NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Olaparib for adjuvant treatment of high-risk HER2-negative, BRCA-positive early breast cancer after chemotherapy [ID3893]

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Olaparib for adjuvant treatment of high-risk HER2-negative, BRCA-positive early breast cancer after chemotherapy [ID3893]

Contents:

The following documents are made available to consultees and commentators:

The **final scope and final stakeholder list** are available on the NICE website.

1. **Company submission** from AstraZeneca

2. **Clarification questions and company responses**

3. **Patient group, professional group and NHS organisation submissions** from:
   a. Breast Cancer Now
   b. Royal College of Physicians

4. **Evidence Review Group report Bristol Technology Assessment Group**

5. **Evidence Review Group report – factual accuracy check**

6. **Technical engagement response from company**

7. **Technical engagement responses and statements from experts:**
   a. Prof. Andrew Tutt, clinical expert, nominated by AZ
   b. Prof. Stuart McIntosh, clinical expert, nominated by AZ
   c. Holly Heath, patient expert, nominated by Breast Cancer Now
   d. Melanie Sturtevant, patient expert, nominated by Breast Cancer Now

8. **Technical engagement responses from consultees and commentators:**
   a. NHSE Genomics Unit

9. **Evidence Review Group critique of company response to technical engagement** prepared by Bristol Technology Assessment Group
   a. EAG additional scenario results

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Olaparib for adjuvant treatment of high-risk HER2-negative, *BRCA*-positive early breast cancer after chemotherapy [ID3893]

Document B

Company evidence submission

May 2022

File name	Version	Contains confidential information	Date
ID3893_olaparib_Document B_19May2022 ACIC REDACTED	1.1	Yes	19th May 2022

Contents

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE 1
Single technology appraisal 1
Document B 1
Company evidence submission 1
Contents 2
List of figures 2
List of tables 3
B.1 Decision problem, description of the technology and clinical care pathway 6
B.1.1 Decision problem 7
B.1.2 Description of the technology being evaluated 10
B.1.3 Health condition and position of the technology in the treatment pathway 12
B.1.4 Equality considerations 29
B.2 Clinical effectiveness 30
B.2.1 Identification and selection of relevant studies 31
B.2.2 List of relevant clinical effectiveness evidence 31
B.2.3 Summary of methodology of the relevant clinical effectiveness evidence 32
B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence 41
B.2.5 Critical appraisal of the relevant clinical effectiveness evidence 44
B.2.6 Clinical effectiveness results of the relevant studies 44
B.2.7 Subgroup analysis 52
B.2.8 Meta-analysis 54
B.2.9 Indirect and mixed treatment comparisons 54
B.2.10 Adverse reactions 54
B.2.11 Ongoing studies 62
B.2.12 Interpretation of clinical effectiveness and safety evidence 62
B.3 Cost-effectiveness 67
B.3.1 Published cost-effectiveness studies 68
B.3.2 Economic analysis 68
B.3.3 Clinical parameters and variables 78
B.3.4 Measurement and valuation of health effects 110
B.3.5 Cost and healthcare resource use identification, measurement and valuation 117
B.3.6 Summary of base-case analysis inputs and assumptions 131
B.3.7 Base-case results 134
B.3.8 Exploring uncertainty 135
B.3.9 Subgroup analysis 143
B.3.10 Validation of the cost-effectiveness analysis 143
B.3.11 Interpretation and conclusions of economic evidence 144
B.4 References 146

List of figures

Figure 1: Proportion of female breast cancer by histological subtype 15
Figure 2: Breast cancer staging according to the AJCC TNM staging criteria (8th edition) 19
Figure 3. Relevance of iDFS as an endpoint in eBC 22
Figure 4: Current treatment pathway in high-risk eBC patients 24
Figure 5: Annual rate of distant recurrence following diagnosis of invasive breast cancer among patients with TNBC (left) and HR+ (right) disease 25
Figure 6: Treatment pathway for HER2-negative, eBC and proposed positioning of olaparib (based on current standard of care) 28

Figure 7: Overview of OlympiA study design 33
Figure 8. Multiple testing procedure (MTP) used in OlympiA 43
Figure 9: Kaplan-Meier plot of iDFS in OlympiA, early primary analysis (FAS) 47
Figure 10: Kaplan-Meier plot of dDFS in OlympiA, early primary analysis (FAS) 48
Figure 11: Kaplan-Meier plot of OS in OlympiA, early primary analysis (FAS) 49
Figure 12: Mean change from baseline of EORTC QLQ-C30 Global Health QoL Score in patients who had received prior neoadjuvant chemotherapy in OlympiA (PRO analysis set) 51
Figure 13: Mean change from baseline of EORTC QLQ-C30 Global Health QoL Score in patients who had received prior adjuvant chemotherapy in OlympiA (PRO analysis set) 51
Figure 14: Forest plot of iDFS according to stratification factors, early primary analysis (FAS) 53
Figure 15: Schematic of the model structure 70
Figure 16: Log-cumulative hazards versus log-time plot of iDFS for the placebo and olaparib arms of OlympiA (TNBC, left panel, ITT used as a proxy for HR+/HER2-, right panel) 83
Figure 17: Fit of the parametric survival models to the KM data for iDFS in OlympiA (TNBC, left; ITT used as a proxy for HR+/HER2, right) 85
Figure 18: Long-term distant disease-free survival for gBRCAm from the POSH study 89
Figure 19: Base case iDFS extrapolation for the TNBC population (top) and the HR+/HER2- population (bottom) 92
Figure 20: Fit of the parametric survival models to the ITT OlympiA KM data for non-metastatic to metastatic recurrence (left) and for non-metastatic to death (right) in OlympiA, pooled arms 97
Figure 21: KM plot of post-distant metastatic recurrence survival by arm in OlympiA 98
Figure 22: Log-cumulative hazards versus log-time plot of post-metastatic recurrence for the placebo and olaparib arms of OlympiA 99
Figure 23: Fit of parametric survival models to the KM data for metastatic to death by arm in OlympiA 100
Figure 24: Log-cumulative hazards versus log-time plot for first-line subgroup of OlympiAD 104
Figure 25: Fit of parametric survival models to the Kaplan-Meier data for metastatic to death by arm in the 1st line TPC chemotherapy subgroup of OlympiAD (left) and for the 1st line CDK4/6 inhibitor treatment subgroup of Collins et al. (2021) (right) 105
Figure 26: Weighted-average survival probabilities for 'late onset mBC' (TP7) in TNBC (upper) and HR+/HER2- (lower) vs. survival data/extrapolations of the OlympiAD study (TPC), CDK4/6 inhibitor use (Collins et al. (2021)) and atezolizumab plus paclitaxel (left) and the survival probabilities for 'early onset mBC' (TP6) (right) 108
Figure 27: Fit of the aggregated OS to the Kaplan-Meier data in OlympiA (TNBC, top; HR+/HER2 using ITT data, bottom) 109
Figure 28: Time to treatment discontinuation from OlympiA 119
Figure 29: Cost-effectiveness plane, olaparib vs. placebo ("watch & wait") (TNBC) 136
Figure 30: Cost-effectiveness acceptability curve, olaparib vs. placebo ("watch & wait") (TNBC) 136
Figure 31: Cost-effectiveness plane, olaparib vs. placebo ("watch & wait") (HR+/HER2-) 137
Figure 32: Cost-effectiveness acceptability curve, olaparib vs. placebo ("watch & wait") (HR+/HER2-) 137
Figure 33: Deterministic sensitivity analysis results, tornado diagram (TNBC) 139
Figure 34: Deterministic sensitivity analysis results, tornado diagram (HR+/HER2-) 140

List of tables

Table 1: The decision problem 8
Table 2: Technology being appraised 10
Table 3: Risk factors for the development of breast cancer 14
Table 4: UK clinical guidelines for the diagnostic work-up for eBC 16
Table 5: AJCC TNM staging criteria for breast cancer 18
Table 6: Clinical effectiveness evidence 32
Table 7: Summary of OlympiA inclusion and exclusion criteria 33
Table 8. Summary of concomitant medications permitted and disallowed in OlympiA 36
Table 9: Patient demographics in OlympiA (FAS) 40
Table 10: Patient characteristics in OlympiA (FAS) 40
Table 11: Summary of statistical analyses in OlympiA 42

Table 12: Analysis sets in OlympiA 43
Table 13: Overview of quality assessments for OlympiA 44
Table 14: Summary of OlympiA efficacy endpoints, early primary analysis (FAS) 45
Table 15: A summary of all new cancers that occurred post randomisation in OlympiA, early primary analysis, FAS 49
Table 16: Summary of AEs in OlympiA, early primary analysis (SAS) 55
Table 17: Most common AEs (occurring in at least 5% of patients in either arm) reported in OlympiA, early primary analysis (SAS) 55
Table 18: SAEs reported in OlympiA (≥3 patients in either arm), early primary analysis (SAS) 57
Table 19: CTCAE Grade ≥3 AEs reported in OlympiA (≥3 patients in either arm), early primary analysis (SAS) 58
Table 20: AEs of special interest for olaparib, early primary analysis, SAS 60
Table 21: Dose interruptions, reductions, and discontinuations due to AEs, early primary analysis (SAS) 61
Table 22: All deaths in OlympiA, early primary analysis (SAS) 61
Table 23: Adverse events with outcome of death in OlympiA, early primary analysis (SAS) 62
Table 24: Summary of literature evidence on the impact of time to recurrence on post-progression survival outcomes 74
Table 25: Features of the economic analysis and comparisons with previous NICE evaluations in HER2+ eBC 76
Table 26: Comparison of landmark iDFS and OS for HR+/HER2- and TNBC patients in the placebo arm of OlympiA 80
Table 27: Description of transitions and data sources used in the economic model 81
Table 28: AIC and BIC values for the parametric survival models fitted to the OlympiA iDFS data, their respective long-term predicted survival and a comparison with empirical data (independent, TNBC) 93
Table 29: AIC and BIC values for the parametric survival models fitted to the OlympiA iDFS data, their respective long-term predicted survival and a comparison with empirical data (independent, ITT as a proxy for HR+/HER2-) 94
Table 30: AIC and BIC values for the parametric survival models fitted to data on the time from non-distant metastatic recurrence to distant metastatic and the time from non-distant metastatic recurrence to death 95
Table 31: AIC and BIC values for the parametric survival models fitted to data on the time from metastatic recurrence to death 99
Table 32: Summary of study information and clinical characteristics for OlympiAD, Flatiron health database study & IMpassion 130 102
Table 33: AIC and BIC values for the parametric survival models fitted to data on the time from metastatic recurrence to death in OlympiAD and Collins et al. (2021) 104
Table 34: Case mix of treatment in the ‘late onset’ mBC state 106
Table 35: Summary statistics for the mapped HSU values using the Crott and Briggs (2010) algorithm (capped at 1) by arm and study period 111
Table 36: Results of linear regression analysis on mapped HSUs from OlympiA using Crott and Briggs algorithm 112
Table 37: Base case and scenario analysis health state utility values used in the economic model 114
Table 38: Disutility values associated with AEs, and assumed duration of events 116
Table 39: Summary of olaparib drug related costs 118
Table 40: Split of HR+/HER2- patients receiving endocrine therapies in the DF state 120
Table 41: Drug acquisition costs (subsequent treatments) 121
Table 42: Subsequent treatment durations and market shares 122
Table 43: Subsequent radiotherapy and surgery (shares & costs) 126
Table 44: Administration costs 127
Table 45: Resource use by health state 128
Table 46: Resource use costs 128
Table 47: Adverse event costs 129
Table 48: Unit cost and resource use of EoL care 130
Table 49: Summary of the key model assumptions and inputs 131
Table 50: Base case results (TNBC, olaparib PAS price) 134
Table 51: Base case results (HR+/HER2-, olaparib PAS price) 134
Table 52: Base case results (probabilistic) (TNBC) 135

Table 53: Base case results (probabilistic) (HR+/HER2-)..... 135
Table 54: Scenario analysis results (discounted, TNBC & HR+/HER2- analyses) 141

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

Breast cancer is the fourth most common cancer and cause of cancer death in the UK, with an incidence of approximately 55,000 and 370 cases per year among females and males, respectively.[1, 2] Fortunately, 80–90% of these cases are diagnosed at an early stage (Tumour Node Metastasis [TNM] stage I to III) and are considered potentially curable.[3] As such, current standard of care for early breast cancer (eBC) is curative in intent, with the aim to remove the cancer, reduce the risk of disease recurrence, and prevent the spread of disease.[4]

Patients with eBC are segmented according to their hormone receptor (HR) and human epidermal growth factor receptor 2 (HER2) biomarker status, which guide treatment and prognosis;[5, 6] this submission focusses only on HER2-negative (HER2-) disease. Treatment choices and prognosis are guided by the presence of high-risk features, which confer an increased risk of recurrence.[7] Patients with high-risk disease receive more intensive treatment, consisting of surgery, radiotherapy, and neoadjuvant or adjuvant chemotherapy; HR+ patients will also receive endocrine therapies. However, in spite of these treatments, many patients experience recurrence.[7-9]

Underlying tumour genetics are also an important consideration in eBC. Up to approximately 10% of breast cancers are linked to germline inheritance of mutations, most commonly in the breast cancer susceptibility gene 1/2 (*BRCA1/2*) genes, which contribute to genomic instability and are considered a key driver of tumour growth.[10] The presence of a *BRCA* mutation (*BRCA*m) not only confers an increased risk of developing breast, ovarian and prostate cancers, but has been associated with particularly aggressive disease in eBC.[10, 11] Patients with both *BRCA*m and high-risk disease therefore have a particularly high unmet need for an effective therapy which targets their underlying tumour driver, and reduces their risk of recurrence and disease progression. *BRCA*m confers sensitivity to poly (ADP-ribose) polymerase inhibitors (PARPi) such as olaparib; this sensitivity has already been utilised in ovarian cancer, where use of PARPi have transformed patient progression-free survival outcomes compared to placebo.[12] Data from the OlympiA clinical study demonstrate a significant and clinically meaningful improvement in overall survival outcomes of olaparib treatment compared with placebo in *BRCA*m high risk eBC.[13, 14]

OlympiA (NCT02032823) is a high-quality, international, multicentre, Phase III, double-blind, parallel group, placebo-controlled study investigating the efficacy and safety of olaparib as monotherapy for the adjuvant treatment of patients with germline *BRCA*m (g*BRCA*m), HER2-, high-risk, eBC. Results from the early primary analysis of invasive disease-free survival (iDFS) (27 March 2020 data cut-off [DCO]) showed a significantly longer iDFS and distant disease-free survival (dDFS) compared with placebo, with early and sustained separation of the Kaplan-Meier (KM) curves for both endpoints.[13, 14]

- **iDFS**: 41% reduction in the risk of invasive disease recurrence or death (hazard ratio 0.58; 99.5% CI: 0.41–0.82; p=0.0000073).
- **dDFS**: 42.6% reduction in the risk of distant recurrence or death (hazard ratio: 0.57; 99.5% CI: 0.39, 0.83; p=0.0000257)

The early data also indicated a positive trend for overall survival (OS), which reached statistical significance at the 12 July 2021 DCO showing a 32% reduction in risk of death (hazard ratio: 0.68; 98.5% CI 0.47-0.97; p=0.009).[13, 14] Based on these results, the Medicines and Healthcare products Regulatory Agency (MHRA) marketing authorisation for olaparib in this indication is anticipated in [redacted].

Introduction of olaparib in this setting therefore represents a step change in the management and outcomes for g*BRCA*m, HER2-, high-risk eBC patients, moving towards a personalised treatment approach to target the driver of tumour growth. This submission also demonstrates that the use of olaparib in this indication represents a cost-effective use of National Health Service (NHS) resources, and is associated with a modest budget impact (from £[redacted] to £[redacted] in the first 3-years post-reimbursement).

B.1.1 *Decision problem*

The submission covers the technology's full anticipated marketing authorisation for this indication, expected to be listed as below in the updated Summary of Product Characteristics (SmPC):

- [redacted]

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with *BRCA*1- or *BRCA*2-positive, high-risk HER2-, eBC that have been treated with surgery and neoadjuvant or adjuvant chemotherapy.	This submission considers g*BRCA*m, HER2-, high-risk eBC patients.	The population considered in this submission aligns with that considered in the OlympiA trial, and is [redacted].
Intervention	Olaparib	As per the final scope issued by NICE.	N/A
Comparator(s)	Established clinical management without olaparib.	The comparator selected is in line with the final scope issued by NICE. However, we clarify that in this setting "watch and wait" is considered to be the established clinical management without olaparib.	The proposed positioning of olaparib in the treatment pathway for eBC is after neoadjuvant or adjuvant chemotherapy. Established clinical practice in this setting is a "watch and wait" approach whereby patients undergo routine monitoring for disease recurrence. As such this is considered the appropriate comparator for this evaluation. Many patients with HR+ eBC will also receive extended endocrine therapy during this follow up period, and some postmenopausal patients may receive bisphosphonate therapy; however, the use of such therapies is not expected to be impacted or displaced by olaparib. They are included within our definition of "watch and wait".
Outcomes	The outcome measures to be considered include: • iDFS • dDFS • OS	As per the final scope issued by NICE.	N/A

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	• Adverse effects of treatment • 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 (QALY).	Cost-effectiveness is expressed in terms of incremental cost per QALY. The company submission adopts a cost-utility approach using a semi-Markov model and adheres as closely as possible to the reference case and previously accepted submission approaches.	N/A
Subgroups to be considered	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.	In the economic analysis, cost and health outcomes are modelled over a lifetime horizon (assumed to be 57 years), as per the reference case.	N/A
Special considerations including issues related to equity or equality	Costs will be considered from an NHS and Personal Social Services perspective.	As per the final scope issued by NICE.	N/A

Abbreviations: BRCA: breast cancer susceptibility gene; dDFS: distant disease-free survival; eBC: early breast cancer; HER2: human epidermal growth factor receptor 2; HR: hormone receptor; iDFS: invasive disease-free survival; N/A, not applicable; NHS: National Health Service; NICE: National Institute for Heath and Care Excellence; OS: overall survival; TNBC: triple-negative breast cancer; UK: United Kingdom
Source: NICE Draft Scope[15]

B.1.2 *Description of the technology being evaluated*

A description of the technology being appraised is summarised in Table 2.

Table 2: Technology being appraised

UK approved name and brand name	Olaparib (Lynparza®)
Mechanism of action	Olaparib is a PARPi, a type of enzyme that helps repair breaks in the DNA of cells.[16] PARPi work by preventing cancer cells from repairing these breaks, causing them to die.[17] PARPi are thought to be more effective in treating cancer cells with mutations in the *BRCA* genes as they lack another DNA repair mechanism called the 'homologous recombination pathway', which further increases the rate of DNA damage and thereby the death of the cancer cell.[17-20]
Marketing authorisation/CE mark status	MHRA marketing authorisation for olaparib in this indication is anticipated in [redacted].
Indications and any restriction(s) as described in the SmPC	**Anticipated indication of interest to this evaluation:**[21] Olaparib is anticipated to be indicated as monotherapy for [redacted]. **Current indications:**[21] Ovarian cancer Olaparib is indicated as monotherapy for the: • Maintenance treatment of adult patients with advanced (FIGO stages III and IV) *BRCA*1/2-mutated germline and/or somatic) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy. • Maintenance treatment of adult patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy. Olaparib in combination with bevacizumab is indicated for the: • Maintenance treatment of adult patients with advanced (FIGO stages III and IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy in combination with bevacizumab and whose cancer is associated with HRD-positive status defined by either a *BRCA*1/2 mutation and/or genomic instability. Breast cancer • Olaparib is indicated as monotherapy for the treatment of adult patients with g*BRCA*1/2m, who have HER2- advanced or metastatic breast cancer. Patients should have previously been treated with an anthracycline and a taxane in the (neo)adjuvant or metastatic setting unless patients were not suitable for these treatments. Patients with HR+ breast cancer should also have

	progressed on or after prior endocrine therapy, or be considered unsuitable for endocrine therapy. Adenocarcinoma of the pancreas • Olaparib is indicated as monotherapy for the maintenance treatment of adult patients with germline *BRCA1/2* mutations who have metastatic adenocarcinoma of the pancreas and have not progressed after a minimum of 16 weeks of platinum treatment within a first-line chemotherapy regimen. Prostate cancer • Olaparib is indicated as monotherapy for the treatment of adult patients with metastatic castration-resistant prostate cancer and *BRCA*1/2m (germline and/or somatic) who have progressed following prior therapy that included a new hormonal agent. **Restrictions**[21] Contraindications include hypersensitivity to the active substance or to any of the excipients or to breastfeeding during treatment and 1 month after the last dose. For full details of the warnings and precautions for use of olaparib, please refer to the SmPC.[21]
Method of administration and dosage	Olaparib 300 mg (2 x 150 mg tablets) orally administered twice daily (equivalent to a daily dose of 600 mg).[21] In the OlympiA indication, [redacted]
Additional tests or investigations	The presence of g*BRCA*1/2m should be confirmed using a validated testing modality before olaparib treatment is initiated. *BRCA* testing is already well established within the breast cancer pathway, and is already available for many patients, particularly those with high-risk disease.[22-24] Consistent with the UK government's ambitions to create the most advanced healthcare system in the world, and to incorporate the latest genomics advances into routine healthcare to improve outcomes, [redacted], which will ensure that by the time that olaparib is available in the eBC setting, it will be possible to identify all eligible patients in time for treatment initiation.[25-27] HER2 status will also need to be determined prior to initiation of olaparib treatment, however assessment of HER2 status is already considered standard of care for the management of patients with breast cancer within NHS England,[23] so no additional testing would be required for this.
List price and average cost of a course of treatment	The list price of olaparib is: £2,317.50 (56 x 150 mg tablets) per 14-day pack,[28] or £4,635.00 per 28-day cycle.
Patient access scheme (if applicable)	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.

Abbreviations: *BRCA*: breast cancer susceptibility gene; DNA: deoxyribonucleic acid; DSB: double-stranded break; eBC: early breast cancer; FIGO: International Federation of Gynaecology and Obstetrics; HER2: human epidermal growth factor 2; HR: hormone receptor; HRD: homologous recombination deficient; HRR: homologous recombination repair; MHRA: Medicines and Healthcare products Regulatory Agency; NG: NICE Guideline; NHS: National Health Service; PARP: poly (ADP-ribose) polymerase; PARPi: poly (ADP-ribose) polymerase inhibitor; SmPC: Summary of Product Characteristics; SSB: single-stranded break; TNBC: triple negative breast cancer.

