beyond germline BRCA and high-risk studies only"* owing to parcity of data. Full inclusion criteria were as follows: ▪ RCTs ▪ Adult patients (≥18 years) with non-metastatic primary invasive HER2-negative adenocarcinoma of the breast receiving treatment in the post-surgical adjuvant setting. ▪ Interventions of interest were immune-oncology drugs (atezolizumab and pembrolizumab), cyclin-dependent kinase (CDK) 4/6 inhibitors (abemaciclib, palbociclib, and ribociclib), olaparib, capecitabine, and endocrine therapy. ▪ At least one outcome of interest: iDFS, OS, DDFS, DFS, recurrence free survival (RFS), time to first subsequent therapy, time to treatment failure, time to treatment discontinuation, response rates, recurrence, AEs, HRQoL	
1.1 Did the review adhere to pre-defined objectives and eligibility criteria?	PN
1.2 Were the eligibility criteria appropriate for the scope?	N
1.3 Were eligibility criteria unambiguous?	Y
1.4 Were any restrictions in eligibility criteria based on study characteristics appropriate (e.g. date, sample size, study quality, outcomes measured)?	Y
1.5 Were any restrictions in eligibility criteria based on sources of information appropriate (e.g. publication status or format, language, availability of data)?	PN
Concerns that application of the eligibility criteria could have resulted in studies relevant to the scope being excluded from the review	**LOW**
Rationale for concern: The review addressed a much broader question than the scope in terms of both interventions and population. Eligibility criteria were modified post-hoc due to paucity of data. Studies were restricted to English language or studies with an English abstract. Only 1 trial (the OlympiA trial) included in the company SR was relevant to the NICE scope for this appraisal. Despite some limitations in the eligibility criteria the EAG do not think this could have resulted in relevant studies being omitted from the review.	

DOMAIN 2: IDENTIFICATION AND SELECTION OF STUDIES	
A wide range of sources were searched including attempts to locate unpublished data. The search strategies were designed specifically to identify studies focused on people with HER negative breast cancer rather than people with breast cancer generally. Focusing the searches on breast cancer, and selecting studies focused on the condition of interest, would have been more sensitive, and the approach to study identification favoured by the EAG. Study selection processes were unclear. The authors state that *"Records were reviewed based on title and abstract in the first instance by one analyst and checked by a second, and those included were reviewed based on the full publication."* It is not clear whether all titles and abstracts were reviewed independently by two reviewers and what process was used to assess full text studies.	
2.1 Did the search include an appropriate range of databases/electronic sources for published and unpublished reports?	Y
2.2 Were methods additional to database searching used to identify relevant reports?	Y
2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	PY
2.4 Were restrictions based on date, publication format, or language appropriate?	Y
2.5 Were efforts made to minimise error in selection of studies?	NI
Concerns that the searches and selection methods could missed studies relevant to the scope	**LOW**
Rationale for concern: The search is focused explicitly on the trial population, which is restrictive. The EAG have undertaken scoping searches and not identified any eligible trials missed in the submission. The search approach could have been broader in scope, but the EAG are content that this restriction has not led to eligible evidence being overlooked. The process of study selection was not sufficiently well described to be confident that steps were taken to minimize bias and errors in this process. However, as the EAG has not identified any additional studies that should have been included we are content that this has not led to eligible evidence being missed.	

DOMAIN 3: DATA COLLECTION AND STUDY APPRAISAL	
Details on the processes used to extract data and assess risk of bias were not reported. The seven-criteria CRD checklist was used to assess study quality.(14)	
3.1 Were efforts made to minimise error in data collection?	NI
3.2 Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	N
3.3 Were all relevant study results collected for use in the synthesis?	Y
3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	N
3.5 Were efforts made to minimise error in risk of bias assessment?	NI
Concern that the methods used to collect data and appraise studies may have impacted the results	**HIGH**

Rationale for concern:

Although methods used to extract data (number of reviewers involved in data extraction and data to be extracted) were not reported, the EAG have checked data, comparing the submission with published study reports and the CSR. Minor discrepancies were observed but none affect the overall findings of the review.

The tool used to assess risk of bias is not the latest most robust tool for assessing risk of bias in RCTs. The risk of bias assessment was performed at the trial level rather than by individual outcome. The EAG has repeated the risk of bias assessment by three independent reviewers using the ROB 2.0 tool and some concerns were identified regarding missing outcome data for HRQoL. There was low risk of bias for all other outcomes. Full details of the risk of bias assessment are provided in the EAG report (**section 3.2.1**) and in Appendix 2: Risk of bias in the OlympiA trial assessed using the Cochrane Risk of Bias Tool v 2.0

DOMAIN 4: SYNTHESIS AND FINDINGS	
Proposed methods of synthesis were not reported; a narrative synthesis is provided. There was only one trial relevant to the scope.	
4.1 Did the synthesis include all studies that it should?	Y
4.2 Were all pre-defined analyses reported or departures explained?	NI
4.3 Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies?	Y
4.4 Was between-study variation (heterogeneity) minimal or addressed in the synthesis?	Y
4.5 Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	PY
4.6 Were biases in primary studies minimal or addressed in the synthesis?	N
Concerns that the synthesis may have produced biased estimates for input into the model	LOW
Rationale for concern: There was only one study and so no synthesis was conducted.	