B.1.3 *Health condition and position of the technology in the treatment pathway*

Summary of health condition and position of the technology in the treatment pathway

- Breast cancer is the fourth most common cancer and cause of cancer death in the UK, making up 15% of all new cancer cases.[1,29,2]
    - 80–90% of these cases are diagnosed at an early stage,[3] defined as a tumour restricted to the breast and nearby lymph nodes, without metastasis (American Joint Committee on Cancer [AJCC] TNM Stage I–III).
- eBC is often classified into four subgroups according to HR and HER2 biomarker status, which guide treatment and prognosis: HR+/HER2-; HR-/HER2- [TNBC]; HR-/HER2+; HR+/HER2+.[30, 31]
- There are a multitude of known genetic and environmental risk factors for developing breast cancer, including family history, with 5–10% of breast cancers linked to germline inheritance of mutations, most commonly in the *BRCA*1/2 genes.
    - The presence of a *BRCA*m not only confers an increased risk of developing breast, ovarian and prostate cancers,[10] but also impacts eBC prognosis;[11] patients are typically younger, have a higher tumour grade, and higher likelihoods of recurrence and CNS metastasis.
- Patients will also be categorised according to their risk of disease recurrence, which may inform prognosis and treatment. The definition of 'high-risk' varies globally and within the UK,[32-34] but is typically informed by several clinicopathological features, such as tumour size and characteristics, *BRCA* status, and nodal involvement.[8, 9]
    - The OlympiA trial exclusively enrolled high-risk patients, defined based on biomarker status, tumour size, lymph node involvement, CPS+EG score, and residual disease after neoadjuvant chemotherapy.[35]
- The current treatment pathway for HER2- eBC includes (neo)adjuvant chemotherapy, surgical excision (either mastectomy or breast-conserving surgery), radiotherapy, and endocrine therapy and/or bisphosphonates in specific patients.[23]
- For patients with high-risk disease, recurrence remains a concern and these patients are subject to a worse prognosis.[36, 37]
    - A US-based study found patients unselected by surgical outcome to have an overall cumulative risk of developing distant metastases of 20%, 30% and 36% at 4, 8 and 12 years post-diagnosis,[36] contrasting with a German study finding a 10-year recurrence rate of 16% in patients with free resection margins following surgery.[38]
    - Once distant metastases have developed, the disease is generally considered incurable, and health-related quality of life (HRQoL) worsens compared to that seen in early disease.[1]
- Breast cancer is also associated with a high financial burden and healthcare resource utilisation, particularly in more advanced stages of disease (median cost for relapsed breast cancer in UK per patient [2009]: £31,402.60);[23, 39] treatment for more advanced disease is often more intensive and invasive than that for earlier stages of breast cancer, resulting in increased costs and resource utilisation, in addition to poorer health outcomes.[40, 41]
- There is therefore a substantial unmet need for additional therapies to treat *BRCA*m, HER2-, high-risk eBC patients in the adjuvant setting that prevent or delay disease recurrence, and the

associated clinical, humanistic and economic burden that this would entail.

- Olaparib is a first-in-class orally administered PARPi,[42] and the first genetically targeted treatment for *BRCA*m breast cancer.[43-45]
- Based on the OlympiA study,[13] the current submission considers olaparib as [redacted]. In this indication, olaparib is anticipated to be an alternative to "watch and wait".

B.1.3.1 Disease overview

B.1.3.1.1 Disease background and types of breast cancer

Breast cancer is a malignant disease that forms in tissues of the breast, most commonly the ducts or lobules, and is the fourth most common cause of cancer death in the UK.[2, 15, 16] It is a clinically and biologically heterogeneous disease, characterised by dysregulation of multiple cellular pathways and different sensitivities to treatment.[29] Breast cancer can be divided into four subgroups according to HR (either progesterone or oestrogen) and HER2 biomarker status, which guide treatment and prognosis (subgroups of interest to this evaluation in bold):[5, 6]

- **HR+/HER2-**
- HR+/HER2+
- HR-/HER2+
- **HR-/HER2- (TNBC)**

Additionally, several known genetic and environmental risk factors influence the development of breast cancer (Table 3). Family history of breast cancer represents one of the key risk factors, and breast cancer is often associated with genetic background.[46] Accordingly, there is an increasing awareness of the role of genetic mutations in breast cancer;[10] between 5–10% of breast cancers have been linked to inheritance of genetic mutations, with mutations in the *BRCA1/2* genes the most prevalent.[10] *BRCA* mutations may be either germline or somatic:

- **Germline *BRCA* mutations (g*BRCA*m)** are mutations that occur in germline cells (sperm or ova), and can therefore be inherited by offspring. They affect every cell in the body, and predispose patients to multiple cancers, including breast, ovarian, and prostate[47 10]
- **Somatic *BRCA* mutations (s*BRCA*m)** are mutations originating in a non-germline cell; they only affect tissues derived from the affected cell, and are not inherited by offspring.[47]

*BRCA*m contribute to genomic instability by impacting the ability of cells to repair DNA damage by homologous recombination, and as such are considered a key driver of tumour growth.[48] While g*BRCA*m confer an increased risk of initially developing breast, ovarian and prostate cancers,[10] *BRCA*m have also been shown to result in a more aggressive phenotype once such a tumour has developed.[11, 49] In breast cancer patients specifically, *BRCA*m have been shown to impact chemosensitivity, in particular conferring platinum-sensitivity;[11, 50] as well as an increased sensitivity to treatment with PARPi, such as olaparib (see Section B.1.2).[50]

Table 3: Risk factors for the development of breast cancer

Category	Risk factors leading to increased risk of breast cancer
Family history	Patients that have close blood relatives with breast cancer; alterations (mutation and/or amplification) in the following genes can be associated with an increased risk of breast cancer: *BRCA1/2*, *PIK3CA*, *TP53*, *PTEN*, *PALB2*, *CHEK2* and *CDH1*
Race and ethnicity	Caucasian women are slightly more likely to develop breast cancer than African American women
Factors related to ovulation	Use of oral contraceptives, although the risk returns to baseline following cessation of contraception Nulliparous women, or those who had their first child aged >30 years
Medical history	Certain proliferative breast lesions, (e.g. ductal hyperplasia, fibroadenoma, sclerosing adenosis, papillomatosis, radial scar) Lobular carcinoma in situ or lobular neoplasia Presence of benign breast conditions (e.g. dense breasts on a mammogram)
Previous medical interventions	Post-menopausal combined HRT: HRT also increases the chances of dying from breast cancer, and the likelihood that the cancer may be found only at a more advanced stage; this risk is reversible, and only applies to current and recent users Exposure to DES Previous treatment with chest radiotherapy when women were aged <40 years
Lifestyle and environmental factors	Excessive alcohol consumption, obesity, and lack of physical exercise

Abbreviations: *BRCA*: breast cancer susceptibility gene; *CDH1*: cadherin-1; *CHEK2*: checkpoint kinase 2; DES: diethylstilbesterol; HRT: hormone replacement therapy; *PALB2*, partner and localizer of the *BRCA* gene 2; *PTEN*: phosphatase and tensin homolog; *PIK3CA*: phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.
Source: Feng 2018.[10]

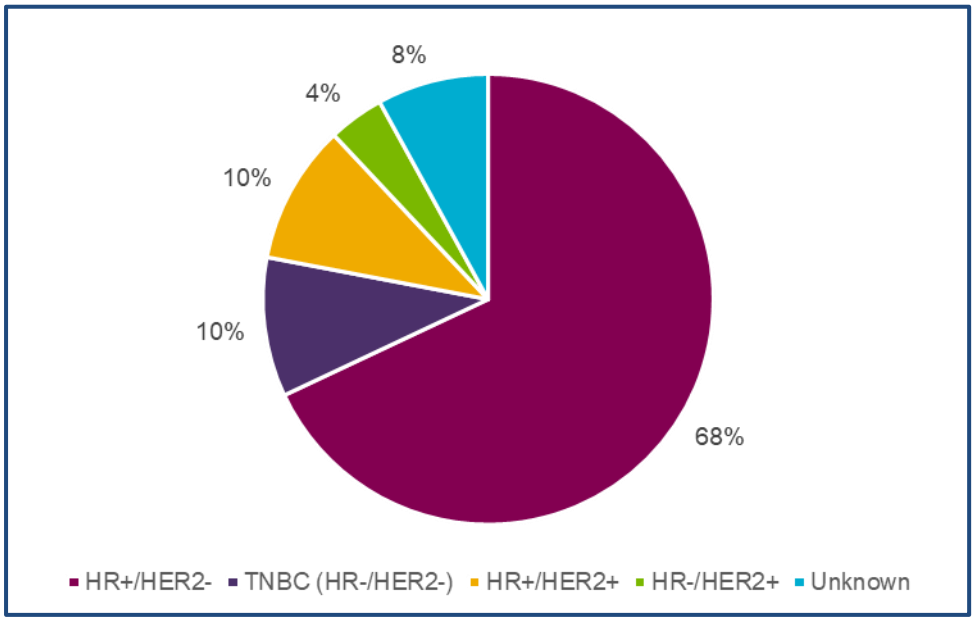
B.1.3.1.2 Epidemiology

Breast cancer is the most common cancer in the UK, accounting for 15% of all new cancer cases, and occurring at an incidence of approximately 55,000 and 370 cases per year (between 2016–2018) among females and males, respectively.[1] In 2018, the age standardised rate (ASR) per 100,000 was 87.7 incident cases and 663.4 prevalent cases.[51]

As described above, there are four main histological subgroups of breast cancer. Data from the Surveillance, Epidemiology, and End Results (SEER) Program (2014–2018) indicate that the majority (approximately 68%) of breast cancer patients have HR+/HER2- disease, whilst TNBC accounts for ~10% of breast cancer diagnoses (Figure 1).[52] Similarly, a study of breast cancer patients from the North East London Cancer Network (NELCN; N=2,417), demonstrated that 10% of women (with available data) were diagnosed with TNBC.[53]

BRCA mutations are more commonly found in HER2- breast cancer.[54-60] Recent SEER data and meta-analyses in breast cancer and across tumour types, respectively, have estimated that 10.7% of TNBC and 2.7% of HR+/HER2- patients will have a g*BRCA*m.[59, 60] Some factors, including younger age of onset and family history, can be predictive of *BRCA*m disease.[50]

Figure 1: Proportion of female breast cancer by histological subtype



Abbreviations: HER2: human epidermal growth factor receptor 2; HR: hormone receptor; TNBC: triple negative breast cancer..
Source: NCI SEER Program, 2020.[52]

B.1.3.1.3 Diagnosis of breast cancer

Approximately 80–90% of breast cancers are diagnosed at an early stage of disease,[61] largely due to the screening strategies in place. In the UK, women aged between 50 and <71 years are invited for triennial breast cancer screening as part of the NHS Breast Cancer Screening Programme (NHSBSP). As a result, 17,771 cases of cancer were detected through screening in 2019–2020, equating to 8.4 cases per 1,000 women screened.[62] Furthermore, women with an elevated risk of breast cancer due to inheritance of a *BRCA*1/2m are offered yearly magnetic resonance imaging (MRI) scans from ~30 years of age.[63, 64] Based on this additional screening, approximately 7,600 new cases of breast cancer are detected in women in their 40s every year, and approximately 2,300 new cases in women aged ≤39 years.[65]

Symptoms of breast cancer

Not all patients are identified through screening, and some patients may present to their general practitioner (GP) with symptoms.[66] Symptoms of eBC vary, and may include a lump in the breast, dimpling in the skin, nipple retraction, nipple discharge, redness/thickening of the nipple-areolar, and/or a change in the size or shape of the breast.[67, 68]

Diagnostic evaluation

In the UK, National Institute for Health and Care Excellence (NICE) guideline (NG)101 ("Early and locally advanced breast cancer: diagnosis and management") indicates that people with symptoms reflective of breast cancer should be referred by their GP to designated breast clinics in local hospitals.[23] Initial investigations for suspected breast cancer should be performed if a patient is:[23]

- Aged ≥30 years with an unexplained breast lump with or without pain
- Aged ≥50 years with discharge, retraction, or other changes of concern in at least one nipple

- Experiencing skin changes suggestive of breast cancer

Patients identified through screening should also be referred to a breast clinic, for further investigations.[23]

Several guidelines exist for the diagnosis of breast cancer, including those published by NICE (Table 4).[22] General consensus is that clinical assessment should comprise physical examination of breasts and lymph nodes, followed by imaging (mammography and ultrasound).[23, 30, 31] Guidelines also recommend a confirmed pathological assessment based on biopsy, with NICE additionally recommending a histological assessment of HR and HER2 status.[23, 30]

Table 4: UK clinical guidelines for the diagnostic work-up for eBC

Diagnostic step	Description
Clinical assessment	
Assessment of general health status	• Medical history and menopausal status[69] • General physical exam, FBC and liver, renal and cardiac function tests[69]
Physical examination of breasts and lymph nodes	• Bimanual palpitation of the breasts and regional lymph nodes, and assessment for distant metastases (bone, liver, lungs)[69]

Imaging	• Breast imaging should involve bilateral mammogram and ultrasound of breasts and axillae in all cases[70]
	  ○ In women under 40 years, ultrasound is the initial imaging modality of choice; mammography is only indicated in strongly suspicious cases and in all cases found to be malignant on biopsy, to exclude other incidental lesions.
	  ○ In women over 40 years of age, both mammography and ultrasound should be performed.
	  ○ Digital mammography should be considered in all cases in the dense breast and in younger women.
	• MRI should not routinely be used in pre-operative assessment;[69, 70] MRI should be offered to people with invasive breast cancer:[23, 70]
	  ○ If there is discrepancy regarding the extent of disease from clinical examination, mammography and ultrasound assessment for planning treatment.
	  ○ If breast density precludes accurate mammographic assessment.
	  ○ To assess the tumour size if breast-conserving surgery is being considered for invasive lobular cancer
	• Imaging should precede needle aspiration or tissue sample procedures[70]

Pathological assessment	
Biopsy and cytological/histological assessment	• Pathological diagnosis should be based on a core needle biopsy, although fine needle aspiration may be used in certain circumstances[69] • The pathological report should include histological type, grade, immunohistochemical evaluation of HR (ER and PR), HER2, Ki67 (or other marker of proliferation) status[23, 69]

Abbreviations: eBC: early breast cancer; ER: oestrogen receptor; FBC: full blood count; HER2: human epidermal growth factor receptor 2; HR: hormone receptor; MRI: magnetic resonance imaging; NICE: National Institute of Health and Care Excellence; PR: progesterone receptor.

Current use of genetic testing for g*BRCA*m

g*BRCA*m are associated with a higher risk of developing breast cancer, and have an important impact on prognosis and chemosensitivity (further details provided in Section B.1.3.2).[10, 11, 49] However, g*BRCA* testing (specifically to identify germline mutations) is currently only offered to women with a high pre-test carrier probability, and tumour *BRCA* (t*BRCA*) testing (to identify mutations which are germline or somatic in origin) is not routinely performed in the eBC setting.

NICE guideline CG164 (2013) recommended that an appropriate pre-test carrier probability threshold for g*BRCA* testing in patients with breast cancer is ≥10% (combined *BRCA*1 and *BRCA*2),[22] and NG101 (2018) noted that with this threshold in mind, eligibility should include women <50 years with TNBC.[23] However, more recently, the National Genomic Test Directory (NGTD) has defined more specific eligibility criteria for g*BRCA* testing according to multiple factors which influence pre-test carrier probability, such as age, family history, and tumour characteristics; these criteria currently drive clinical practice. The full NGTD eligibility criteria are outlined in Appendix M, but the two criteria most applicable to this appraisal are:[24]

- g*BRCA* testing offered to women aged <60 years with TNBC
- g*BRCA* testing offered to women aged <30 years for other breast cancer types (including HR+/HER2- patients)

Detection of g*BRCA*m has the potential to inform the management plan for both the patient and their family. For the patient themselves, it may inform the choice of surgical approach and chemotherapy regimen, and will influence how physicians counsel them about their risk of developing secondary malignancies (see Section B.1.3.2 for a summary of the burden of disease);[71, 72] For the patient's family, identification of g*BRCA*m may allow for the identification of affected family member carriers via cascade testing. Affected family members may then derive benefit from increased monitoring to allow for early detection and treatment of breast/ovarian cancer, or treatment such as chemoprevention and risk-reducing mastectomy and/or oophorectomy.[22]

Given the potential to both prevent *BRCA*-related cancers and to improve outcomes via early detection and more targeted treatments, widespread g*BRCA* testing has been shown to be a cost-effective healthcare intervention. A multi-country (including UK) cost-effectiveness analysis of population-based *BRCA* testing found it to be extremely cost-effective in comparison with criteria/familial history-based testing, with an ICER of $5,639 per quality-adjusted life year (QALY) and $21,191 per QALY from UK societal and payer perspectives (perspectives defined according to WHO guidelines), respectively.[73] The adoption of more widespread genetic testing also aligns with broader NHS priorities including a move towards improved outcomes through personalised medicine,[25, 26] and an ambition to be the world's most advanced genomic healthcare ecosystem via the Genome UK strategy.[27] [redacted]

B.1.3.1.4 Breast cancer staging

Once patients are diagnosed, breast cancer is clinically staged according to the eighth edition of the AJCC TNM system.[41] These criteria are used to indicate the clinical severity of a patient's breast cancer according to the extent of the primary tumour (T), the extent of spread to the lymph nodes (N), and the presence of metastasis (M), as presented in Table 5.[41]

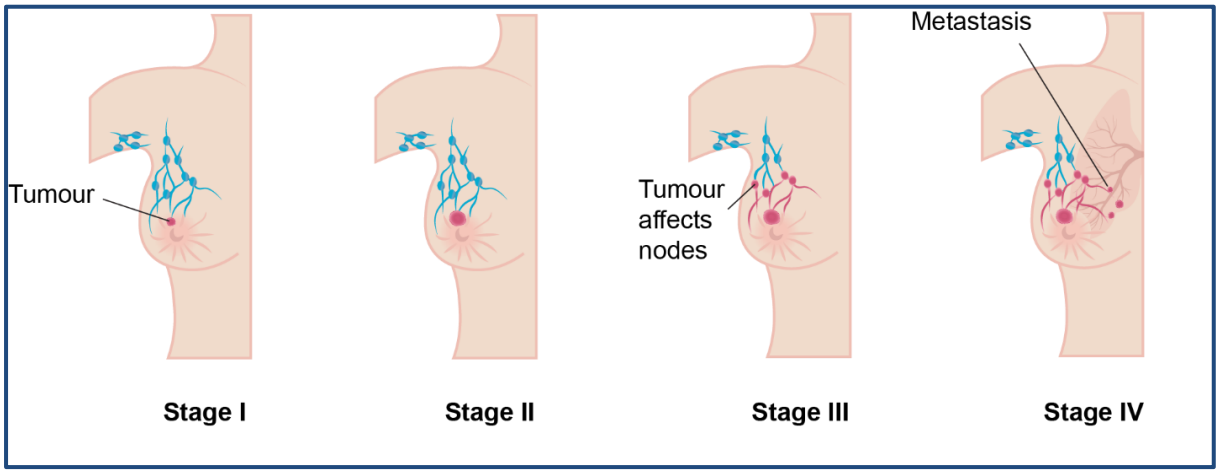
Table 5: AJCC TNM staging criteria for breast cancer

Stage		T	N	M
Non-invasive breast cancer – carcinoma *in situ*	0	Tis	N0	M0
Localised breast cancer (tumour size ≤2 cm)	IA	T1[a]	N0	M0
	IB	T0 T1[a]	N1mi N1mi	M0 M0
Early, locally advanced breast cancer	IIA	T0 T1[a] T2	N1[b] N1[b] N0	M0 M0 M0
	IIB	T2 T3	N1 N0	M0 M0
Late, locally advanced breast cancer	IIIA	T0 T1[a] T2 T3 T3	N2 N2 N2 N1 N2	M0 M0 M0 M0 M0
	IIIB	T4 T4 T4	N0 N1 N2	M0 M0 M0
	IIIC	Any T	N3	M0
Advanced/metastatic breast cancer	IV	Any T	Any N	M1

Footnotes: The AJCC TNM staging system describes tumour size (T), the spread of cancer to nearby lymph nodes (N) and the presence of metastases (M). [a]T1 includes T1mi; [b]T0 and T1 tumours with nodal micro metastases only are excluded from Stage IIA and are classified Stage IB.
Abbreviations: AJCC: American Joint Committee on Cancer; M: metastasis; mi: micro metastases; N:node; T: tumour; TNM: tumour, node, metastasis.
Source: AJCC TNM Classification of Tumours (8th Edition), 2017.[41]

eBC comprises tumours that are restricted to the breast, or to the breast and nearby lymph nodes, without metastasis (AJCC TNM stages I–III, see Figure 2).[41] Patients may also be categorised according to the presence/absence of high-risk clinicopathological features such as biomarker status, and the presence of residual disease or positive pathologically confirmed lymph node involvement, following local treatment and chemotherapy.[14] Genetic factors and other tumour characteristics may also be used when determining risk. The definition of high-risk disease is discussed below.

Figure 2: Breast cancer staging according to the AJCC TNM staging criteria (8th edition)



Abbreviations: AJCC: American Joint Committee on Cancer; TNM: tumour, node, metastasis.
Source: AJCC TNM Classification of Tumours (8th Edition), 2017.[41]

B.1.3.1.5 Defining 'high-risk' disease

In UK clinical practice, clinicians routinely assess patients for high-risk disease (i.e. the anticipated risk of recurrence). Currently, this risk assessment is primarily used to inform whether or not to offer the patient chemotherapy, alongside other considerations such as patient fitness and patient preferences. Patients deemed to be at high-risk of recurrence are more likely to be offered chemotherapy (rather than surgery-alone, or surgery followed by endocrine therapy only), and may be more likely to receive their chemotherapy in the neoadjuvant rather than adjuvant setting.[7-9]

Although risk-assessments are routinely used to inform patient management, there is currently no clear definition of what constitutes a 'high-risk' eBC population, and there is heterogeneity in how risk is defined both at a global level and within the UK. Globally, in clinical studies and other published literature, risk has been defined in a variety of different ways using several prognostic factors; these factors include tumour characteristic (such as size and grade), nodal involvement, genetic factors (including *BRCA* mutation status), and response to prior treatments.[7] A multitude of scoring systems exist which combine these factors in different ways, but these tools often lack a defined threshold for what constitutes "high-risk".[7-9] Regardless of the lack of definition, specific guidance exists for high-risk eBC patients (see Section B.1.3.2).

AstraZeneca consulted with UK clinicians in two rounds of interviews to gain their expert opinion; the first round of interviews gained preliminary feedback, while the second round was used to validate and corroborate these initial findings. This structured method was used to align with the recommended approach in the updated NICE process and methods guide.[74, 75] On the topics of defining "high risk", clinicians stated that they conduct risk assessments based on their individual clinical judgement, incorporating the prognostic factors outlined above, and sometimes alongside risk calculation tools such as the Nottingham Prognostic Index or the PREDICT tool. However, physicians reported variations in the thresholds used for each factor in isolation, as well as how factors are combined.[8, 9] Clinicians also highlighted that, unlike the OlympiA eligibility criteria where it was used in a subpopulation of patients (see Section B.2.3.2 for a summary of the OlympiA eligibility criteria relating to risk), their current approach to risk-assessments does not routinely include the CPS+EG score. Overall, the clinicians agreed that the OlympiA trial

eligibility criteria relating to risk status are considered generalisable to clinical practice, meaning the OlympiA efficacy data can be generalised to the UK high-risk eBC population.[8, 9]

Given this, the identification of high-risk patients eligible for novel therapies in eBC in the UK is expected to be based on prognostic factors and risk assessment tools, and consistent with the approach already used in clinical practice. Prior NICE guidance for novel technologies in eBC has already taken such an approach, and has aimed to simplify and provide consistency in the definition of risk across multiple technologies. For example in DG34 when NICE reviewed three tumour profiling tests in eBC (EndoPredict, MammaPrint, and Oncotype Dx), each of which had slightly different risk-based target populations, the NICE recommendation simplified this to require patients to include ER-, HER2-, lymph node negative eBC with an "*intermediate risk of distant recurrence using a validated tool such as PREDICT or the Nottingham Prognostic Index*".[76]

B.1.3.1.6 Humanistic and economic burden of breast cancer

eBC

Although eBC is associated with high survival rates, patients generally experience a negative impact on their HRQoL, particularly whilst receiving active treatment; AEs related to chemotherapy can be particularly burdensome, including diarrhoea, systemic therapy symptoms, hair loss and fatigue.[77] This treatment-related HRQoL deterioration usually declines or disappears entirely following cessation of treatment, although some symptoms (such as anticipatory nausea, weight gain, endocrine effects, disturbed sleep and sexual dysfunction) may persist for three to 24 months after completion of chemotherapy.[77] Furthermore, the initial diagnosis of breast cancer affects patients' psychological and social QoL, and up to 65% of patients experience anxiety during treatment. [78] For patients with high-risk disease, their poorer prognosis (Section B.1.3.2) may confer an additional humanistic burden, as a result of enhanced psychological and emotional stresses due to their disease status.

eBC is also associated with a large economic burden, due to direct costs incurred from diagnosis, treatment and other utilisation of healthcare services.[79] A UK-based study reported that the average predicted total costs of eBC care within one year of diagnosis are £6,774, with this observed to vary by stage and age of patients.[79] However, these costs remain substantially lower than costs incurred at later stages of disease.[39]

Recurrent and metastatic breast cancer (mBC)

Despite the curative intent of treatment for eBC, recurrence and subsequent progression to mBC remain relatively common, especially in patients with high-risk disease (Section B.1.3.2). Disease recurrence negatively impacts patients' HRQoL, especially if metastases develop beyond the locoregional setting.[80, 81] The impact of recurrence on HRQoL is evidenced by a Dutch real-world study which found patients with stage I–III breast cancer (N=2,684) who experienced either a local recurrence or developed distant metastases reported a lower HRQoL than patients who remained disease-free.[80] Specifically, patients who developed distant metastases experienced a greater HRQoL decline than those who experienced local recurrence.[80] Furthermore, compared to patients who remained disease-free, patients with disease recurrence report significantly poorer levels of physical and social functioning, pain, emotional role limits, energy/fatigue and general health perceptions.[81]

Individuals with mBC may experience increased fatigue, appetite loss, pain and dyspnoea;[82] this increasing symptom burden observed as disease progresses occurs alongside increases in depression, fatigue, and anxiety scores, and has been shown to be correlated with a lower HRQoL.[82] In the UK, a questionnaire-based cross-sectional study conducted in two cancer centres and online via the Breast Cancer Care website found that among 235 breast cancer patients, lower overall scores were reported for physical, social, emotional and functional wellbeing in women with a higher symptom burden.[83] Patients who progress to mBC experience the highest symptom burden and experience a further decline in HRQoL.[84]

In addition to the humanistic burden, there is a substantial economic impact of disease recurrence and progression. In 2009, analysis of NHS patient-level data (N=77), demonstrated that the estimated median cost of treating relapsed breast cancer in the UK was £31,402.60, when costs associated with hospital and community care are considered.[39] This is likely to have since increased due to the availability of more targeted therapies in the metastatic setting.

There exists a significant unmet need for a treatment which effectively prevents or delays disease recurrence, thus reducing the substantial associated humanistic and economic burdens. Furthermore, the economic burden of mBC is considerable, with the gross annual national cost of incident mBC (any subtype) estimated at $22 million (2002 GBP) in the UK.[85] Additionally, breast cancer progression also contributes directly to lower rates of employment among affected individuals, and patients with mBC experience a substantial loss in productivity, compared to patients living with non-metastatic disease.[86]

Patients with *BRCA*m disease

The unique characteristics of patients with g*BRCA*m breast cancer can magnify the humanistic burden of disease in these individuals. Patients in this indication are typically younger than the overall breast cancer population and may therefore be establishing their careers and/or have childcare responsibilities which will be affected by a breast cancer diagnosis. Patients with g*BRCA*m may also experience worse social wellbeing, with a UK-based study of breast cancer patients demonstrating that social wellbeing is significantly lower in younger women ($p<0.001$).[83] Patients with g*BRCA*m also have a higher risk of developing new primary and secondary tumours, CNS metastasis, and a four-fold increased risk for developing contralateral and ipsilateral recurrence, which has the potential to worsen patient QoL.[87] Furthermore, these patients may also experience an additional humanistic burden associated with communicating the results of genetic testing to family members.[88, 89]

The typically young age of patients with g*BRCA*m breast cancer may further contribute to the economic burden of disease; an English population-based study demonstrated that patients aged 18–64, regardless of breast cancer stage, incurred a higher number of hospital admissions and a markedly higher increment in the cost of care, compared to patients aged ≥65 years.[90] Furthermore, severe indirect financial implications may arise if a patient's diagnosis and treatment has career implications, and if they occur when they are also supporting young families.

Patients with *BRCA*m breast cancer therefore face an elevated humanistic and economic burden with respect to patients without *BRCA*m disease, emphasising the unmet need for an effective treatment that prevents or delays recurrence in this patient population.

B.1.3.2 Treatment aims and the current clinical pathway of care

B.1.3.2.1 Treatment aims

In the UK, treatment of eBC is curative in intent, aiming to remove the cancer, reduce the risk of disease recurrence, and prevent the spread of disease.[4] Accordingly, prolonging iDFS, defined as living free of loco-regional, distant recurrence, or new cancer,[35] is a key aim for eBC treatment. The relevance of iDFS as an endpoint in eBC is summarised in Figure 3.

Figure 3. Relevance of iDFS as an endpoint in eBC

According to guidance provided by the EMA and FDA, OS should be used as the standard clinical benefit endpoint in oncology clinical trials.[91, 92] However, the use of OS in early-stage oncology clinical trials is subject to a number of limitations:[91-93]

- Development of effective oncology therapies has increased survival rates, meaning longer trial follow-up periods are required to collect mature OS data; in some cases, using OS could delay patient access to treatment
- Survival rates in eBC are often influenced by treatment effects of subsequent therapy lines as the disease progresses, meaning adequate survival benefit assessment of early-stage treatments is difficult

In the OlympiA indication, accurate estimation of OS would require a long follow-up time; therefore, iDFS is considered an appropriate primary endpoint to assess treatment efficacy. iDFS represents a direct measure of olaparib's efficacy as, unlike measures of OS, it is not confounded by the efficacy of subsequent therapies used following recurrence. Furthermore, substantial evidence supports the use of disease-free survival (DFS) endpoints as surrogates for OS in patients with eBC:

- A recent evaluation assessing the relationship between OS and DFS in HER2-, eBC patients found a nominally significant positive correlation between OS and DFS in HER2-, eBC, indicating that DFS can be used as a valid surrogate for OS:[94] the Spearman's rank correlation coefficient between OS and DFS was 0.803 (p=0.016) when weighted by study size
- A strong association between DFS and OS in HER2+ breast cancer has also been acknowledged[95]
- Another evaluation assessing a range of potential surrogate endpoints in breast cancer found that, compared with relapse-free survival (RFS), locoregional RFS and dDFS, iDFS had the highest association with OS[96]

iDFS can also be considered a **patient-relevant endpoint**; iDFS reflects a patient's anticipated disease status, which may have broader implications than survival alone. Recurrence of disease is associated with an increased symptom burden, poorer prognosis, initiation of further treatment and a corresponding reduction in HRQoL (due to the impact of symptoms and psychological factors).[82, 97-99] Accordingly, a Dutch real-world study has demonstrated that recurrence is associated with a reduction in health-state utility values (Section B.1.3.1).[80]

In addition to this, iDFS was the primary endpoint in the KATHERINE trial of T-DM1 for patients with residual invasive disease after surgery for HER2+ eBC, and was accepted in the accompanying NICE evaluation (TA632)[100]; similarly, iDFS was accepted as the primary outcome in NICE evaluation for pertuzumab (TA569)[101] and neratinib (TA612)[102] in HER2+ eBC, based on the APHINITY and ExteNET trials, respectively.

B.1.3.2.2 Clinical pathway of care for HER2- eBC

The current UK treatment pathway for eBC involves a combination of local therapy and systemic anticancer therapy, either in the adjuvant or neoadjuvant setting, and varies based on HR and HER2 expression status, and whether the patient is assessed as having high-risk disease. The following sub-sections provide an overview of the treatment pathway for patients with HER2-

breast cancer in the UK, summarised in Figure 4. There is currently no formally accepted NICE treatment pathway delineated specifically for patients with g*BRCA*m.

Local therapy

In current clinical practice, and per treatment guidelines, most patients receive surgical treatment, which consists of either a mastectomy or lumpectomy (breast-conserving surgery).[23] Patients usually receive breast-conserving surgery as the first surgical option, with further surgery (re-excision or mastectomy), offered where invasive cancer or ductal carcinoma *in situ* is present.[23, 70] However, in cases where a patient receives a g*BRCA* diagnosis pre-operatively, they may instead be offered a bilateral risk-reducing mastectomy to minimise risk of recurrence.[22] Surgery can be initiated with or without adjuvant radiation, although radiation is preferred if patients undergo breast-conserving surgery and have invasive breast cancer;[23, 70] women who have undergone breast-conserving surgery may undergo partial-breast radiotherapy if they are considered to be at high risk of recurrence.[23]

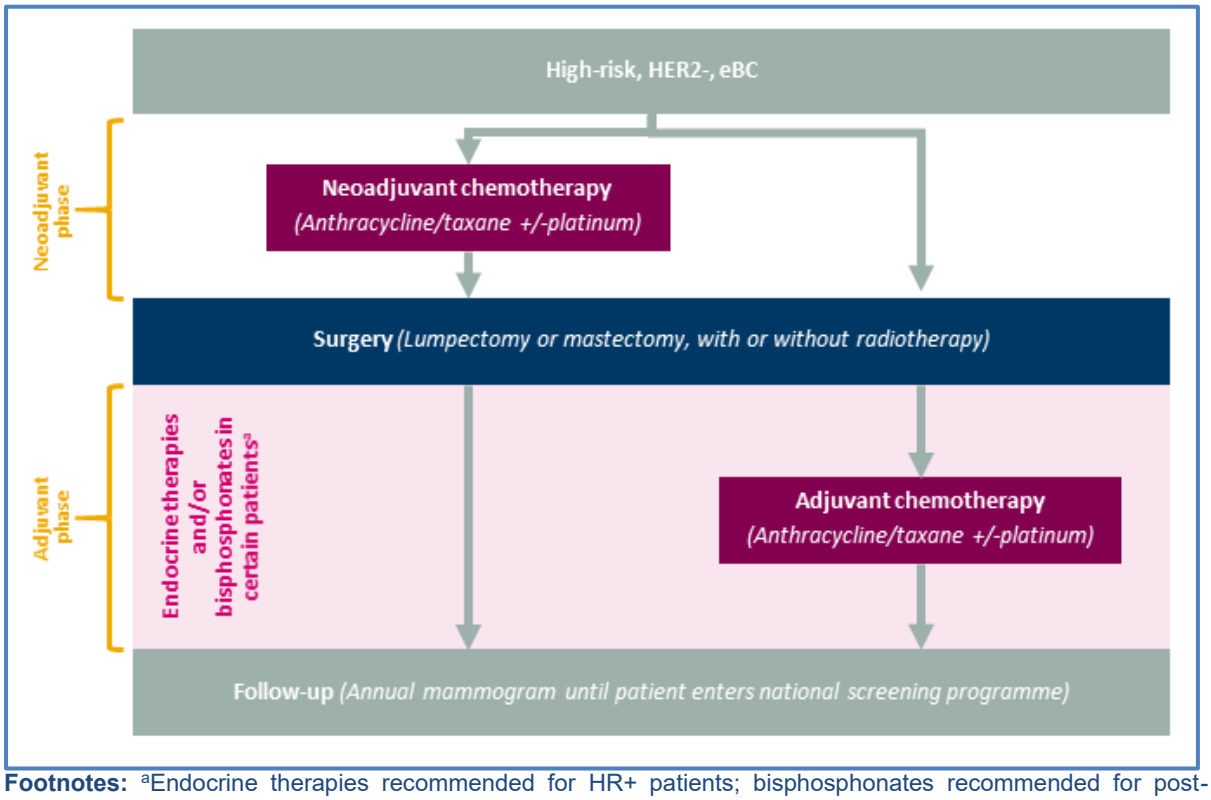
Systemic anticancer therapy

Systemic treatment for patients with eBC includes chemotherapy either in the neoadjuvant or adjuvant setting, endocrine therapy, and other supplementary treatments such as bisphosphonates.[23]

High-risk eBC patients, as defined by individual clinical judgement, are all recommended to undergo chemotherapy; this can be offered either in the neoadjuvant or adjuvant setting, and usually consists of an anthracycline/taxane with or without a platinum regimen.[23] The decision to undergo neoadjuvant or adjuvant chemotherapy is influenced by a number of factors, including the need to reduce tumour size for optimal surgery, or the presence of specific tumour characteristics.[23] Following chemotherapy, off-label adjuvant bisphosphonates may be used in some patients, particularly in post-menopausal women.[23]

Systemic treatment patterns differ between breast cancer subgroups defined by HR status. Patients with TNBC are often recommended to undergo neoadjuvant chemotherapy,[23] as their subsequent response is a prognostic indicator. HR+/HER2- patients are recommended to undergo 5–10 years of endocrine therapy, with high-risk patients typically receiving treatment for closer to 10 years.[23] Furthermore, high-risk patients are also likely to be given ovarian cancer suppression medication, particularly pre-menopausal women. Patients with *BRCA*m disease are more likely to receive a platinum-containing chemotherapy regimen.[30]

Figure 4: Current treatment pathway in high-risk eBC patients



Footnotes: [a]Endocrine therapies recommended for HR+ patients; bisphosphonates recommended for post-menopausal women.
Abbreviations: ER: oestrogen receptor; HER2: human epidermal growth factor receptor 2; HR: hormone receptor; PR: progesterone receptor; TNBC, triple-negative breast cancer
Source: NG101[23]; AstraZeneca Data on File (UK clinical expert Interviews, December 2021 and March 2022).[8, 9]

B.1.3.2.3 Clinical burden of BRCAm, HER2-, high-risk eBC associated with the current standard of care

Despite the curative intent of treatment for eBC, recurrence remains relatively common, particularly in patients with high-risk clinicopathologic features;[37] furthermore, when breast cancer recurs it usually presents as distant metastases rather than locoregional recurrence.[103] Following development of mBC, breast cancer is generally considered incurable and survival dramatically decreases; the 5-year survival rate of women with mBC in England (at diagnosis) is only 26.2%.[104] This decrease in survival for patients with mBC highlights the importance of therapies that prevent or reduce the rate of disease progression in eBC patients.

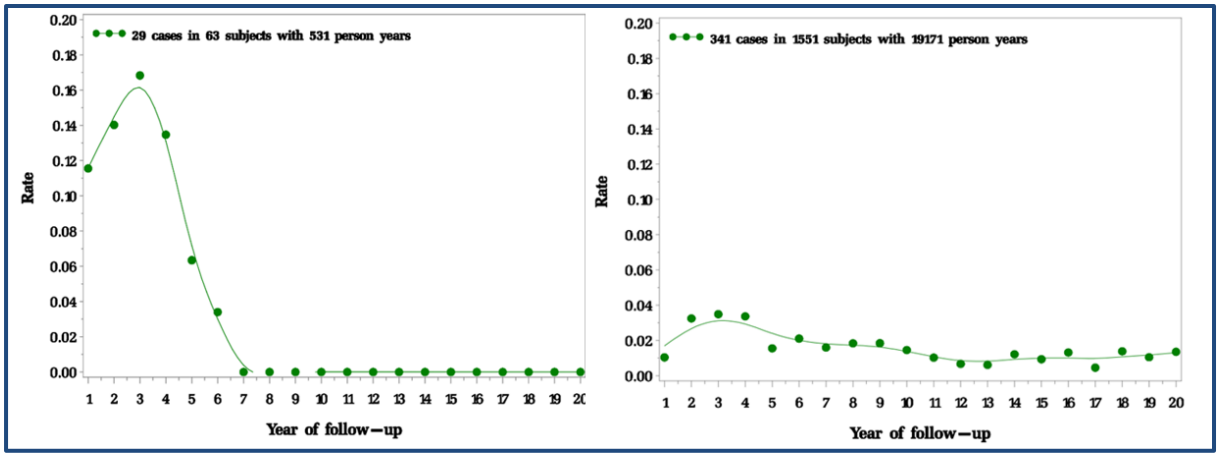
Historically, it has been assumed that patients with TNBC have a worse prognosis and fewer treatment options, and therefore a greater unmet need, than those with HR+/HER2- disease. As a result, much of the past literature on HR+/HER2- patients considered this whole patient group as 'lower risk'. However, there is now a growing understanding regarding the poor prognosis of certain HR+/HER2- patients; accordingly, trials such as OlympiA and monarchE enrolled HR+/HER2- patients with high-risk disease, highlighting the poorer prognosis in this patient population.[105, 106] Evidence obtained from interviews, involving four UK clinicians, has highlighted that clinicians currently see histological subtype as one factor within a broader risk assessment; they acknowledge that TNBC is a negative prognostic factor, but that this does not preclude HR+/HER2- patients from also being considered high-risk and experiencing similarly poor outcomes to patients with TNBC.[8, 9]

Irrespective of histology, high-risk clinicopathological features result in a worse patient prognosis.[36, 107] In a cohort of US patients with stage I–III disease and unselected by surgical outcome (and therefore potentially including high-risk patients with residual disease after surgery) the overall cumulative incidence of developing distant metastases was observed to be 20%, 30% and 36% at 4, 8 and 12 years post-diagnosis.[36] This contrasts with the lower recurrence rates observed in patients not considered to be high-risk; a German registry study demonstrated a 10-year recurrence rate of 16% in patients with free resection margins following surgery.[108] Moreover, in a recent (2021) US-based retrospective database study of 4,028 breast cancer patients (including HR+/HER2- high-risk patients) who had received surgery and adjuvant endocrine therapy, 11.9% of patients with high-risk clinicopathologic features had experienced invasive disease recurrence or death only two years after initiating adjuvant endocrine therapy; this compared with 2.6% and 2.9% in patients with node negative disease (N0) and those categorised as low risk, respectively.[107] Therefore, although high-risk disease is defined heterogeneously in the literature, a similar trend is observed across studies assessing the impact of high-risk clinicopathological features on prognosis.

Although patients can be considered as “high-risk” irrespective of histological subtype, their histology can inform their prognosis, particularly in how risk of recurrence evolves over time. For patients with TNBC, studies have shown that the risk of recurrence is highest during the first five years after becoming disease-free, with a significant decrease and plateauing of the recurrence rate over subsequent decades. In contrast, patients with HR+/HER2- disease have been shown to remain at a constant risk of recurrence for at least 20 years after diagnosis. The risk of recurrence of patients with HR+/HER2- and TNBC high-risk disease will therefore eventually cross over time, and HR+/HER2- patients will ultimately experience a worse long-term prognosis.

An illustration of these contrasting risk patterns is provided in Figure 5, obtained from a study by Sopik, Sun & Narod (2018), which aimed to identify factors that predict survival after distant recurrence in a large cohort of eBC patients (N=2,312) in Toronto, Canada.[109] Figure 5 depicts the annual rate of distant recurrence following diagnosis; for TNBC patients, all distant recurrences occurred in the first six years following diagnosis, whilst for HR+ disease they occurred at an approximately constant rate throughout the 20-year follow-up.[109]

Figure 5: Annual rate of distant recurrence following diagnosis of invasive breast cancer among patients with TNBC (left) and HR+ (right) disease



Abbreviations: HR+: hormone receptor positive; TNBC: triple-negative breast cancer
Source: Sopik, Sun & Narod (2018)[109]

Further data in support of these contrasting risk patterns comes from a 2019 study conducted in the Netherlands, which assessed recurrence rates across breast cancer subtypes; patients with TNBC had the highest recurrence rates in the second year after diagnosis, whereas HR+ patients showed a more continuous recurrence pattern over time.[110] Furthermore, UK clinical expert opinion suggests that these trends would also be expected in a *BRCA*m, HER2-, high-risk eBC cohort, with the risk of recurrence for TNBC patients expected to decrease and plateau between five and ten years, while HR+/HER2- patients experience a constant and indefinite risk of relapse.

Finally, *BRCA*m breast cancer has distinct tumour characteristics compared to the sporadic breast cancer population and can be characterised by a more aggressive disease with a higher risk of recurrence.[11] For example, in a study assessing a matched cohort of eBC patients, those with *BRCA*m disease had a significantly higher risk of recurrence when compared with patients with non-*BRCA*m breast cancer (*BRCA*1: hazard ratio 1.14; 95% CI 1.02–1.28; p=0.02; *BRCA*2: hazard ratio 1.32; 95% CI 1.19–1.47; p<0.001).[111] This is further supported by a large meta-analysis in stage I–III breast cancer, which demonstrated that patients with g*BRCA*m breast cancer had a significantly worse recurrence-free survival and distant metastasis-free survival compared to patients with non-*BRCA*m disease (hazard ratio 1.76 [95% CI: 1.05–2.95] and 1.80 [95% CI: 1.25–2.60], respectively).[112]

Together, these data demonstrate that there remains a substantial clinical burden in *BRCA*m, HER2-, high-risk eBC, which is not sufficiently addressed by currently available treatments. *BRCA* mutations are known tumour drivers, and their presence is predictive of tumour sensitivity to PARPi, highlighting a clear rationale for the potential use of PARPi for the treatment in *BRCA*m eBC.[17, 113]

B.1.3.2.4 Unmet need in BRCAm, HER2-, high-risk eBC

Beyond (neo)adjuvant chemotherapy, surgery, radiotherapy, endocrine therapy, and bisphosphonates, no therapies are available for the treatment of HER2-, high-risk eBC in the UK with the aim of preventing or further delaying recurrence. Furthermore, there are no treatments available that specifically target *BRCA* mutations, and these patients do not have a delineated treatment pathway. Consequently, patients with *BRCA*m, HER2-, high-risk eBC still experience disease recurrence and progression. Furthermore these patients have a higher risk of recurrence compared to non-*BRCA*m patients, and often experience disease onset at a younger age.[111] In addition to this clinical burden, disease recurrence and progression have been shown to negatively impact patient HRQoL and are associated with a high economic burden to the NHS. Therefore, there is a clear and substantial unmet need for an effective, targeted treatment option that prevents or delays disease recurrence, progression to mBC and the additional burden that this imposes on patients and the NHS.