Y=YES, PY=PROBABLY YES, PN=PROBABLY NO, N=NO, NI=NO INFORMATION

Phase 3: Judging risk of bias

Summarize the concerns identified during the Phase 2 assessment:

Domain	Concern	Rationale for concern
1. Concerns that application of the eligibility criteria could have resulted in studies relevant to the scope being excluded from the review	Low	Although there were some concerns with the eligibility criteria the EAG does not consider this to have been likely to have resulted in relevant studies being excluded from the review.
2. Concerns that the searches and selection methods could missed studies relevant to the scope	Low	Although there were some concerns regarding how studies were identified and selected for inclusion the EAG does not consider the likely to have result in relevant studies being missed.
3. *Concerns regarding methods used to collect data and appraise studies*	High	The EAG are concerned that the risk of bias assessment did not identify limitations in terms of missing data for the outcome of HRQoL
4. *Concerns that the synthesis may have produced biased estimates for input into the model*	Low	The methodological concerns identified by the EAG were not taken into consideration.

Overall: High risk of bias

The review conducted by the company addressed a much broader question than the question specified by the scope; it is unclear why they did not focus down the review to match the scope rather than reporting their much broader systematic review – this would have been more appropriate. We have critiqued the systematic review only for those aspects that match the scope. Despite limitations in how the review was conducted and reported, the EAG are confident that the OlympiA trial is the only trial relevant to the submission. The EAG are concerned that the risk of bias assessment did not limitations in terms of missing data for the outcome of HRQoL.

9.2 Appendix 2: Risk of bias in the OlympiA trial assessed using the Cochrane Risk of Bias Tool v 2.0(15)

9.2.1 Risk of bias in the effect of **assignment** to intervention

For effectiveness outcomes the key effect of interest is assignment to the intervention – the intention to treat effect.

Domain	Signalling question	iDFS	dDFS	OS	AEs	HRQoL	Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	Y	Y	Y	Y	"Randomization was done using a permuted block algorithm."
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y	Y	Y	Y	Y	"All patients, treating physicians, and study personnel were blinded to treatment allocation"
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	N	N	N	N	No baseline differences between groups to suggest a problem with the randomisation process.
	Risk of bias judgement	**Low**	**Low**	**Low**	**Low**	**Low**	**No concerns regarding to randomisation**
Bias due to deviations from intended interventions	2.1.Were participants aware of their assigned intervention during the trial?	PN	PN	PN	PN	PN	Study was double-blind. Study was unblinded early; very high proportion of follow up time was blinded.
	2.2.Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	PN	PN	PN	PN	PN	Study was double-blind.
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	Y	Y	Y	Y	Intention-to-treat analysis used.
	Risk of bias judgement	**Low**	**Low**	**Low**	**Low**	**Low**	**Study blinded and ITT analysis used**
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	PY	PY	PY	PY	N	Data were available for most participants who were randomised for efficacy and safety data. Compliance was low for HRQoL data with data only available for around 65% participants at 24 month follow-up
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	NA	NA	NA	N	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	NA	NA	NA	Y	Low HR QoL could have impacted compliance; rates similar between arms.
	Risk of bias judgement	**Low**	**Low**	**Low**	**Low**	**Some concerns**	**Some concerns for HRQoL outcome due to missing data**

Domain	Signalling question	iDFS	dDFS	OS	AEs	HRQoL	Comments
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	N	N	N	N	Methods of measuring were reported and considered appropriate for all outcomes.
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	N	N	N	N	Outcomes were measured in the same way in each intervention group
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	N	N	N	N	Study was double blinded
	Risk of bias judgement	**Low**	**Low**	**Low**	**Low**	**Low**	**No concerns regarding measurement of outcomes**
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y	Y	Y	Y	Y	Data were analysed in line with a pre-specified statistical analysis plan, finalised in 18 May 2018.
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	N	N	N	N	Outcomes and timepoints prespecified in protocol.
	5.3 ... multiple eligible analyses of the data?	N	N	N	N	N	Analysis pre-planned in protocol.
	Risk of bias judgement	**Low**	**Low**	**Low**	**Low**	**Low**	**Low risk of bias across all outcomes.**
Overall bias	**Risk of bias judgement**	**Low**	**Low**	**Low**	**Low**	**Some concerns**	

9.2.2 Risk of bias in the effect of **adhering** to intervention

For safety analysis it is more relevant to consider whether adhering to the intervention (the "per-protocol" effect), so taking all doses of olaparib, is associated with a greater risk of AEs compared to placebo. The effect of interest is assignment to the intervention. Domain 2 (Bias due to deviations from intended interventions) was therefore assessed separately for the effect of adhering to the intervention for the safety analysis:

RoB2 assessments using adhering to intervention (the 'per-protocol' effect)			
Bias due to deviations from intended interventions	2.1 Were participants aware of their assigned intervention during the trial?	PN	Study was double-blind. Study was unblinded early, however a very high proportion of follow up time was blinded.
	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	PN	
	2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	Y	At the start of the trial 10 patients in the intervention group and 11 in the control group did not receive the assigned regimen; these were excluded from the safety analysis. 97 patients in the intervention group did not complete study treatment due to adverse events, compared to 41 in the control group.
	2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	N	Safety analysis was based on all those who received at least one dose of the intervention.
	Risk of bias judgement	**High**	
Overall bias	**Risk of bias judgement**	**High**	Overall risk of bias was high due to non-adherence to the assigned intervention and analysis based on all those who received at least one dose of study drug.