Despite differences in baseline risk of recurrence and treatment options between HR+/HER2- and TNBC, the unmet need for an effective, targeted treatment to prevent or delay disease progression is largely consistent in HER2- eBC when considering those patients with a high-risk of disease progression. There is a lack of adjuvant treatment options with demonstrated efficacy for TNBC patients who have residual disease following neoadjuvant chemotherapy, and, aside from endocrine therapy, there are no treatments for HR+/HER2- patients to prevent disease recurrence following adjuvant chemotherapy. This contrasts with HER2+ disease, where patients

can benefit from therapies that target the underlying tumour driver, such as trastuzumab emtansine, following adjuvant chemotherapy.[114]

The emergence of targeted therapies, such as PARPi, has transformed the treatment landscape of mBC, alongside other cancer types including ovarian and prostate cancer, and has demonstrated long term efficacy. These therapies now have the potential to drive a step change in the clinical management of eBC and address the considerable unmet clinical need for individualised, targeted treatments in this treatment setting.

B.1.3.3 Proposed use and positioning of adjuvant olaparib

B.1.3.3.1 Overview of olaparib

Olaparib is a first-in-class orally administered PARPi,[42] and the first genetically targeted treatment for breast cancer associated with a mutation in the *BRCA*1/2 genes.[43-45] Olaparib is currently reimbursed in the following indications in England:

- As maintenance treatment for *BRCA*m-positive advanced ovarian, fallopian tube or peritoneal cancer after response to first-line platinum-based chemotherapy (TA598).[115]
- As maintenance treatment of relapsed platinum-sensitive ovarian, fallopian tube or peritoneal cancer (TA620).[116]
- In combination with bevacizumab for the maintenance treatment of advanced ovarian, fallopian tube, or primary peritoneal cancer, after response to first-line platinum-based chemotherapy in combination with bevacizumab, in patients whose cancer is associated with HRD (TA693).[117]

Olaparib in BRCAm breast cancer

Olaparib is a PARPi, inhibiting a type of enzyme required for the repair of breaks in one of the two paired strands making up DNA. This inhibition prevents the PARP-mediated repair of single DNA strand breaks (SSBs).[118-120] Preventing one strand of DNA from being repaired leads to a break in the other strand. These double-stranded DNA breaks (DSBs) are more harmful to the cell than SSBs, but can normally be repaired by a second pathway, using a process called 'homologous recombination'.[121] Therefore, in healthy cells, inhibition of PARP enzymes is less damaging, as the homologous recombination pathway is present to repair DNA damage.[119] However, mutations in the genes encoding factors required for homologous recombination, such as the *BRCA* genes, are common in cancer. Cancer cells that do not have functional homologous recombination rely on PARP-mediated DNA repair to prevent genomic instability. PARPi are therefore more effective in treating cancer cells which have mutations in the *BRCA* genes and therefore lack the homologous recombination pathway.[19, 20]

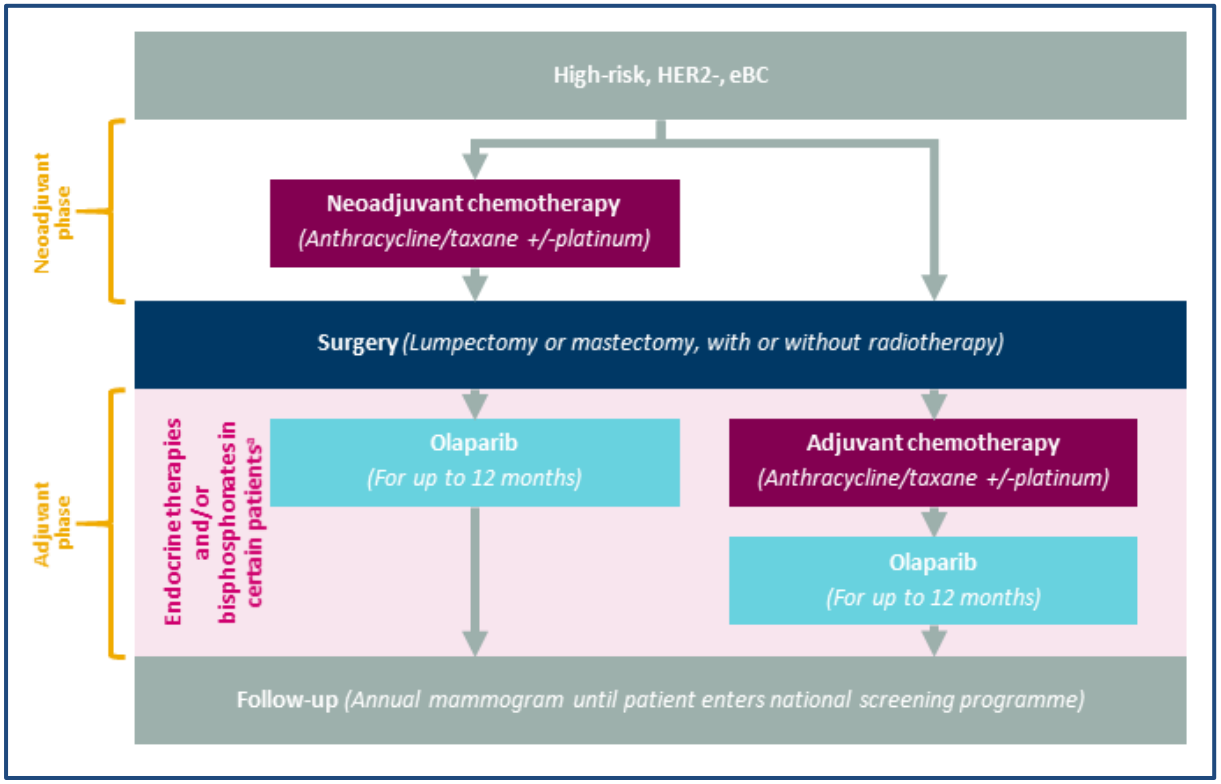
As olaparib works by inhibiting PARP enzymes and preventing the repair of SSBs, leading to DSBs during DNA replication, *BRCA*m tumour cells cannot repair these breaks via homologous recombination repair; consequently, the rate of DNA damage and genomic instability increases, resulting in the death of the cancer cell.[17, 18]

B.1.3.3.2 Proposed positioning of olaparib

Within the context of this evaluation, olaparib is positioned as an adjuvant therapy for the treatment of *BRCA*m, HER2-, high-risk eBC patients, who have previously been treated with neoadjuvant or adjuvant chemotherapy (Figure 6).

As described in Section B.1.3.2, beyond (neo)adjuvant chemotherapy, surgery, radiotherapy, endocrine therapy, and bisphosphonates, no therapies are available for the treatment of *BRCA*m, HER2-, high-risk eBC in the UK. Therefore, in this positioning, olaparib would be considered as an alternative to 'watching and waiting'.

Figure 6: Treatment pathway for HER2-negative, eBC and proposed positioning of olaparib (based on current standard of care)



Footnotes: [a]Endocrine therapies recommended for HR+ patients; bisphosphonates recommended for post-menopausal women.
Abbreviations: ER: oestrogen receptor; HER2: human epidermal growth factor receptor 2; PR: progesterone receptor; TNBC, triple-negative breast cancer.
Source: NG101[23]; AstraZeneca Data on File (UK clinical expert Interviews, December 2021 and March 2022).[8, 9]

B.1.3.3.3 Future genetic testing pathways to identify BRCA1/2 mutations

Eligibility for olaparib will require confirmation of the presence of germline *BRCA*1/2 mutations, and *BRCA*m status should be confirmed using a validated testing modality before olaparib treatment is initiated. Given the current *BRCA* testing eligibility criteria, many patients potentially eligible for olaparib in this indication are currently offered g*BRCA* testing. Furthermore, updates to the NGTD *BRCA* testing eligibility criteria are already underway; these are expected to be broadened, and will encompass all patients potentially eligible for olaparib. The recent inclusion of tumour *BRCA*1/2 testing on the National Test Directory "desirables list" is the first step in this process.

Expansion of *BRCA* testing is expected to confer wider benefits to both patients and their families, outside of simply establishing eligibility for olaparib. These benefits include optimisation of the clinical management strategy (i.e. chemotherapy and surgery options) for the patient themselves, as well as identification of germline mutation carriers in their family via cascade testing. In these carriers, risk-reducing interventions and increased monitoring can subsequently prevent eBC cases, or diagnose them earlier to improve outcomes (see Section B.1.3.1 for an overview of the current and evolving *BRCA* testing landscape). Furthermore, expanding *BRCA* testing in breast cancer patients and initiating cascade testing has been observed to be cost-effective in Australia, suggesting this may similarity be cost-effective in the UK, should it be implemented.[122]

B.1.4 *Equality considerations*

It is not considered that the introduction of olaparib is likely to lead to recommendations which differentially impact any patients protected by equality legislation or disabled persons.

B.2 Clinical effectiveness

Summary of identification of relevant clinical effectiveness evidence

- A systematic literature review (SLR) was conducted to identify published randomised controlled trial (RCT) data for the management of patients with HER2-, eBC.[123] This SLR identified one relevant RCT of direct relevance to the decision problem in this evaluation, OlympiA.[13, 14, 105]

Summary of clinical effectiveness of olaparib in the OlympiA trial

- OlympiA was a high-quality, international, Phase III, double-blind, parallel group, placebo-controlled trial that assessed the efficacy and safety of olaparib in comparison with placebo as monotherapy for the adjuvant treatment of patients with g*BRCA*m, HER2-, high-risk eBC, who had completed definitive local treatment and adjuvant or neoadjuvant chemotherapy.[13]
    - OlympiA randomised 1,836 patients to the two treatment arms (1:1 olaparib [n=921], placebo [n=915]), stratified by HR status, receipt of prior neoadjuvant or adjuvant chemotherapy, and prior platinum therapy.
    - Patients were treated with olaparib or placebo until recurrence of disease, diagnosis of a second primary malignancy, treatment discontinuation or treatment completion. Treatment duration was for up to a maximum of 12 months.
    - Patient demographics and baseline characteristics were well-balanced between treatment arms.
- **OlympiA demonstrates that adjuvant olaparib administered for up to one-year significantly improved the outcomes of patients with g*BRCA*m, HER2-, high-risk eBC**. At the early primary analysis for iDFS (DCO: 27 March 2020):
    - A **statistically and clinically meaningful investigator-assessed iDFS benefit** was observed in patients treated with olaparib compared with those treated with placebo (41.9% reduction risk of invasive disease; hazard ratio [HR]: 0.58; 99.5% confidence interval [CI]: 0.41, 0.82; p=0.0000073).
    - Subgroup analyses showed that there was **no statistical evidence of heterogeneity between any subgroup** and the ITT iDFS treatment effect, irrespective of prior chemotherapy (neoadjuvant vs adjuvant), *BRCA* status (*BRCA*1 vs *BRCA*2 mutations) or HR status.
    - Consistent with the primary endpoint, a **statistically and clinically meaningful investigator-assessed dDFS benefit** was observed in patients treated with olaparib compared with those treated with placebo (42.6% reduction risk of invasive disease; HR: 0.57; 99.5% CI: 0.39, 0.83; 95% CI: 0.46–0.74; p=0.0000257).
    - Early data showing a positive trend in OS for olaparib compared with placebo (31.7% reduction in risk of death; hazard ratio: 0.68; 99% CI: 0.44, 1.05; 95% CI: 0.49–0.95; p=0.0236)
        - At the second interim analysis for OS (DCO: 12 July 2021), statistical significance was reached in this key secondary endpoint (hazard ratio: 0.68; 98.5% CI 0.47-0.97; p=0.009),[124] which is **remarkable for an interim DCO in an eBC adjuvant setting, and clearly demonstrates the sustained benefit of olaparib**
    - No clinically meaningful differences in HRQoL scores were observed between patients receiving olaparib and placebo over the course of the study.
- Underlining the significance of the observed efficacy and the clinical value that olaparib can offer in the OlympiA indication, **the iDFS results led the IDMC to unblind the OlympiA trial earlier than expected**.[105]

Summary of safety of olaparib in the OlympiA trial

- Olaparib demonstrated an acceptable safety and tolerability profile, consistent with that observed in previous studies,[97, 125-127] and AEs observed across the treatment course with olaparib had no negative effect on patient HRQoL. Most AEs were non-serious, mild or moderate in severity, and did not result in treatment discontinuation.

Conclusion

- Olaparib is an **innovative treatment option for *BRCA*m eBC**, specifically targeting the underlying genetic driver of disease and exploiting tumour sensitivity to PARPi
- The OlympiA study is the first study to report the effect of a PARPi as adjuvant therapy on survival endpoints in patients with *BRCA*m, HER2-, high-risk eBC;
    - OlympiA clearly demonstrated a significant increase in iDFS and dDFS observed with olaparib compared to placebo, which was achieved with an acceptable safety profile and no detrimental impact to patients' HRQoL in patients with g*BRCA*m, HER2-, high-risk eBC
    - OlympiA also demonstrated an OS benefit for olaparib when compared to placebo at the second interim analysis[124]
- **Olaparib represents a step-change in the treatment paradigm**; the introduction of olaparib could address the unmet need for an effective, targeted treatment in the adjuvant setting that prevents or further delays disease recurrence, thereby reducing the additional burden that this imposes on patients and the NHS.

B.2.1 *Identification and selection of relevant studies*

A SLR was conducted to identify published RCT data for the management of patients with HER2-, eBC.[123] On November 22nd 2020, searches of electronic databases were performed, along with hand searching of conference proceedings, health technology assessment agencies and reference lists. Updated searches were performed on January 11th 2022. Across the original and updated SLRs, the electronic database searches identified 5,701 articles (excluding duplicates). Overall, a total of 48 publications, reporting on 32 clinical trials, were deemed relevant for extraction. Only one trial identified in the SLR provides clinical evidence that is directly relevant to this evaluation, the OlympiA trial, which is described in detail in the following sections.

Full details of the SLR search strategy, study selection process and results can be found in Appendix D.

B.2.2 *List of relevant clinical effectiveness evidence*

OlympiA was the only identified trial to provide clinical evidence on the efficacy and safety of olaparib as an adjuvant treatment in the patient group proposed for this evaluation. The clinical effectiveness evidence presented in this submission is therefore based on OlympiA; a summary of the OlympiA trial is presented in Table 6.

Table 6: Clinical effectiveness evidence

Study	OlympiA
Study design	A Phase III, multi-centre, randomised, double-blind, placebo-controlled trial
Population	Adult patients with HER2-, early invasive adenocarcinoma of the breast, with a documented germline mutation in *BRCA*1 or *BRCA*2 (predicted to be deleterious or suspected deleterious), having undergone adequate breast surgery and completed at least six cycles of neoadjuvant or adjuvant chemotherapy.
Intervention(s)	Olaparib 300 mg (2 x 150 mg tablets) orally administered twice daily (equivalent to a daily dose of 600 mg).
Comparator(s)	Placebo tablets orally administered twice daily.
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	Yes
Rationale if study not used in model	OlympiA is the only Phase III RCT that provides clinical efficacy and safety outcomes for olaparib as an adjuvant therapy for patients with HER2-, *BRCA*m high-risk eBC, aligned with the intervention and population of interest for this evaluation.
Reported outcomes specified in the decision problem	• iDFS • dDFS • OS • HRQoL • Adverse effects of treatment
All other reported outcomes	• Incidence of new primary breast or ovarian cancers

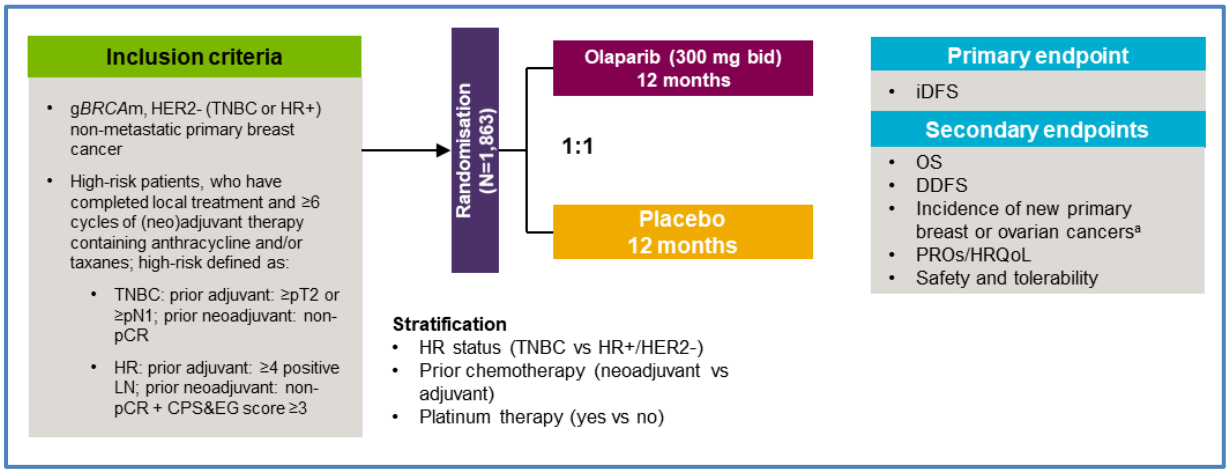
Abbreviations: *BRCA*: breast cancer susceptibility gene; dDFS: distant disease-free survival; eBC: early breast cancer; HER2: human epidermal growth factor receptor 2; HRQoL: health-related quality of life; iDFS: invasive disease-free survival; OS: overall survival; RCT: randomised controlled trial.
Source: AstraZeneca Data on File (OlympiA CSR).[13]

B.2.3 *Summary of methodology of the relevant clinical effectiveness evidence*

B.2.3.1 Trial design

OlympiA was a high-quality, international, Phase III, double-blind, parallel group, placebo-controlled trial that assessed the efficacy and safety of olaparib in comparison with placebo as monotherapy for the adjuvant treatment of patients with g*BRCA*m, HER2-, high-risk eBC, who had completed definitive local treatment and adjuvant or neoadjuvant chemotherapy. The trial design is summarised in Figure 7.

Figure 7: Overview of OlympiA study design



Footnotes: [a]Incidence of any new cancers, including new primary breast cancer, new primary ovarian cancer, new primary fallopian tube cancer, and new primary peritoneal cancer.
Abbreviations: bid: twice daily; *BRCA*: breast cancer susceptibility gene; dDFS: distant disease-free survival; HER2: human epidermal growth factor receptor 2; HR: hormone receptor; HRQoL: health related quality of life; iDFS: invasive disease free survival; LN: lymph node; OS: overall survival; PRO: patient reported outcome; TNBC: triple-negative breast cancer; vs: versus.
Source: AstraZeneca Data on File (OlympiA CSP);[35] Tutt 2021b.[105]

B.2.3.2 Eligibility criteria

Patients eligible for inclusion in OlympiA were those ≥18 years of age with histologically confirmed non-metastatic primary invasive adenocarcinoma of the breast that had high-risk clinicopathological features.[14, 35] Patients were also required to have suspected or deleterious g*BRCA*m, and to have completed adequate breast and axilla surgery, with at least six cycles of anthracycline and/or taxane-based (neo)adjuvant chemotherapy. Patients were not eligible if they had evidence of mBC or were considered at high-risk of having disseminated disease.[14, 35] A summary of key eligibility criteria is presented in Table 7; full inclusion and exclusion criteria are presented in Appendix M.

The OlympiA trial initially exclusively enrolled *BRCA*m, high-risk TNBC patients; however, following a 2015 protocol amendment due to FDA input on the trial design, HR+/HER2- patients became eligible to be enrolled in OlympiA; while it was foreseen that events in these patients might not accumulate at the same rate as in patients with *BRCA*m, high-risk TNBC, extrapolations from the metastatic setting supported the expectation that HR+ patients would also benefit from adjuvant olaparib treatment.[13]

Table 7: Summary of OlympiA inclusion and exclusion criteria

Inclusion Criteria	Exclusion Criteria
• Female or male patients aged ≥18 years with histologically confirmed non-metastatic primary invasive adenocarcinoma of the breast that have a high-risk phenotype, defined as: ○ For patients who underwent initial surgery and received adjuvant chemotherapy: ▪ TNBC patients must have been axillary node-positive (≥pN1, any	• Patients who do not have deleterious or suspected deleterious gBRCAm. • Evidence of mBC, or patients considered at high-risk of having disseminated disease (i.e. those with locally-advanced disease, clinical N2 to 3 or pathological N1 to 3, with the exception of pN1a in adjuvant patients). • Exposure to an investigational product within 30 days or five half-lives prior to

Inclusion Criteria	Exclusion Criteria
tumour size) or axillary node-negative (pN0) with invasive primary tumour pathological size >2 cm (≥pT2). ▪ ER and/or PR-positive/HER2- 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/HER2- patients must have had residual invasive cancer in the breast and/or the resected lymph nodes (non pCR) and a CPS+EG score ≥3. • Documented germline mutation in BRCA1/2 that is predicted to be deleterious or suspected deleterious. • Completed adequate breast and axilla surgery (patients with breast conserving surgery must have had adjuvant chemotherapy). • Completed at least six cycles of neoadjuvant or adjuvant chemotherapy, which contain anthracyclines, taxanes, or a combination of both. • Adequate organ and bone marrow function measured within 28 days prior to randomisation and with no blood transfusions 29 days prior to testing. • ECOG performance status 0 to 1. • Postmenopausal or evidence of childbearing status for women of childbearing potential, prior to first dose of olaparib in study period. • Patients should be randomised in the trial, ideally within a maximum of eight weeks of completion of their last treatment, but in no case longer than 12 weeks.	randomisation. • Any previous treatment with a PARPi and/or known hypersensitivity to any of the excipients of olaparib. • Patients considered at poor medical risk due to a serious, uncontrolled medical disorder, or non-malignant systemic disease. • Patients receiving systemic chemotherapy within three weeks prior to randomisation or receiving adjuvant radiotherapy within two weeks prior to randomisation. • Pregnant or lactating women.

Abbreviations: *BRCA*: breast cancer susceptibility gene; CPS+EG: clinical stage (CS), oestrogen receptor status (E), nuclear grade (G), and post-treatment pathologic stage (PS); ECOG: Eastern Cooperative Oncology Group; ER: oestrogen receptor; HER2: human epidermal growth factor receptor 2; N: node; PARPi: poly (ADP-ribose) polymerase inhibitor; PR: progesterone receptor; TNBC: triple-negative breast cancer.
Source: AstraZeneca Data on File (OlympiA CSP);[35] Tutt 2021a.[14]

B.2.3.3 Settings and locations where the data were collected

OlympiA was a multicentre study, conducted in 600 study centres across 24 countries worldwide, including: Argentina (10 centres), Australia (11 centres), Austria (17 centres), Belgium (11

centres), Canada (10 centres), China (14 centres), France (24 centres), Germany (51 centres), Hungary (2 centres), Iceland (1 centre), Israel (4 centres), Italy (20 centres), Japan (25 centres), South Korea (9 centres), the Netherlands (7 centres), Poland (7 centres), Portugal (6 centres), Puerto Rico (1 centre), Spain (38 centres), Sweden (6 centres), Switzerland (3 centres), Taiwan (9 centres), UK (22 centres), and USA (364 centres).

B.2.3.4 Trial drugs and concomitant medications

B.2.3.4.1 Trial drugs

Patients (N=1,836) that met the eligibility criteria were randomised 1:1 to receive either:[13]

- Olaparib: 300 mg olaparib (consisting of to 150 mg tablets, taken orally; 100 mg tablet available to manage dose reductions), twice daily (BID)
- Placebo: placebo tablets (matched to olaparib, taken orally) BID

Following the first dose of olaparib or placebo, patients were treated until recurrence of disease, diagnosis of a second primary malignancy, treatment discontinuation or treatment completion. Treatment duration was for up to a maximum of 12 months.[13]

Randomisation of patients to each study arm was based on the following stratification factors:[13]

- HR receptor status (ER and/or PR+/HER2- vs TNBC)
- Chemotherapy type (neoadjuvant vs adjuvant)
- Platinum therapy for current breast cancer (yes vs no)

B.2.3.4.2 Concomitant medications

Investigators could prescribe concomitant medications or treatments that were considered necessary for the patient's welfare, where it was considered to not impact the study results. A summary of the permitted and disallowed concomitant medications is presented in Table 8, with full details in Appendix M. The administration of all medication (including investigational products), and any unplanned diagnostic, therapeutic, or surgical procedures performed during the study (including blood transfusions) were recorded.[13]

Table 8. Summary of concomitant medications permitted and disallowed in OlympiA

Permitted concomitant medications	Disallowed concomitant medications
• Endocrine therapy (permitted while the patient was receiving study drug, administered per local policy and/or international guidelines) • Anti-emetics and anti-diarrheals • Anti-coagulants (including warfarin, subcutaneous heparin and low molecular weight heparin) • Bisphosphonates or denosumab	• Strong CYP3A inhibitors (e.g. itraconazole, telithromycin, clarithromycin, protease inhibitors boosted with ritonavir or cobicistat, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) or moderate CYP3A inhibitors (e.g., ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil) • Strong CYP3A inducers (e.g., phenobarbital, enzalutamide, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine and St John's Wort) or moderate CYP3A inducers (e.g., bosentan, efavirenz, modafinil) • Live viral and bacterial vaccines (whilst the patient is receiving olaparib and during the follow up period) • Any other concurrent anti-cancer therapy, including investigational agents

Abbreviations: CYP3A: cytochrome P450 family 3; INR: international normalised ratio.
AstraZeneca Data on File (OlympiA CSR).[13]

[redacted] of the patients in each treatment arm received permitted concomitant medications during the study (olaparib arm: [redacted]%; placebo arm: [redacted]%).[13] The most common anatomical therapeutic chemical (ATC) groups of concomitant medications taken by patients during study treatment were: [redacted]. The most commonly used agents at the generic term were: [redacted].[13] Overall, the concomitant treatments administered were representative of those commonly prescribed for patients in the target population and were not considered to have had a relevant influence on the study results.[13]

A [redacted] of patients received disallowed concomitant medication with agents classified as [redacted]. However, overall, the use of disallowed concomitant medication was low, balanced between the treatment arms, and did not raise concerns about the conduct of the study.[13]

B.2.3.5 Discontinuation of study treatment or withdrawal from study

Administration of olaparib or placebo continued for a maximum of 12 months, until recurrence of disease, diagnosis of a primary/secondary malignancy, treatment discontinuation or treatment completion (whichever occurred first).

Patients could discontinue at any point during the study, at the discretion of the investigator. Reasons for discontinuation covered: patient decision, adverse event, completion of one-year treatment period, confirmed pregnancy during treatment, severe non-compliance with the CSP, loco-regional or distant breast cancer recurrence, contralateral invasive breast cancer or new primary non-breast invasive cancer, death or bone marrow findings consistent with myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML). Patients discontinuing

treatment were not seen as withdrawing from the study, and remained in follow-up, as per the protocol schedule.

Patients could also withdraw from the study at any point, without prejudice to further treatment. Patients could withdraw from the study for the following reasons: voluntary withdrawal by the patient, incorrectly enrolled patients, for example, if the patient does not meet the required inclusion/exclusion criteria for the study (non-randomised patients only), patient lost to follow-up, death.

At the time of the early primary analysis for iDFS (DCO: 27 March 2020), 423 (23.0%) patients had discontinued study treatment (olaparib arm: 236 [25.6%]; placebo arm: 187 [20.4%]).[14] The majority of patients who discontinued study treatment did so due to:

- AEs: 97 patients (10.5%) in the olaparib arm versus 41 patients (4.5%) in the placebo arm
- Disease recurrence: 40 patients (4.3%) in the olaparib arm versus 80 patients (8.7%) in the placebo arm
- Patient decision: 60 patients (6.5%) in the olaparib arm versus 32 patients (3.5%) in the placebo arm

Further information on patient disposition at the time of the early primary analysis for iDFS is provided in Appendix D.

B.2.3.6 Primary, secondary and exploratory endpoints

The primary endpoint in OlympiA was **iDFS**. iDFS was defined as the time from date of randomisation to date of first recurrence, where recurrence is defined as loco-regional, distant recurrence, new cancer or death from any cause. iDFS was investigator-assessed using the standardised terms for efficacy endpoints (STEEP) system definition, and had to be cytologically/histologically confirmed.

Secondary efficacy and safety objectives of OlympiA included:[13, 35]

- **dDFS**, defined as the time from the date of randomisation until documented evidence of the first recurrence of breast cancer, the occurrence of second primary non-breast invasive cancer, or death from any cause
- **OS**, defined as the time from the date of randomisation until death due to any cause
- **Incidence of new primary breast/ovarian cancers**, defined as the number and percentage of patients with documented evidence of contralateral invasive breast cancer, contralateral non-invasive breast cancer, and new primary ovarian, fallopian tube and peritoneal cancers
- **HRQoL** measures, including:
    - European Organisation for Research and Treatment of Cancer quality of life questionnaire (EORTC QLQ-C30) global health status/QoL scores: A questionnaire that assesses the quality of life, global health status, HRQoL, functioning domains and common cancer symptoms of patients

    - Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue score: A 40-item measure that assesses self-reported fatigue and its impact upon daily activities and function

- **Safety and tolerability analyses**, including AEs, serious adverse events (SAEs), discontinuation of investigational product due to AE(s), deaths, laboratory data, vital signs and echocardiograms (ECGs)

Further information on key endpoints, including definitions, can be found in Section 3 of the OlympiA CSP.[35]

B.2.3.6.1 Assessment schedule

Following randomisation, efficacy assessments (medical history and physical examination) were performed on a three-monthly basis during the first two years. Following end of study treatment, this increased to six-monthly assessments for years three to five, and annually thereafter.[13] All patients had safety assessments every two weeks during the first month, every four weeks for the following five months (up to week 24), and three monthly for the remaining six months of study treatment, plus 30 days after its discontinuation.[13]

Radiological assessments to exclude a second primary breast cancer (ipsilateral and/or contralateral) were mandatory before enrolment (within 12 months prior to screening) and during study participation (starting at week 24 and yearly thereafter) for patients with any remaining intact breast tissue (including male patients).[13]

If the patient met the iDFS endpoint due to a breast cancer-related distant relapse, the patient entered the survival follow-up phase of the trial, with annual assessments from the date of distant relapse, which are to continue until 10 years after the last patient was randomised.[13] If the iDFS endpoint was met due to events other than distant relapse, the patient continued the efficacy assessment visit study schedule until breast cancer related distant relapse occurred, or approximately 10 years following their randomisation into the study, whichever occurs first. They then entered the survival follow-up phase of the trial.[13]

B.2.3.7 Pre-planned subgroup analyses

Subgroup analyses to assess the consistency of reported efficacy endpoints, including iDFS, dDFS and OS, were conducted. Subgroups were based on potential or expected prognostic factors, including but not limited to the baseline stratification factors. The following subgroups were of primary interest:[13, 35]

- Hormone receptor status (ER+ and/or PgR+, and HER2-; TNBC)
- Prior chemotherapy setting (Neoadjuvant; adjuvant)
- Prior platinum therapy for current breast cancer (Yes; No)
- *BRCA* mutation type (*BRCA*1; *BRCA*2; both)

Hormone receptor status by prior chemotherapy setting (if there were sufficient events to split into the four groups):

- ER and/or PR positive with neoadjuvant chemotherapy

- ER and/or PR positive with adjuvant chemotherapy
- ER and PR negative with neoadjuvant chemotherapy
- ER and PR negative with adjuvant chemotherapy
- *BRCA* status by prior platinum therapy setting:
    - *BRCA*1 with prior platinum therapy for current breast cancer
    - *BRCA*1 with no prior platinum therapy for current breast cancer
    - *BRCA*2 with prior platinum therapy for current breast cancer
    - *BRCA*2 with no prior platinum therapy for current breast cancer

Section 9.7 of the CSR presents the details of additional subgroups that were to be analysed to assess consistency in treatment effect across a broader set of baseline characteristics known before start of study medication, including age at randomisation, type of breast surgery and geographic region.

B.2.3.8 Baseline characteristics

EBC patients who received olaparib or placebo were well-balanced across key baseline characteristics (Table 9 and Table 10). Patients were well matched in terms of age, sex, Eastern Cooperative Oncology Group (ECOG) performance status, and prior treatment (neoadjuvant vs adjuvant chemotherapy).

Most of the patients in the OlympiA study (olaparib arm: 81.8%; placebo arm: 82.8%) had TNBC, as OlympiA initially only enrolled patients with TNBC. Patients with HR+ eBC were not enrolled until a late protocol amendment, due to the FDA input on the OlympiA trial design (Section B.2.3.1). The lower proportion of HR+ patient numbers than seen in the real world reflects the shorter recruitment time for these patients.[35] Additionally, OlympiA exclusively enrolled high-risk patients; a lower proportion of HR+/HER2- patients are generally considered to be high-risk compared with TNBC patients, therefore, fewer HR+/HER2- patients were included in OlympiA, due to difficulties in rapidly enrolling patients who met the eligibility criteria.[14]

Table 9: Patient demographics in OlympiA (FAS)

Patient Demographics	Olaparib (N=921)	Placebo (N=915)
Age (years)[a]		
Median (range)	42.0 (22–77)	43.0 (24–78)
Sex, n (%)		
Female	919 (99.8)	911 (99.6)
Male	2 (0.2)	4 (0.4)
Race, n (%)		
White	[redacted]	[redacted]
Asian	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]
Native Hawaiian or other Pacific Islander	[redacted]	[redacted]
American Indian or Alaska native	[redacted]	[redacted]
Other	[redacted]	[redacted]
Missing	[redacted]	[redacted]

Footnotes: DCO: 27 March 2020. [a]Age was calculated as the patients age at randomisation.
Abbreviations: DCO: data cut-off; FAS: full analysis set.
Source: AstraZeneca Data on File (OlympiA CSR);[13] Tutt 2021a;[14] Tutt 2021b.[105]

Table 10: Patient characteristics in OlympiA (FAS)

Patient Characteristics	Olaparib (N=921)	Placebo (N=915)
ECOG Performance Status, n (%)		
0	[redacted]	[redacted]
1	[redacted]	[redacted]
≥2	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Pathological AJCC Stage (adjuvant chemotherapy only), n/N (%)		
0	0/461 (0.0)	0/455 (0.0)
IA (7)	5/461 (1.1)	2/455 (0.4)
IB	15/461 (3.3)	11/455 (2.4)
IIA	264/461 (57.3)	250/455 (54.9)
IIB	70/461 (15.2)	75/455 (16.5)
IIIA	73/461 (15.8)	70/455 (15.4)
IIIB	0/461 (0.0)	2/455 (0.4)
IIIC	28/461 (6.1)	41/455 (9.0)
NA[a]	6/461 (1.3)	4/455 (0.9)
CPS+EG score (neoadjuvant chemotherapy only), n/N (%)		
CPS+EG score of 2,3 or 4	398/460 (86.5)	387/460 (84.1)
CPS+EG score of 5 or 6	22/460 (4.8)	15/460 (3.3)
HR status, n (%)		
TNBC	753 (81.8)	758 (82.8)
ER+ and/or PR+, HER2-	168 (18.2)	157 (17.2)
***BRCA* status, n (%)**		

Patient Characteristics	Olaparib (N=921)	Placebo (N=915)
*BRCA*1 mutated	[redacted]	[redacted]
*BRCA*2 mutated	[redacted]	[redacted]
*BRCA*1 and *BRCA*2 mutated	[redacted]	[redacted]
No g*BRCA*m	[redacted]	[redacted]
Missing	[redacted]	[redacted]
Prior chemotherapy		
Adjuvant	461 (50.1)	455 (49.7)
Neoadjuvant	460 (49.9)	460 (50.3)
Prior therapy in the neoadjuvant/adjuvant setting		
Anthracycline and taxane regimen	871 (94.6)	849 (92.8)
Anthracycline regimen (without taxane)	7 (0.8)	13 (1.4)
Taxane regimen (without anthracycline)	43 (4.7)	52 (5.7)
Missing	0	1 (0.1)
Prior breast cancer surgery, n (%)		
Non-conservative surgery (mastectomy)	698 (75.8)	673 (73.6)
Conservative surgery	223 (24.2)	240 (26.2)
Unknown	0	2 (0.2)

Footnotes: DCO: 27 March 2020. [a]Includes 2 occult breast cancer (placebo arm: n=2), 6 pTx (olaparib arm: n=4; placebo arm: n=2) and 2pNx (olaparib arm: n=2).
Abbreviations: AJCC: The American Joint Committee on Cancer; *BRCA*: breast cancer susceptibility gene; CPS+EG: clinical stage (CS), oestrogen receptor status (E), nuclear grade (G), and post-treatment pathologic stage (PS); DCO: data cut-off; ECOG: Eastern Cooperative Oncology Group; FAS: full analysis set; NA: not applicable; SD, standard deviation.
Source: AstraZeneca Data on File (OlympiA CSR);[13] Tutt 2021a;[14] Tutt 2021b.[105]

B.2.4 *Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence*

B.2.4.1 Statistical and analytical methods

OlympiA efficacy and safety analyses were performed in accordance with a comprehensive Statistical Analysis Plan (Section 9.8 of the CSR and Section 12 of the OlympiA Clinical Study Protocol [CSP]);[13, 35] this is summarised in Table 11.

High-level data from a planned second interim analysis for OS (DCO: 12 July 2021), completed once 330 iDFS events have been reported, became available in March 2022 (initial results have been presented at ESMO).[128] Full analyses of the data are expected to become available over the course of the appraisal and will be provided to NICE as soon as possible. The database lock including a formal analysis of OS, and descriptive analyses for iDFS and dDFS, was completed in December 2021.

The final OS analysis of OlympiA will be conducted once the trial follow-up is complete (i.e., 10 years from when the last patient is randomised).

Table 11: Summary of statistical analyses in OlympiA

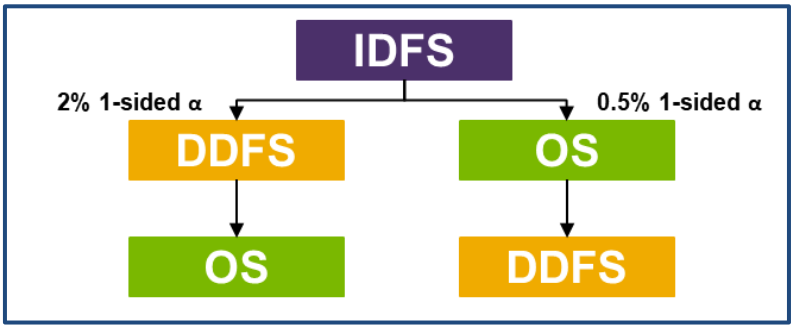
Hypothesis objective	The study was designed to test the hypothesis that olaparib tablets 300 mg BID in the adjuvant setting for up to 12 months in patients with g*BRCA*m and high-risk, HER2-, eBC who have completed definitive local treatment and adjuvant or neoadjuvant chemotherapy has superior efficacy and acceptable tolerability compared with no further treatment.

Statistical analysis	**Primary endpoint: iDFS**
	• iDFS was defined as the time from randomisation to date of first treatment failure that is loco-regional or distant recurrence or new cancer or death from any cause
	  ○ It was planned for iDFS to be analysed at an early primary analysis (165 iDFS events in the first 900 patients; first DCO) and a primary analysis (330 iDFS events; second DCO). Secondary endpoints were to be formally tested at the early primary analysis based on the MTP outline below (Figure 8), if iDFS was statistically significant at the early primary analysis, based on the ITT population. A separate alpha spending function was applied to each endpoint to account for multiple analyses on each endpoint
	  ○ All planned analyses were to be performed, regardless of the outcome of the MTP (Figure 8). No claims regarding the statistical significance of a subsequent analysis in the MTP were to be made if the full test mass was used on an earlier test in the MTP
	  ○ Loco-regional recurrence of the disease was cytologically/histologically confirmed. Appropriate imaging (CT, MRI, bone and/or PET scan) of the chest/abdomen/pelvis or any other area as clinically indicated was performed at the time of local recurrence to exclude further spread of the disease. Distant recurrence was diagnosed by radiological examination and/or histopathological confirmation when the metastatic lesion was easily accessible for biopsy. Invasive contralateral breast cancer was assessed histopathologically
	• To evaluate the robustness of the early primary iDFS analysis result, sensitivity analyses were performed
	Key secondary endpoints
	• For the secondary endpoints, OS and dDFS, data were to be analysed at the time of iDFS analysis as per the MTP (Figure 8), using the same methodology and model as described for iDFS
	• If applicable, a sensitivity analysis for DFFS and OS was to be conducted, using the same model as for iDFS, but based on all randomised patients confirmed to have a g*BRCA*m by the central test. This analysis is only required if the analysis population differs from the early primary ITT population
	• Subgroup analyses of the secondary endpoints of dDFS and OS were to be conducted using the same methods for iDFS
	• dDFS and OS will be analysed at the second DCO for iDFS (when 330 iDFS events are reported)
	• The final OS analysis will be performed once the trial follow-up is complete, from when the last patient is randomised
	• Another analysis will be performed halfway between the primary iDFS analysis and the final OS analysis. At this time point, both dDFS and OS will be analysed and some alpha will be reserved for formal hypothesis testing

Sample size, power calculation	• It was planned that a total of 1,800 patients were to be randomised (1:1) into the study to achieve 330 iDFS events. If the true HR between olaparib and placebo is 0.7, with 330 events, the study would therefore have 90% power to demonstrate a statistically significant difference in iDFS, assuming a 2-sided 5% significance level. The critical HR value at the time of early primary analysis was 0.805
Multiplicity	• In order to describe the nature of the effects of olaparib treatment iDFS, dDFS, and OS were tested at a 2-sided significance level of 5%. Additionally, in order to strongly control the overall type I error at 5% 2-sided, an MTP was employed across the primary endpoint (iDFS) and all key secondary endpoints intended for label claims (dDFS and OS). The MTP accounted for any interim analyses on iDFS, dDFS, and OS and also planned further analyses • A hierarchical testing strategy was employed where iDFS was tested, first using the full test mass (full 5%, two-sided alpha). dDFS and OS were then tested if iDFS was significant, based on a weighted proportion of test mass (4.0% for dDFS and 1.0% for OS), which could be recycled to secondary endpoints not yet rejected. Testing was to be stopped when the entire test mass was allocated to non-rejected endpoints

Abbreviations: BID: twice daily; *BRCA*: breast cancer susceptibility gene; CI: confidence interval; DCO: data cut-off; dDFS: distant disease-free survival; eBC: early breast cancer; HER2: human epidermal growth factor 2; iDFS: invasive disease-free survival; ITT: intention-to-treat; MTP: multiple testing procedure; OS: overall survival.
Source: AstraZeneca Data on File (OlympiA CSR);[13] AstraZeneca Data on File (OlympiA CSP).[35]

Figure 8. Multiple testing procedure (MTP) used in OlympiA



Abbreviations: dDFS: distant disease-free survival; iDFS: invasive disease-free survival; OS: overall survival.
Source: Adapted from AstraZeneca Data on File (OlympiA CSP).[35]

B.2.4.2 Analysis sets

The main analysis sets of the OlympiA clinical trial that are presented in this submission are summarised in Table 12. All 1,836 patients randomised are included in the Full Analysis Set (FAS), representing the ITT population. Ten patients (1.1%) in the olaparib arm and 11 patients (1.2%) in the placebo arm did not receive treatment, hence 1,815 patients are included in the Safety Analysis Set (SAS).[13, 14]

Table 12: Analysis sets in OlympiA

Analysis Set	Description	Number	Outcomes analysed
Full analysis set (FAS)[a]	ITT, all randomised patients	1,836 patients in total (921 olaparib, 915 placebo)	Efficacy
	Mature cohort ITT, the first 900 randomised patients only	900 patients in total (449 olaparib, 451 placebo)	Efficacy

Analysis Set	Description	Number	Outcomes analysed
Safety analysis set (SAS)	All patients who received at least one treatment dose, and had at least one safety follow-up assessment	1,815 patients in total (911 olaparib, 904 placebo)	Safety and tolerability
PRO Analysis Set	Patients who started treatment and who provided evaluable baseline FACIT-Fatigue or EORTC QLQ-C30 data, (evaluable meaning at least one sub-scale baseline score was determined)	[redacted] patients in total ([redacted] olaparib, [redacted] placebo)	HRQoL

Footnotes: [a]Analysis based on treatment arm randomised to, rather than treatment received.
Abbreviations: EORTC-QLQ-C30: European Organisation for Research and Treatment of Cancer, quality of life questionnaire; FACIT: Functional Assessment of Chronic Illness Therapy; FAS: full-analysis set; HRQoL: health-related quality of life; ITT: intention to treat; PRO: patient-reported outcomes; SAS: safety analysis set.
Source: AstraZeneca Data on File (OlympiA CSR);[13] Tutt 2021a.[14]

B.2.5 *Critical appraisal of the relevant clinical effectiveness evidence*

OlympiA was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with International Council for Harmonisation/Good Clinical Practice guidelines, applicable regulatory requirements and the AstraZeneca policy of bioethics, under the auspices of an independent data and safety monitoring committee.[13] A complete quality assessment in accordance with the NICE-recommended checklist for assessment of bias in RCTs is presented in Table 13 and Appendix D. The risk of bias in OlympiA is confirmed as being low.

Table 13: Overview of quality assessments for OlympiA

OlympiA (NCT02032823)	Risk of bias
Was randomisation carried out appropriately?	Low
Was the concealment of treatment allocation adequate?	Low
Were the groups similar at the outset of the study in terms of prognostic factors?	Low
Were the care providers, participants and outcome assessors blind to treatment allocation?	Low
Were there any unexpected imbalances in dropouts between groups?	Low
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Low
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Low

Adapted from Systematic reviews: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination).

B.2.6 *Clinical effectiveness results of the relevant studies*

OlympiA met its primary objective, demonstrating a statistically and clinically meaningful improvement in iDFS with olaparib over placebo at the early primary analysis (DCO: 27 March

2020; 41.9% reduction in risk of invasive disease recurrence; hazard ratio: 0.58; 99.5% confidence interval [CI]: 0.41, 0.82; p=0.0000073).[13, 14] No statistical evidence of heterogeneity between any subgroup and the ITT population iDFS treatment effect was found. Additionally, the treatment benefit of olaparib observed for iDFS is further supported by the secondary endpoint of dDFS, where a statistically and clinically meaningful difference between the olaparib and placebo groups was also seen.

The observed efficacy in OlympiA led the IDMC to unblind the OlympiA trial earlier than expected; this serves to reinforce the clinical value that olaparib can offer to patients with g*BRCA*m, HER2-, high-risk eBC.

An overview of the key efficacy endpoints can be found in Table 14, with subgroup analyses presented in Section B.2.6.

Table 14: Summary of OlympiA efficacy endpoints, early primary analysis (FAS)

		Olaparib (N=921)	Placebo (N=915)
iDFS			
Number of events, n (%)		106 (11.5)	178 (19.5)
Estimate of hazard ratio[a]		0.581	
95% CI for hazard ratio[b, c]		[redacted]	
99.5% CI for hazard ratio[b, c]		0.409–0.816	
Log-rank test: p-valued		0.0000073	
Percentage (95% CI) of patients free of invasive disease at:	1 year	93.3 [redacted]	88.4 [redacted]
	2 year	89.2 [redacted]	81.5 [redacted]
	3 year	85.9 ([redacted]	77.1 [redacted]
Median clinical follow-up time (years) (minimum-maximum)		[redacted]	[redacted]
Type of iDFS event			
Distant CNS recurrence		22 (2.4)	36 (3.9)
Distant excluding CNS recurrence		50 (5.4)	84 (9.2)
Regional (ipsilateral) recurrence		6 (0.7)	14 (1.5)
Local (ipsilateral) recurrence		7 (0.8)	11 (1.2)
Contralateral invasive breast cancer		8 (0.9)	12 (1.3)
New primary cancers (non-breast)		11 (1.2)	21 (2.3)
Deaths without a prior iDFS event		2 (0.2)	0
dDFS			
Number of events, n (%)		89 (9.7)	152 (16.6)
Estimate of hazard ratio[a]		0.574	
95% CI for hazard ratio[b, c]		[redacted]	
99.5% CI for hazard ratio[b, c]		0.392–0.831	
log-rank test: p-valued		0.0000257	
Percentage (95% CI) of patients free of distant disease at:	1 year	94.3 [redacted]	90.2 [redacted]
	2 year	90.0 [redacted]	83.9 [redacted]
	3 year	87.5 [redacted]	80.4 [redacted]

		Olaparib (N=921)	Placebo (N=915)
Median clinical follow-up time (years) (minimum-maximum)		[redacted]	[redacted]
OS			
Number of events, n (%)		59 (6.4)	86 (9.4)
Estimate of hazard ratio[a]		0.683	
95% CI for hazard ratio[b, c]		[redacted]	
99% CI for hazard ratio[b, c]		0.438–1.053	
log-rank test: p-valued		0.0236	
Percentage (95% CI) of patients alive at:	1 year	98.1 [redacted]	96.9 [redacted]
	2 year	94.8 [redacted]	92.3 [redacted]
	3 year	92.0 [redacted]	88.3 [redacted]
Median clinical follow-up time (years) (minimum-maximum)		[redacted]	[redacted]

Footnotes: DCO: 27 March 2020. [a]Estimate of the treatment hazard ratio based on the stratified Cox's Proportional Hazards Model, <1 indicates a lower risk with olaparib compared with placebo arm. Stratification factors are the same as those used in the stratified log-rank test. [b]The CI for the hazard ratio was estimated using the profile likelihood approach. [c]Exploratory, not inferential. [d]p-value from a stratified log-rank test. Stratification is by chemotherapy type (2 levels: adjuvant vs neoadjuvant), hormone receptor status (2 levels: ER+ and/or PR+ /HER2- vs TNBC), and prior platinum therapy (2 levels: yes vs no). Stratification factors were based upon the categories used in the randomisation system and were chosen by the pooling strategy.
Abbreviations: CI: confidence interval; DCO: data cut-off; dDFS: distant disease-free survival; FAS: full analysis set; iDFS: invasive disease-free survival; OS: overall survival.
Source: AstraZeneca Data on File (OlympiA CSR);[13] Tutt 2021a;[14] Tutt 2021b.[105]

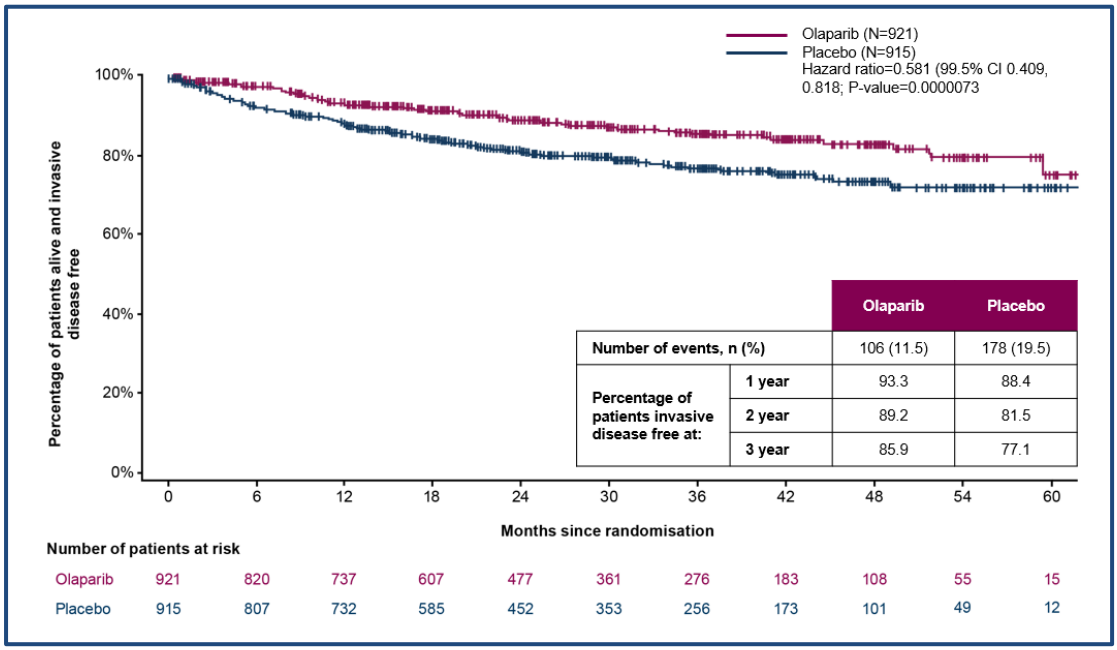
B.2.6.1 Primary endpoint: iDFS

At the early primary analysis (DCO: 27 March 2020), OlympiA met its primary endpoint at 15.4% maturity (284 iDFS events, 106/921 olaparib treated patients [11.5%] and 178/915 placebo-treated patients [19.5%] known to have experienced invasive disease recurrence), demonstrating a statist**ically and clinically meaningful investigator-assessed iDFS benefit in the ITT population for olaparib** compared with placebo (Table 14, Figure 9). A 41.9% reduction in risk of invasive disease recurrence or death was observed for patients in the olaparib arm compared with the placebo arm (hazard ratio: 0.58; 99.5% CI: 0.41, 0.82; p=0.0000073). Median duration of follow-up for iDFS was [redacted] in the olaparib arm and [redacted] in the placebo arm.

Early and sustained separation observed in the KM curves further demonstrates the clinical benefits of olaparib. At all timepoints, a higher proportion of patients in the olaparib arm remained alive and free of invasive disease compared to the placebo arm, demonstrating that the statistically significant iDFS hazard ratio translates into clinically meaningful outcomes for patients.

A number of sensitivity analyses were conducted (details provided in Section 12.2.1.2 of the OlympiA CSP),[35] all of which demonstrated consistency with the early primary analysis.

Figure 9: Kaplan-Meier plot of iDFS in OlympiA, early primary analysis (FAS)



Footnotes: DCO: 27 March 2020.
Abbreviations: DCO: data cut-off; FAS: full analysis set; iDFS : invasive disease-free survival.
Source: AstraZeneca Data on File (OlympiA CSR);[13] Tutt 2021a;[14] Tutt 2021b.[105]

For all categories of iDFS (invasive loco-regional, distant recurrence, contralateral invasive breast cancer, second primary non-breast invasive malignancy, or death from any cause), the incidence was either lower in the olaparib arm compared with the placebo arm or similar in both arms (Table 14).[13, 14] Distant disease recurrence occurred more frequently than local disease recurrence. Recurrence of distant CNS disease occurred in 2.4% of patients in the olaparib arm vs 3.9% in the placebo arm and non-CNS distant recurrence occurred in 5.4% vs 9.2% in the olaparib and placebo arms, respectively. Local disease occurrence occurred in 0.8% and 1.2% of patients in the in the olaparib and placebo arms respectively.[13, 14]

Together these data underline the compromised outcomes in patients with *BRCA*m, HER2-, high-risk eBC treated with current standard of care, as well as the tangible survival benefit of adjuvant treatment with olaparib.

B.2.6.2 Secondary endpoints

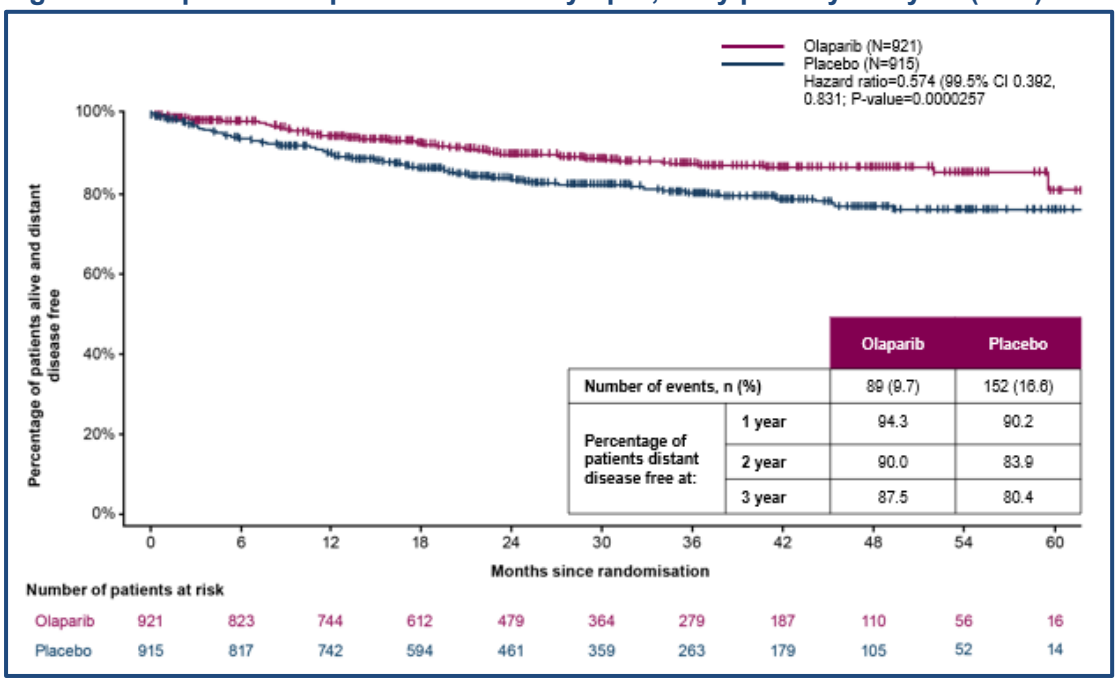
B.2.6.2.1 dDFS

At the early primary analysis for iDFS (DCO: 27 March 2020), dDFS data were 13.1% mature (241 events/1,836 patients); consistent with the observed iDFS benefit, **olaparib treatment also demonstrated a statistically and clinically meaningful benefit in dDFS compared with placebo** (Table 14, Figure 10). As with iDFS, an early and sustained separation in KM curves was observed for dDFS. Based on Kaplan-Meier estimates, there a greater proportion of patients treated with olaparib remained free of distant disease over 3 years, compared with placebo.

Overall, 89 patients (9.7%) in the olaparib arm and 152 patients (16.6%) in the placebo arm had experienced a dDFS event, with a 42.6% reduction in risk of distant recurrence observed for patients treated with olaparib vs placebo (hazard ratio: 0.57; 99.5% CI: 0.39, 0.83; p=0.0000257).

The median duration of follow-up was [redacted] in the olaparib arm and [redacted] in the placebo arm.

Figure 10: Kaplan-Meier plot of dDFS in OlympiA, early primary analysis (FAS)



Footnotes: DCO: 27 March 2020.
Abbreviations: DCO: data cut-off; dDFS: distant disease-free survival; FAS: full analysis set.
Source: AstraZeneca Data on File (OlympiA CSR);[13] Tutt 2021a;[14] Tutt 2021b.[105]

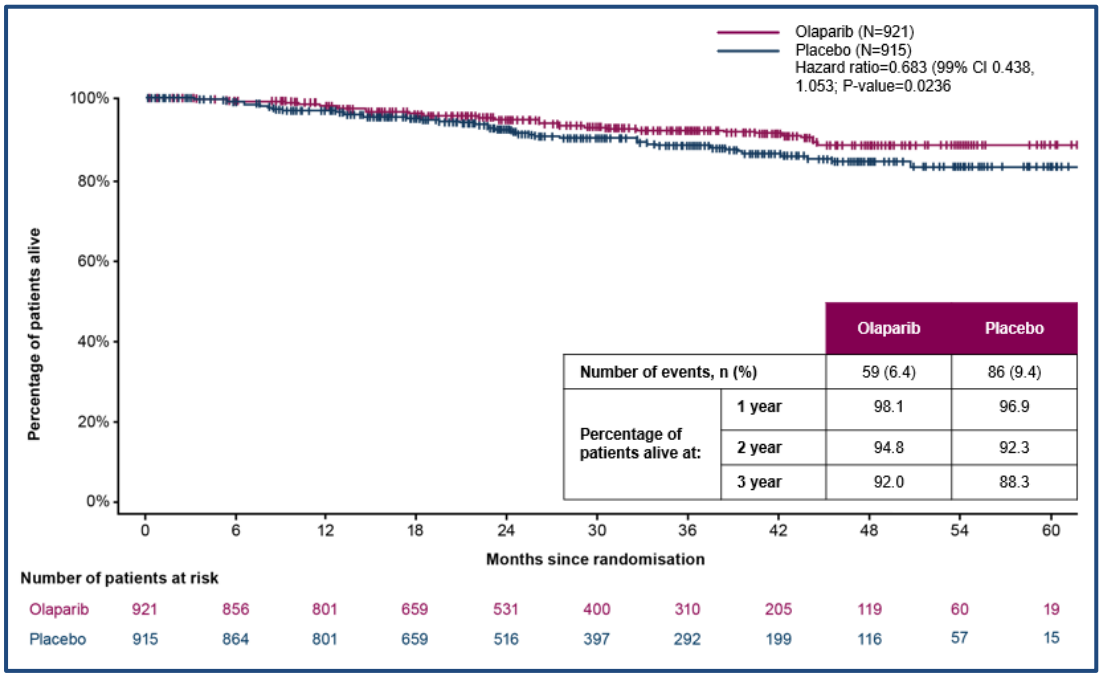
B.2.6.2.2 OS

At the early primary analysis for iDFS (DCO: 27 March 2020), the primary OS data were 7.9% mature (145 events/1,836 patients), and the vast majority of patients were still alive in both study arms. The statistical analysis plan for OlympiA dictated that p<0.01 must be achieved in order for the OS benefit to be considered significant at this analysis; therefore, statistical significance was not expected at this early analysis. Despite this low maturity, data from OlympiA showed a numerical OS benefit in favour of olaparib versus placebo, with a 31.7% reduction in risk of death observed for patients treated with olaparib in comparison with placebo (hazard ratio: 0.68; 99% CI: 0.44, 1.05; p=0.0236; Table 14, Figure 11).[13] The median follow-up for OS was [redacted] in the olaparib arm and [redacted] in the placebo arm.[13]

A separation in OS KM curves can be observed from approximately 24-months post-randomisation, after which separation was sustained for the duration of follow-up. Based on Kaplan-Meier estimates, the percentage of patients who remained alive over 3 years was higher in the olaparib arm than the placebo arm.[13] Together, these early data suggest that, in patients with g*BRCA*m, HER2-, high-risk eBC, olaparib treatment provides a clinically meaningful improvement in OS, compared with placebo.

At the second interim analysis for OS (DCO: 12 July 2021), statistical significance was reached in this key secondary endpoint (hazard ratio: 0.68; 98.5% CI 0.47-0.97; p=0.009), which is **remarkable for an interim DCO in an eBC adjuvant setting**, and **clearly demonstrates the sustained survival benefit of olaparib**.

Figure 11: Kaplan-Meier plot of OS in OlympiA, early primary analysis (FAS)



Footnotes: DCO: 27 March 2020.
Abbreviations: DCO: data cut-off; FAS: full analysis set; OS: overall survival.
Source: AstraZeneca Data on File (OlympiA CSR);[13] Tutt 2021a;[14] Tutt 2021b.[105]

B.2.6.2.3 Incidence of new primary breast or ovarian cancers

The incidence of new primary breast or ovarian cancers was included in OlympiA as an exploratory endpoint, and the statistical analysis plan specified that the comparison should only be undertaken if ≥5 events occurred in each arm. As this threshold was met at the early primary analysis of OlympiA, a summary of all new cancers that occurred post-randomisation is provided in Table 15. At the early primary analysis for iDFS (DCO: 27 March 2020), the incidences of new primary contralateral breast cancers (invasive and non-invasive), new primary ovarian cancer, new primary fallopian tube cancer, and new primary peritoneal cancer without considering competing risks were generally [redacted], but slightly [redacted] in the olaparib arm [redacted] compared with the placebo arm [redacted].

Table 15: A summary of all new cancers that occurred post randomisation in OlympiA, early primary analysis, FAS

Number (%) of patients with	Olaparib (N=921)	Placebo (N=915)
New primary contralateral invasive breast cancer	[redacted]	[redacted]
New primary contralateral non-invasive breast cancer	[redacted]	[redacted]
New primary ovarian cancer[a]	[redacted]	[redacted]
Ovarian cancer	[redacted]	[redacted]
Fallopian tube cancer	[redacted]	[redacted]
Peritoneal cancer	[redacted]	[redacted]
New primary invasive non-breast non-ovarian malignancies	[redacted]	[redacted]

Footnotes: DCO: 27 March 2020. Summary of new cancers without considering competing risks. [a]Includes new primary ovarian, fallopian, and peritoneal cancers, without considering competing risks.
Abbreviations: DCO: data cut-off; FAS: full-analysis set.
Source: AstraZeneca Data on File (OlympiA CSR).[13]

B.2.6.3 Health-related quality of life (HRQoL)

In OlympiA, FACIT-Fatigue score and EORTC QLQ-C30 global health status/QoL score were secondary outcome measures. Patient-reported outcomes (PROs) for HRQoL were gathered using EORTC QLQ-C30 global health status/QoL scores and FACIT-Fatigue score in the OlympiA PRO Analysis Set (n=1,751; see Section B.2.4.2). These questionnaires were completed at baseline (before randomisation) and every six months for a period of two years.[13, 35]

B.2.6.3.1 EORTC QLQ-30

The EORTC QLQ-C30 is a disease-specific questionnaire that assesses the quality of life of cancer patients; as well as assessing global health status and HRQoL, it assesses important functioning domains (e.g. physical, emotional and role) and common cancer symptoms (e.g. fatigue, pain, nausea/vomiting and appetite loss). All EORTC QLQ-C30 domains range in score from 0 to 100; higher scores on HRQoL and functioning scales indicate better HRQoL/functioning, whereas higher scores on symptom scales indicating a worse symptom severity. A score difference of 10 points is defined as a clinically meaningful change. Change from baseline in EORTC QLQ-C30 was analysed using a MMRM analysis of the change from baseline in EORTC QLQ-C30 for each visit.

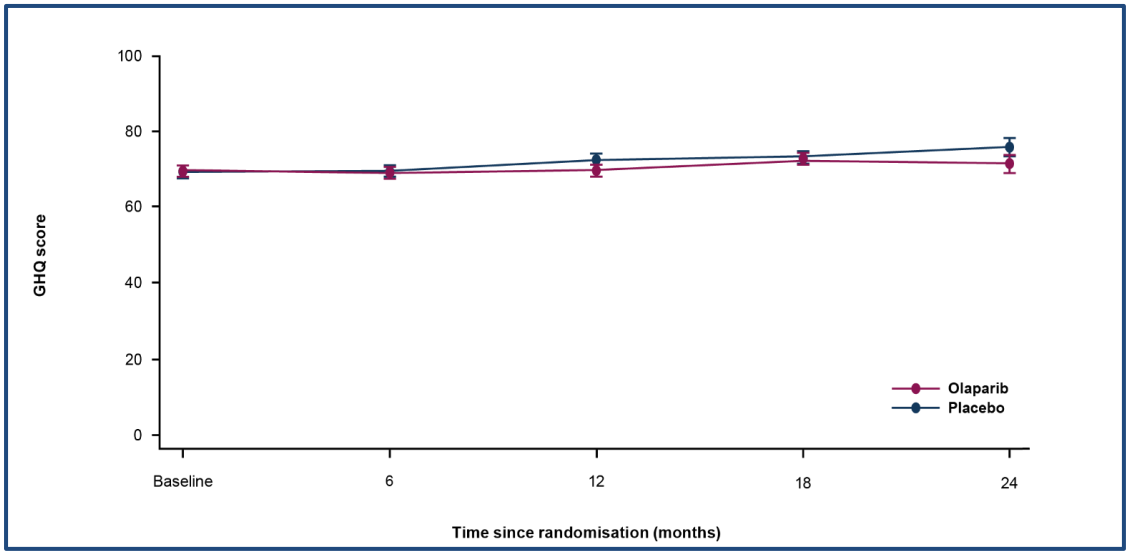
Compliance rates for the EORTC QLQ-C30 questionnaire were [redacted] at baseline ([redacted] for olaparib; [redacted] for placebo) and [redacted] to [redacted] at 6 and 12 months, [redacted] at 18 months, and [redacted] at 24 months in both the olaparib and placebo arms.

Mean (SD) baseline EORTC QLQ-C30 global health status/QoL functioning scores were comparable between the treatment arms for patients who had received prior neoadjuvant treatment and prior adjuvant treatment. The EORTC QLQ-C30 global health status/QoL functioning scores remained stable for both the olaparib and placebo arms at 6 and 12 months (Figure 12 and Figure 13); [redacted] from baseline were observed in global health status/QoL, role functioning, and social functioning in both arms at 18 and 24 months, although [redacted] between treatment arms were observed. Together, these data indicate that the 12 months of olaparib treatment does not cause a decline in global health quality, maintaining HRQoL compared with placebo.

Mean (SD) baseline EORTC GI symptom (nausea/vomiting) scores were also [redacted] between the treatment arms for patients regardless of the timing of their prior chemotherapy. As expected given the known safety profile for olaparib, EORTC QLQ-C30 GI symptom scores (nausea/vomiting) were [redacted] in the olaparib arm vs the placebo arm after 6 and 12 months of treatment; however, at 18 and 24 months, scores [redacted] between the olaparib and placebo arms, with no clinically meaningful differences observed.

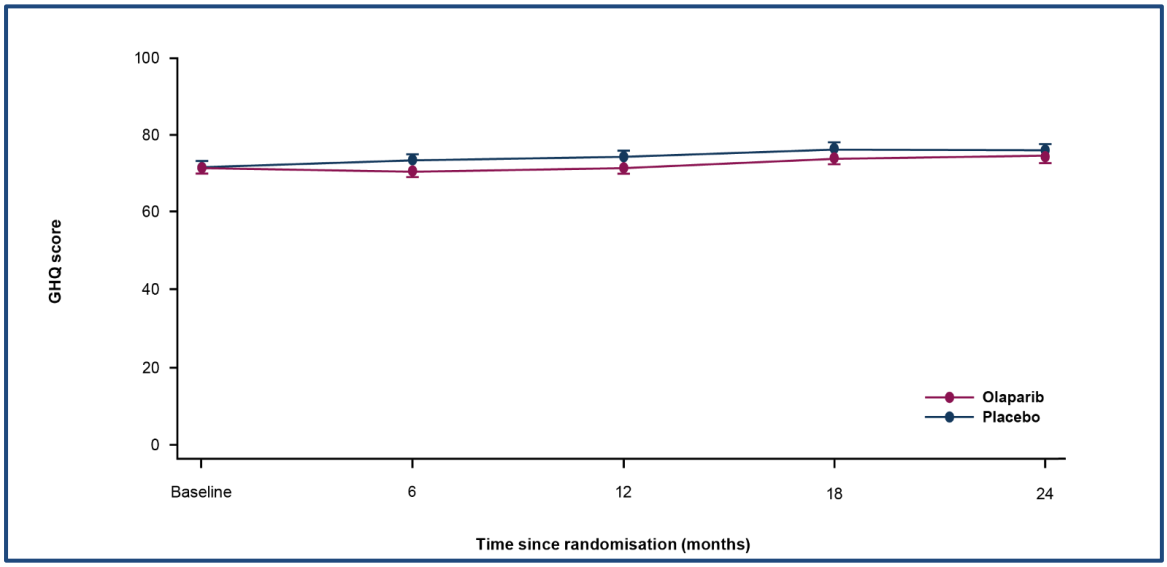
These data suggest that olaparib does not [redacted] patient HRQoL, with [redacted] seen in EORTC QLQ-C30 global health status/HRQoL functioning scores between olaparib and placebo. A detailed summary of EORTC QLQ-C30 scores in OlympiA can be found in Appendix M.

Figure 12: Mean change from baseline of EORTC QLQ-C30 Global Health QoL Score in patients who had received prior neoadjuvant chemotherapy in OlympiA (PRO analysis set)



Footnotes: DCO: 27 March 2020. GHQ score ranges from 0 to 100 with higher score indicating better QoL. Adjusted least-square mean responses and 95% CI are obtained from MMRM analysis of the GHQ score. The model includes treatment, time and treatment by time interaction, corresponding baseline score and the baseline score by time interaction.
Abbreviations: CI: confidence interval; DCO: data cut-off; FACIT: functional assessment of chronic illness therapy; GHQ: Global Health Quality; MMRM: mixed model for repeated measures; PRO: patient reported outcome.
Source: AstraZeneca Data on File (OlympiA CSR);[13] Tutt 2021a;[14] Tutt 2021b.[105]

Figure 13: Mean change from baseline of EORTC QLQ-C30 Global Health QoL Score in patients who had received prior adjuvant chemotherapy in OlympiA (PRO analysis set)



Footnotes: DCO: 27 March 2020. GHQ score ranges from 0 to 100 with higher score indicating better QoL. Adjusted least-square mean responses and 95% CI are obtained from MMRM analysis of the GHQ score. The model includes treatment, time and treatment by time interaction, corresponding baseline score and the baseline score by time interaction.
Abbreviations: CI: confidence interval; DCO: data cut-off; FACIT: functional assessment of chronic illness therapy; MMRM: mixed model for repeated measures; PRO: patient reported outcome.
Source: AstraZeneca Data on File (OlympiA CSR);[13] Tutt 2021a;[14] Tutt 2021b.[105]

B.2.6.3.2 FACIT-Fatigue

The FACIT-Fatigue is a 40-item measure that assesses self-reported fatigue and its impact upon daily activities and function, with a higher score indicating less fatigue.[13, 35] Baseline compliance rates in OlympiA were high (99.4% for olaparib; 99.7% for placebo). Compliance rates were >80% at 6 and 12 months, >70% at 18 months, and >65% at 24 months in both the olaparib and placebo arms.

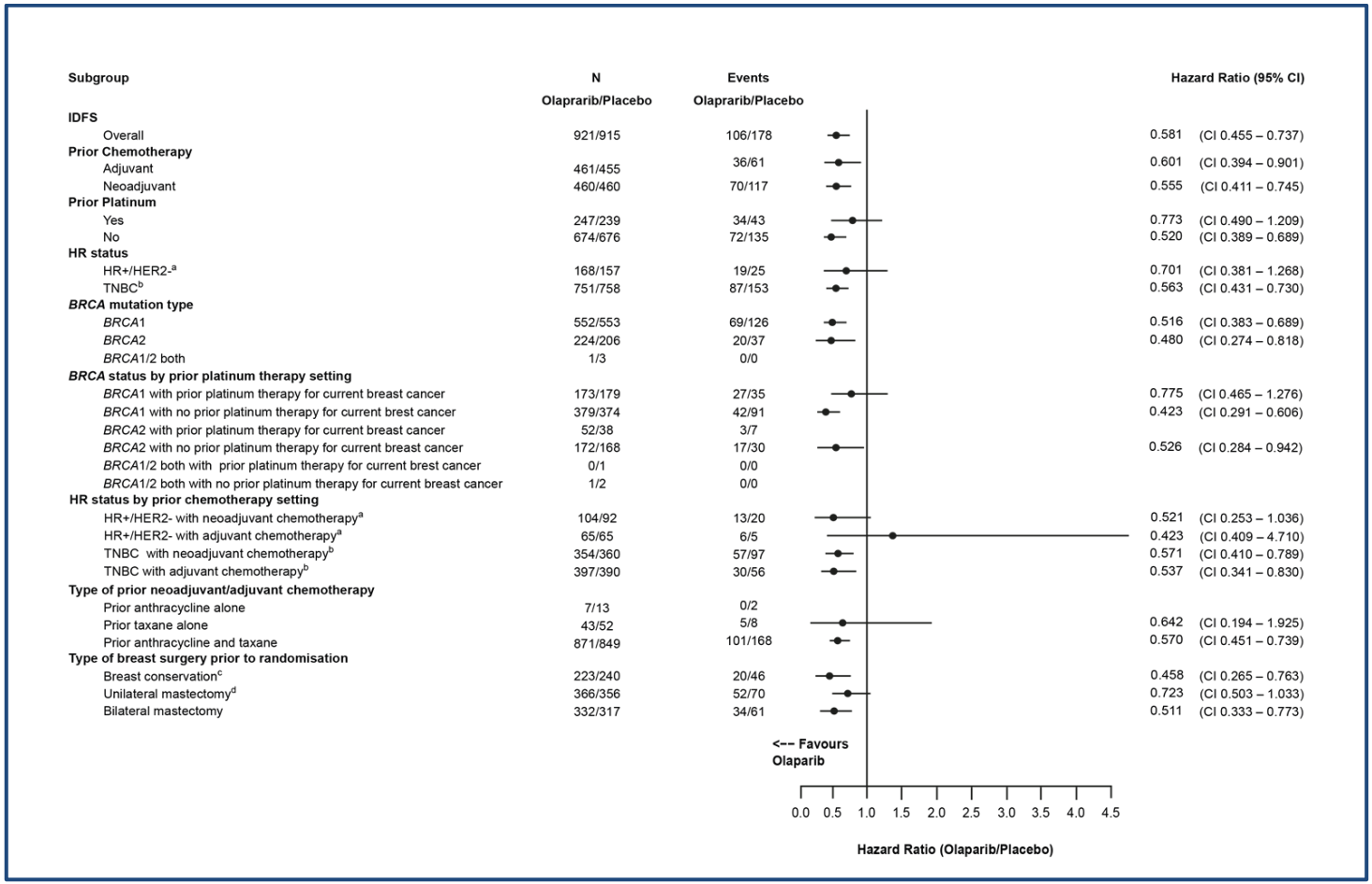
Results from the analysis of FACIT-Fatigue scores indicate that olaparib has [redacted] on patient QoL, with [redacted] HRQoL scores observed between placebo and treatment groups; FACIT-Fatigue results are presented in Appendix M.

B.2.7 *Subgroup analysis*

The subgroup analyses for the primary endpoint of iDFS demonstrate that the benefit observed in the ITT population was generally consistent across stratification and pre-specified subgroups (Figure 14).

Considering subgroups defined by HR-status, the HR+/HER2- subgroup data are too immature to provide reliable estimates of the benefits of olaparib in the HER2- subgroup. However, no meaningful differences between subgroups were observed, and there is no statistical evidence of heterogeneity between any subgroup and the ITT iDFS treatment effect; the test of heterogeneity for this subgroup factor (HR status by prior chemotherapy setting) was not significant (p=0.536). Furthermore, clinical experts noted that there are no clinical or biological reasons to suspect that the efficacy of olaparib in TNBC and HR+/HER2- subgroups would differ, given selection on *BRCA* status; these groups would only be expected to differ in terms of their baseline prognosis.[129] The overall results of OlympiA are considered generalisable to the HR+/HER2- patient subgroup, especially as the findings seem to be aligned with expectations for this patient population based on the outcomes from OlympiAD.[126]

Figure 14: Forest plot of iDFS according to stratification factors, early primary analysis (FAS)



Footnotes: DCO: 27 March 2020. [a]HR+ is defined as ER-positive and/or PR-positive; [b]two patients are excluded from the summary of the TNBC subset because they do not have confirmed negative HER2 status

Abbreviations: CI: confidence interval; DCO: data cut-off; ER: oestrogen receptors; FAS: full analysis set; HER2: human epidermal growth factor receptor 2; HR: hormone receptor; iDFS: invasive disease-free survival; PR: progesterone receptor; TNBC: triple-negative breast cancer.

Source: AstraZeneca Data on File (OlympiA CSR);[13] Tutt 2021a;[14] Tutt 2021b.[105]

B.2.8 *Meta-analysis*

As only one study evaluating the efficacy and safety of olaparib in the relevant patient population was identified, no meta-analysis was necessary.

B.2.9 *Indirect and mixed treatment comparisons*

No indirect or mixed treatment comparisons have been conducted, as the decision problem does not include any comparators not captured by OlympiA. The comparator in the final NICE scope is established clinical management without olaparib, i.e., “watching and waiting”. This comparison is reflected by OlympiA, as the placebo arm allows investigation of olaparib compared with no further treatment (watching and waiting).

B.2.10 *Adverse reactions*

Safety data for OlympiA are taken from the Safety Analysis Set (SAS), comprising all patients who received at least one treatment dose and had at least one safety follow-up assessment. At the early primary analysis for **iDFS** (DCO: 27 March 2020), safety and tolerability data were assessed in terms of adverse events (AEs; including serious AEs [SAEs]), deaths, laboratory data, vital signs, electrocardiograms (ECGs) and treatment exposure.

The median duration of treatment was [redacted] and [redacted] in the olaparib and placebo arms, respectively.[13]

Overall, the safety profile of olaparib was consistent with that observed in previous trials.[97, 125-127] Most patients experienced one or more AE during the study course, with the incidence of AEs observed to be higher in the olaparib arm than the placebo arm; around a quarter of the patients in the olaparib arm had Grade ≥3 AEs (24.3%) compared with 11.3% in the placebo arm (Table 16). Most AEs observed were non-serious, mild or moderate in severity and did not result in treatment discontinuation. The incidences of AEs leading to death and SAEs were similar between the treatment arms.

Despite the observed incidence of AEs, no detrimental impact of treatment on HRQoL was observed in OlympiA (Section B.2.6.3). This suggests that the AEs experienced during treatment with olaparib do not negatively impact overall patient HRQoL. Furthermore, the overall safety and tolerability data of olaparib in OlympiA are generally consistent with the known safety profile of olaparib treatment across the various indications in which it has been studied.

Table 16: Summary of AEs in OlympiA, early primary analysis (SAS)

AEs	Olaparib (N=911)	Placebo (N=904)
All grade AEs, n (%)	835 (91.7)	753 (83.3)
Grade ≥3 AEs, n (%)	221 (24.3)	102 (11.3)
SAEs, n (%)	79 (8.7)	76 (8.4)
Deaths, n (%)	1 (0.1)	2 (0.2)
Dose interruptions due to AEs, n (%)	[redacted]	[redacted]
Dose reductions due to AEs, n (%)	[redacted]	[redacted]
Discontinuations due to AEs, n (%)	90 (9.9)	38 (4.2)

Footnotes: DCO: 27 March 2020. Patients with multiple events in the same category were counted only once in that category. Patients with events in more than one category were counted once in each of those categories. CTCAE Version 4.03. MedDRA Version 22.1.
Abbreviations: AEs: adverse events; DCO: data cut-off; SAEs: serious adverse events; SAS: safety analysis set.
Source: AstraZeneca Data on File (OlympiA CSR);[13] Tutt 2021a;[14] Tutt 2021b.[105]

B.2.10.1 Common AEs

Most patients in the OlympiA trial experienced one or more AE during the study course. The most common AE in the olaparib arm was nausea (518 patients [56.9%]), whereas the most common AE in the placebo arm was fatigue (245 patients [27.1%]). A summary of the most common AEs (occurring in ≥5% of patients in either treatment arm) reported in the OlympiA trial can be found in Table 17. Aside from those mentioned above, the most frequently reported AEs (occurring in ≥20% of patients) included vomiting, fatigue and anaemia in the olaparib arm, and fatigue in the placebo arm.

Table 17: Most common AEs (occurring in at least 5% of patients in either arm) reported in OlympiA, early primary analysis (SAS)

AEs	Olaparib (N=911)		Placebo (N=904)	
	All grades, N (%)	Event rate (per 1000 pt years)[a]	All grades, N (%)	Event rate (per 1000 pt years)[a]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	518 (56.9)	[redacted]	211 (23.3)	[redacted]
Vomiting	206 (22.6)	[redacted]	74 (8.2)	[redacted]
Diarrhoea	160 (17.6)	[redacted]	124 (13.7)	[redacted]
Abdominal pain	[redacted]	[redacted]	[redacted]	[redacted]
Constipation	[redacted]	[redacted]	[redacted]	[redacted]
Stomatitis	[redacted]	[redacted]	[redacted]	[redacted]
Dyspepsia	[redacted]	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	365 (40.1)	[redacted]	245 (27.1)	[redacted]
Pain	[redacted]	[redacted]	[redacted]	[redacted]

AEs	Olaparib (N=911)		Placebo (N=904)	
	All grades, N (%)	Event rate (per 1000 pt years)[a]	All grades, N (%)	Event rate (per 1000 pt years)[a]
Influenza like illness	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]	[redacted]	[redacted]
Headache	180 (19.8)	[redacted]	152 (16.8)	[redacted]
Dysgeusia	107 (11.7)	[redacted]	38 (4.2)	[redacted]
Dizziness	104 (11.4)	[redacted]	67 (7.4)	[redacted]
Infections and infestations	[redacted]	[redacted]	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]	[redacted]	[redacted]
Investigations	282 (31.0)	[redacted]	184 (20.4)	[redacted]
Neutrophil count decreased	146 (16.0)	[redacted]	59 (6.5)	[redacted]
White blood cell count decreased	143 (15.7)	[redacted]	52 (5.8)	[redacted]
Lymphocyte count decreased	[redacted]	[redacted]	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]	[redacted]	[redacted]
Arthralgia	84 (9.2)	[redacted]	107 (11.8)	[redacted]
Back pain	[redacted]	[redacted]	[redacted]	[redacted]
Pain in extremity	[redacted]	[redacted]	[redacted]	[redacted]
Myalgia	[redacted]	[redacted]	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	214 (23.5)	[redacted]	35 (3.9)	[redacted]
Respiratory, thoracic and mediastinal disorders	[redacted]	[redacted]	[redacted]	[redacted]
Cough	[redacted]	[redacted]	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]	[redacted]	[redacted]
Decreased appetite	119 (13.1)	[redacted]	53 (5.9)	[redacted]
Vascular disorders	[redacted]	[redacted]	[redacted]	[redacted]
Hot flush	[redacted]	[redacted]	[redacted]	[redacted]
Psychiatric disorders	[redacted]	[redacted]	[redacted]	[redacted]

AEs	Olaparib (N=911)		Placebo (N=904)	
	All grades, N (%)	Event rate (per 1000 pt years)[a]	All grades, N (%)	Event rate (per 1000 pt years)[a]
Insomnia	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: DCO: 27 March 2020. [a]For any event, each SOC and each PT, the event rate is presented and was defined as the number of patients with that AE (counting AEs from date of first dose up to 30 days following the date of last dose of study medication) divided by the total number of days at risk across all patients in a given group multiplied by 365.25×1000. The denominator, total number of days at risk, was, (a) for patients who had the event, the number of days between date of first treatment to start date of the first event, (b) for patients who did not have the event, the number of days between date of first treatment and end of safety follow-up (where end of safety follow-up was defined as the minimum of 30 days following last dose of study medication, withdrawal and death). Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories. Includes AEs with an onset date on or after the date of first dose and up to and including 30 days following the date of last dose of olaparib/placebo. MedDRA Version 22.1.
Abbreviations: AE: adverse event; DCO: data cut-off; MedDRA: Medical Dictionary for Regulatory Activities; pt: patient; SAS: safety analysis set.
Source: AstraZeneca Data on File (OlympiA CSR);[13] Tutt 2021a;[14] Tutt 2021b.[105]

B.2.10.2 Serious AEs

SAEs were reported in a similar proportion of patients in both treatment arms, 8.7% in the olaparib arm vs 8.4% in the placebo arm. The most common system organ class for reported SAEs in the olaparib arm was blood and lymphatic system disorders and in the placebo arm was neoplasms benign, malignant and unspecified (including cysts and polyps). Anaemia was the most common SAE but was only reported in 15 patients (1.6%) in the olaparib arm and 1 patient (0.1%) in the placebo arm. A summary of SAEs reported in OlympiA can be found in Table 18.

Table 18: SAEs reported in OlympiA (≥3 patients in either arm), early primary analysis (SAS)

SAEs	N (%) of patients	
	Olaparib (N=911)	Placebo (N=904)
Patients with any SAEs	79 (8.7)	76 (8.4)
Blood and lymphatic system disorders	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]
Device related infection	[redacted]	[redacted]
Mastitis	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]
Neoplasms benign, malignant and unspecified (including cysts and polyps)	[redacted]	[redacted]

SAEs	N (%) of patients	
	Olaparib (N=911)	Placebo (N=904)
Breast cancer	[redacted]	[redacted]
Malignant melanoma	[redacted]	[redacted]
Ovarian cancer	[redacted]	[redacted]
Injury, poisoning and procedural complications	[redacted]	[redacted]
Wound dehiscence	[redacted]	[redacted]

Footnotes: DCO: 27 March 2020. Includes SAEs with an onset date on or after the date of first dose and up to and including 30 days following the date of last dose of olaparib/placebo. Sorted by decreasing frequency in the olaparib arm for SOC and PT. Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories. MedDRA Version 22.1.
Abbreviations: DCO: data cut-off; MedDRA: Medical Dictionary for Regulatory Activities; PT: preferred term; SAE: serious adverse event; SAS: safety analysis set; SOC: system organ class.
Source: AstraZeneca Data on File (OlympiA CSR).[13]

B.2.10.3 Grade ≥3 AEs

AEs of Common Terminology Criteria for Adverse Events (CTCAE) Grade ≥3 were reported in 24.3% of olaparib-treated patients and 11.3% of placebo-treated patients (Table 19). In the olaparib arm, the most common Grade ≥3 AEs (reported in >2% of patients) were in the system organ classes of [redacted]. In the placebo arm no system organ classes were reported at a frequency of >2% of patients; Grade ≥3 AEs were most common (reported in >1% of patients) in the system organ classes of [redacted]. Anaemia was [redacted] reported in ≥5% of patients (8.7% of olaparib-treated patients vs 0.3% of placebo-treated patients).

Table 19: CTCAE Grade ≥3 AEs reported in OlympiA (≥3 patients in either arm), early primary analysis (SAS)

Grade ≥3 AEs	N (%)[a]	
	Olaparib (N=911)	Placebo (N=904)
Patients with any CTCAE Grade ⩾3 AE	221 (24.3)	102 (11.3)
Blood and lymphatic system disorders	[redacted]	[redacted]
Anaemia	79 (8.7)	3 (0.3)
Febrile neutropenia	[redacted]	[redacted]
Investigations	[redacted]	[redacted]
Neutrophil count decreased	44 (4.8)	7 (0.8)
White blood cell count decreased	27 (3.0)	3 (0.3)
Lymphocyte count decreased	[redacted]	[redacted]
ALT increased	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]

Grade ≥3 AEs	N (%)[a]	
	Olaparib (N=911)	Placebo (N=904)
Mastitis	[redacted]	[redacted]
Device related infection	[redacted]	[redacted]
Gastroenteritis	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]
Fatigue	16 (1.8)	6 (0.7)
Gastrointestinal disorders	[redacted]	[redacted]
Nausea	7 (0.8)	0
Vomiting	6 (0.7)	0
Diarrhoea	3 (0.3)	3 (0.3)
Abdominal pain	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]
Syncope	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]
Embolism	[redacted]	[redacted]
Neoplasms benign, malignant and unspecified (including cysts and polyps)	[redacted]	[redacted]
Ovarian cancer	[redacted]	[redacted]
Psychiatric disorders	[redacted]	[redacted]
Depression	[redacted]	[redacted]

Footnotes: DCO: 27 March 2020. Number (%) of patients with AEs of CTCAE Grade ≥3, sorted by decreasing frequency for SOC and by decreasing frequency in the olaparib arm order for PT. Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories. Includes AEs with an onset date or that worsened on or after the date of first dose and up to and including 30 days following the date of last dose of olaparib/placebo. CTCAE Version 4.03. MedDRA Version 22.1.
Abbreviations: AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; DCO: data cut-off; MedDRA: Medical Dictionary for Regulatory Activities; N: total number of patients; PT: preferred term; SAS: safety analysis set; SOC: system organ class.
Source: AstraZeneca Data on File (OlympiA CSR);[13] Tutt 2021a;[14] Tutt 2021b.[105]

B.2.10.4 AEs of special interest

AEs of special interest for olaparib, which are AEs considered to be potential risks associated with olaparib treatment, are summarised in Table 20. Myelodysplastic syndrome (MDS), acute myeloid leukaemia (AML) and new primary malignancies were considered AEs of special interest in OlympiA as they may be related to agents that affect DNA repair, including chemotherapy. Pneumonitis has been observed in previous trials of olaparib.

At the early primary analysis for iDFS (DCO: 27 March 2020), the incidence of MDS/AML in olaparib-treated patients was low and in line with the previously reported frequency. Notably,

since study onset, MDS/AML has been reclassified as an adverse drug reaction for olaparib and has also been categorised as an important identified risk in the risk management plan.

New primary malignancies were reported in [redacted] in the olaparib arm and [redacted] in the placebo arm.

A small proportion of pneumonitis events (9 patients, 1.0%) occurred in the olaparib arm, a similar rate to that reported in the placebo group (11 patients, 1.2%).

Table 20: AEs of special interest for olaparib, early primary analysis, SAS

AEs	N (%) of patients	
	Olaparib (N=911)	Placebo (N=904)
MDS/AML	2 (0.2)	3 (0.3)
Anaemia (any occurrence)	216 (23.7)	35 (3.9)
New primary malignancies	[redacted]	[redacted]
Pneumonitis/ILD, n (%)	9 (1.0)	11 (1.2)

Footnotes: DCO: 27 March 2020.
Abbreviations: DCO: data cut-off; ILD: interstitial lung disease; MDS: myelodysplastic syndrome; SAS: safety analysis set.
Source: AstraZeneca Data on File (OlympiA CSR);[13] Tutt 2021a;[14] Tutt 2021b.[105]

B.2.10.5 Dose interruptions, reductions and discontinuations due to Aes

A summary of all dose reductions, dose interruptions, and treatment discontinuations can be seen in Table 21.

At the early primary analysis for iDFS (DCO: 27 March 2020), dose interruptions of olaparib or placebo due to AEs occurred in a [redacted] proportion of patients in the olaparib arm [redacted] compared to the placebo arm [redacted]. Similarly, dose reductions occurred in a higher proportion of patients in the olaparib arm ([redacted] in the placebo arm). Nausea, anaemia, and decreased neutrophil count were the most common AEs leading to olaparib dose reduction or interruption:

- **Nausea:** In the olaparib arm, [redacted] and [redacted] of patients experienced nausea leading to dose reductions and interruptions, respectively. In the placebo arm, [redacted] and [redacted] of patients experienced nausea leading to dose reductions and interruptions, respectively.
- **Anaemia:** In the olaparib arm, [redacted] and [redacted] of patients experienced anaemia leading to dose reductions and interruptions, respectively. In the placebo arm, [redacted] and [redacted] of patients experienced anaemia leading to dose reductions and interruptions, respectively.
- **Decreased neutrophil count:** In the olaparib arm, [redacted] and [redacted] of patients experienced decreased neutrophil count leading to dose reductions and interruptions, respectively. In the placebo arm, [redacted] and [redacted] of patients experienced decreased neutrophil count leading to dose reductions and interruptions, respectively.

AEs leading to both dose reduction and interruption occurred in [redacted] of patients in the olaparib arm and [redacted] of patients in the placebo arm.

The majority of patients did not report an AE leading to discontinuation, with 90 patients (9.9%) in the olaparib arm and 38 patients (4.2%) in the placebo arm reporting an AE with an outcome of study treatment discontinuation. The most common AEs leading to discontinuation of olaparib (reported in ≥1.0% of patients) were nausea, anaemia, fatigue, and neutrophil count decreased.

Table 21: Dose interruptions, reductions, and discontinuations due to AEs, early primary analysis (SAS)

	N (%) of patients	
	Olaparib (N=911)	Placebo (N=904)
Dose interruption due to AEs[a]	[redacted]	[redacted]
Dose reduction due to AEs[b]	[redacted]	[redacted]
Discontinuation due to AEs[c]	90 (9.9)	38 (4.2)

Footnotes: DCO: 27 March 2020. [a]Dose interruption is an AE leading to temporary discontinuation of olaparib or placebo. [b]Dose reduction is an AE leading to dose reduction of olaparib or placebo. Patients may have had more than one AE leading to dose reduction. [c]Olaparib or placebo permanently stopped.
Abbreviations: AE: adverse event; DCO: data cut-off; SAS: safety analysis set.
Source: AstraZeneca Data on File (OlympiA CSR);[13] Tutt 2021a;[14] Tutt 2021b.[105]

B.2.10.6 Deaths

Overall, 59 (6.4%) patients treated with olaparib and 86 (9.4%) patients treated with placebo had died by the early primary analysis (DCO: 27 March 2020; Table 22). Of the reported deaths, 55 (93.2%) in the olaparib arm and 82 (95.3%) in the placebo arm were attributed to breast cancer recurrence, and [redacted] were attributed to fatal AEs.

Three patients experienced an AE with an outcome of death (Table 23) that started during randomised treatment or within the 30-day follow-up (one patient in the olaparib arm and two in the placebo arm). [redacted]

Table 22: All deaths in OlympiA, early primary analysis (SAS)

	Olaparib (N=921)	Placebo (N=915)
Total number of deaths, n (%)[a]	59 (6.4)	86 (9.4)
Primary cause of death[b]		
Breast cancer recurrence	55 (93.2)	82 (95.3)
AE	[redacted]	[redacted]
Other[c]	3 (5.1)	1 (1.2)
Time to death from last dose[b]		
≤30 days	[redacted]	[redacted]
>30 days	[redacted]	[redacted]

Footnotes: DCO: 27 March 2020. [a]As reported on the CRF (Death page); [b]Percentages were calculated from the number of patients who died; [c]In the olaparib arm, other includes pulmonary embolism, pneumonia, and unknown causes of death in 1 patient each, and in the placebo arm includes 1 patient with an unknown cause of death.

Abbreviations: AE: adverse event; CRF: case report form; DCO: data cut-off; SAS: safety analysis set.
Source: AstraZeneca Data on File (OlympiA CSR);[13] Tutt 2021a.[14]

Table 23: Adverse events with outcome of death in OlympiA, early primary analysis (SAS)

	Olaparib (N=911)	Placebo (N=904)
AE with outcome of death, n (%)	[redacted]	[redacted]
Cardiac arrest	[redacted]	[redacted]
AML	[redacted]	[redacted]
Ovarian cancer	[redacted]	[redacted]

Footnotes: DCO: 27 March 2020. Includes AEs with an onset date or that worsened on or after the date of first dose and up to and including 30 days following the date of last dose of olaparib/placebo.
Abbreviations: AE: adverse event; DCO: data cut-off; SAS: safety analysis set.
Source: AstraZeneca Data on File (OlympiA CSR).[13]

B.2.11 *Ongoing studies*

There are no ongoing studies, other than OlympiA, that support the use of olaparib in the indication under consideration.

High-level data from a second interim analysis for OS (DCO: 12 July 2021), completed once 330 iDFS events have been reported, became available in March 2022 (initial results have been presented at ESMO).[128] Full analyses of the data are expected to become available over the course of the appraisal and will be provided to NICE as soon as possible. The database lock including a formal analysis of OS, and descriptive analyses for iDFS and dDFS, was completed in December 2021.

The final OS analysis of OlympiA will be conducted once the trial follow-up is complete (i.e. 10 years from when the last patient is randomised).

B.2.12 *Interpretation of clinical effectiveness and safety evidence*

Principal findings of the clinical evidence base

The OlympiA clinical study demonstrates that adjuvant olaparib administered for up to one-year is associated with a significantly longer iDFS, dDFS, and OS in patients with g*BRCA*m, HER2-, high-risk eBC, following surgical treatment and neoadjuvant or adjuvant chemotherapy, compared with placebo.

OlympiA met its primary endpoint, with a statistically and clinical meaningful improvement in iDFS with olaparib in comparison to placebo at the early primary analysis (41.9% reduction in risk of invasive disease recurrence; hazard ratio: 0.58; 99.5% CI: 0.41, 0.82; p=0.0000073). Early and sustained separation in iDFS Kaplan-Meier survival curves was observed, with the benefit of olaparib being maintained over three years of treatment. This iDFS benefit was consistent across stratification and prespecified subgroups defined by clinically relevant characteristics, as indicated by the lack of statistical evidence of heterogeneity between any subgroup and the ITT iDFS treatment effect.[105] The secondary endpoint of dDFS is also supportive of the clinical benefit of olaparib, with a statistically and clinically meaningful difference observed between the

olaparib and placebo arms. A positive trend in OS is also indicated by high-level data from a second interim analysis for OS (DCO: 12 July 2021), with olaparib treatment providing an improvement in OS, compared with placebo.[128] Underlining the significance of the observed efficacy and the clinical value that olaparib can offer in the OlympiA indication, the iDFS results led the IDMC to unblind the OlympiA trial earlier than expected.[105]

No clinically meaningful differences in HRQoL were observed between patients in the olaparib arm compared with the placebo arm, signifying that patients treated with olaparib are able to benefit from an increased iDFS whilst maintaining their HRQoL. Data from OlympiA also indicate that olaparib has an acceptable safety and tolerability profile, consistent with its known safety profile.[105]

Together, these data indicate that olaparib provides a clinically and statistically meaningful benefit for patients with g*BRCA*m, HER2- high-risk eBC, by preventing or delaying disease recurrence, and improving survival; in this way, olaparib represents a potential step-change in the treatment of patients with *BRCA*m, HER2-, high-risk eBC, addressing the unmet need for an effective treatment in the adjuvant setting.

B.2.12.1 Strengths and limitations of clinical evidence base

B.2.12.1.1 Internal validity of OlympiA

OlympiA is a robust, high quality, double-blind, placebo-controlled RCT that directly compared the intervention and comparator of interest (established clinical management without olaparib, or 'watch and wait') for this evaluation in a large sample of patients with g*BRCA*m, HER2-, high-risk eBC, who had completed definitive local treatment and adjuvant or neoadjuvant chemotherapy (N=1,836). The number of important protocol deviations was low ([redacted] and [redacted] in the olaparib arm and placebo arm, respectively), and treatment arms were well balanced with respect to the percentage of patients with early censoring; these are therefore unlikely to have influenced the study conclusions.[13] Finally, a number of sensitivity analyses were conducted, which demonstrated consistency with the early primary analysis.[13] The quality assessment presented in Section B.2.5 confirmed the risk of bias within this study to be low. Overall, the OlympiA study represents a definitive source of data in the BRCAm eBC setting, with outcomes data collected from 1,836 patients across olaparib-treated and standard-of-care (i.e. 'watch and wait') arms.

B.2.12.1.2 External validity of OlympiA

The OlympiA population can be considered generalisable to the UK population, with results that are relevant to the decision problem specified by the final NICE scope.

Population

OlympiA enrolled a representative population of patients with g*BRCA*m, HER2-, high-risk eBC, who had completed definitive local treatment and adjuvant or neoadjuvant chemotherapy (N=1,836). Patient demographics were well balanced between study arms and included patients representative of the eBC patient population in the UK.[14] The mean age of patients in OlympiA

enrolment was 43.0 years, which is similar to the mean age of g*BRCA*m breast cancer population in Europe, at 43–48 years.[130] Prior treatment history received by patients in OlympiA also mirrored that expected in UK clinical practice (see Section B.2.3.8 and Section B.1.3.2).

Although the relative proportion of patients with TNBC and HR+/HER2- disease in OlympiA differs to that seen in UK clinical practice,[52] this can be attributed to the lower prevalence of *BRCA*m among patients with HR+/HER2- breast cancer, the later enrolment of patients with HR+/HER2- disease in the study due to a protocol amendment, and the stringent criteria used to identify HR+/HER2- patients at high risk of recurrence. In general, both the TNBC and HR+/HER2- subgroups are still considered representative of these patients in the UK, as the baseline characteristics of these patients are comparable to those of patients seen in clinical practice. Full analyses of the second interim analysis for OS (DCO: 12 July 2021) are expected to become available over the course of the appraisal, and will provide more mature data for the HR+/HER2- subgroup.

Finally, as previously discussed, globally and in UK clinical practice, a variety of factors and scoring systems may be used to identify patients at high-risk of recurrence, likely based on local practice and clinical experience. The definitions of high-risk used in OlympiA are anticipated to be broadly consistent with these; for example, potential considerations in UK clinical practice are known to include the presence of residual disease after surgery,[131, 132] and gene expression profiles or molecular recurrence scores.[30]

Intervention and comparator

The intervention and comparator in OlympiA are aligned to the decision problem presented in Section B.1.1 and are relevant to UK clinical practice. Olaparib was directly compared with placebo in patients with g*BRCA*m, HER2-, high-risk eBC, who had completed definitive local treatment and adjuvant or neoadjuvant chemotherapy. At the time of study onset, endocrine therapies for patients with HR+/HER2- breast cancer, and bisphosphonates for post-menopausal women, were the only available treatment options after completion of (neo)adjuvant chemotherapy based on UK treatment guidelines.[13, 23] Therefore, the use of a placebo comparator, with endocrine therapy allowed concomitantly in both arms, is appropriate for objectively testing the efficacy of olaparib in a setting reflective of UK clinical practice. As the comparator in this evaluation is established clinical management without olaparib, the use of placebo allows investigation of olaparib compared with no further treatment (as would occur in clinical practice).

Outcomes

The OlympiA trial evaluated a wide range of outcomes, including all outcomes outlined in the NICE scope (iDFS, dDFS, OS, incidence of new primary breast or ovarian cancers, HRQoL and AEs). The primary endpoint, iDFS, and the efficacy endpoints are in line with recommendations from the FDA Guidance on Clinical Trial Endpoints for the Approval of Cancer Drugs Biologics and the Committee for Medicinal Products for Human Use (CHMP) Guidance on the Evaluation of Anticancer Medicinal Products;[91, 92] these endpoints are also directly referenced in the final scope for this evaluation. Additionally, the data observed for iDFS are also further supported by

the other clinically relevant endpoints, such as dDFS and OS, which show statistically and clinically meaningful treatment benefit with olaparib in *BRCA*m, HER2-, high-risk eBC patients.

B.2.12.1.3 Limitations

At the time of the early primary analysis for iDFS (DCO: 27 March 2020), the OS data were immature in both trial arms ([redacted] mature). HR+/HER2- data were also immature, due to late enrolment in the OlympiA trial. Although there is high confidence in the robustness of the clinical effectiveness data presented in this submission, AstraZeneca acknowledge that there is a degree of uncertainty surrounding immaturity and lower patient numbers in the HR+ group that will be realised with longer follow-up. Although, low event numbers are not uncommon for OS in adjuvant treatments. Further analyses of time-to-event endpoints and more mature data for the HR+/HER2- population will be event-driven, for example high-level data from a second interim analysis for OS (DCO: 12 July 2021), completed once 330 iDFS events have been reported, became available in March 2022 (initial results have been presented at ESMO),[128] which reduces uncertainty in the data, particularly for the HR+/HER2- subgroup. Full analyses of the data are expected to become available over the course of the appraisal and will be provided to NICE as soon as possible.

The final OS analysis of OlympiA will be conducted once the trial follow-up is complete (i.e. 10 years from when the last patient is randomised).

B.2.12.2 Conclusions

The OlympiA clinical study demonstrates that **one year of adjuvant olaparib provides a statistically significant and clinically meaningful benefit** for patients with g*BRCA*m, HER2-, high-risk eBC previously treated with neoadjuvant or adjuvant. At the early primary analysis for iDFS (DCO: 27 March 2020):

- A **statistically and clinically meaningful investigator-assessed iDFS benefit** was observed in patients treated with olaparib compared with those treated with placebo (41.9% reduction risk of invasive disease; hazard ratio [HR]: 0.58; 99.5% confidence interval [CI]: 0.41–0.82; p=0.0000073).
- Subgroup analyses showed that there was **no statistical evidence of heterogeneity between any subgroup** and the ITT iDFS treatment effect, irrespective of prior chemotherapy (neoadjuvant vs adjuvant), *BRCA* status (*BRCA*1 vs *BRCA*2 mutations) or HR status.
- Consistent with the primary endpoint, a **statistically and clinically meaningful investigator-assessed dDFS benefit** was observed in patients treated with olaparib compared with those treated with placebo (42.6% reduction risk of invasive disease; HR: 0.57; 99.5% CI: 0.39–0.83; 95% CI: 0.46–0.74; p=0.0000257).
- Early data showing a positive trend in OS for olaparib compared with placebo (31.7% reduction in risk of death; hazard ratio: 0.68; 99% CI: 0.44, 1.05; p=0.0236)
    - At second interim analysis for OS (DCO: 12 July 2021), statistical significance was reached in this key secondary endpoint (hazard ratio: 0.68; 98.5% CI 0.47–0.97;

p=0.009),[124] which is **remarkable for an interim DCO in an eBC adjuvant setting, and clearly demonstrates the sustained benefit of olaparib**

- No clinically meaningful differences in HRQoL scores were observed between patients receiving olaparib and placebo over the course of the study.

The introduction of olaparib in this indication will therefore help address the substantial unmet need for targeted treatments that prevent or delay recurrence and extend OS in a setting where the intention of treatment is curative; in this way, **olaparib has the potential to drive a step-change in the treatment of patients with *BRCA*m, HER2-, high-risk eBC.**

B.3 Cost-effectiveness

Summary of the economic analysis

- As detailed in Section B.2, the Phase III OlympiA study demonstrates that adjuvant olaparib administered for up to one-year **significantly improves the outcomes of patients** with g*BRCA*m, HER2-, high-risk eBC, resulting in a **statistically and clinically meaningful 41.9% reduction in the risk of invasive disease** when compared with placebo (iDFS HR: 0.58; 99.5% CI: 0.41, 0.82; p<0.001).
- The economic analysis presented in this section thus **evaluates the cost-effectiveness of olaparib** as a monotherapy for the adjuvant treatment of adult patients with g*BRCA*m who have HER2-negative, high-risk eBC who have previously been treated with neoadjuvant or adjuvant chemotherapy vs. current standard of care ("watch & wait", placebo), which comprises of routine follow-up and screening for recurrence, and is consistent with the NICE final scope and guidance.
    - In order to capture differences in patterns of long-term disease recurrence and available treatment options for metastatic disease between **triple-negative and HR+/HER2- BC, the model splits the subgroups into two separate analyses**; cost-effectiveness results are thus presented for each subgroup.
- The economic model concentrates on the point from initiation of adjuvant olaparib treatment and is a **five-state semi-Markov state transition model** representing the key stages of disease in HER2- BC: 'disease free', 'non-metastatic recurrence', 'early onset metastatic recurrence', 'late onset metastatic recurrence' and 'death'.
    - The model mainly draws upon clinical data from the OlympiA study, which baseline patient characteristics have been validated by clinical experts and can be considered generalisable to the corresponding UK population.
    - Furthermore, to reflect the availability of different first-line treatment options available to patients with *BRCA*m mBC in the UK, three additional external studies were used to inform patients' survival in this state.
    - All assumptions have undergone a rigorous validation process, including a comparison with relevant (UK) empirical data and RWE and two rounds of interviews with UK clinical oncologists. Where possible, costs and resource use are taken from well-established UK sources and previous NICE appraisals in eBC.
- The base-case results of the economic analysis indicate that **adjuvant treatment with olaparib is cost-effective at the current olaparib PAS price**, with an ICER of £29,732 and £35,312 for the TNBC and HR+/HER2- populations respectively.
    - Compared to placebo ("watch & wait"), olaparib also produces **considerable clinical and patient benefits**, including [redacted] and [redacted] additional life years and [redacted] and [redacted] additional discounted QALYs per patient on average for each population respectively.
    - Running the analysis under a range of key scenarios yielded results highly consistent to the base case, suggesting that the base case ICERs for both the TNBC and HR+/HER2- populations are robust to variations in input parameters.
    - Similar results were demonstrated with the PSA, which was consistent with the deterministic analysis with similar mean incremental costs and QALYs generated to the base case analysis for both TNBC and HR+/HER2-.
- Olaparib is a **highly efficacious, well-tolerated and innovative treatment option for *BRCA*m, HER2-negative eBC and represents a step-change in the treatment paradigm for patients with high-risk, *BRCA*m disease**, a patient group in which the risk of cancer returning can be unacceptably high.
    - Results from the OlympiA trial have shown that olaparib not only reduced the risk of recurrence but also improved overall survival, highlighting the exciting

demonstration of the benefits of targeting the specific *BRCA*m biology of disease for these patients.

- Further to these important clinical benefits of olaparib to patients, it is also a **cost-effective use of NHS resources** when compared against the thresholds commonly used in decision making in England and Wales, as is demonstrated by the results presented in this submission.

B.3.1 *Published cost-effectiveness studies*

An SLR was conducted to identify previous cost-effectiveness studies in the eBC setting, including both HER2+ and HER2- disease. The SLR was initially conducted in December 2020 and subsequently updated in January 2022. A brief summary of the review is provided below; full details of the methodology and results are presented in Appendix G.

The review identified 16 published cost-effectiveness studies in eBC from the UK and Canada, of which the majority reported either on targeted treatments for HER2+ disease or for adjuvant endocrine treatment in HR+[a] disease. No published studies were found that assessed the cost-effectiveness of olaparib in eBC, or for the treatment of *BRCA*m breast cancer or TNBC. Of the ten published studies in the UK, the majority reported using a Markov state transition approach (n=8) and used similar model structures, including health states for disease free, locoregional recurrence, distant recurrence and death.

In addition to the published literature, the review identified 28 health technology evaluations of treatments for eBC covering the UK (5 NICE and 12 SMC evaluations), Canada (2 CADTH evaluations) and Australia (9 PBAC evaluations). As with the published literature, the majority of the evaluations related to treatments for HER2+ or HR+[a] disease; none specifically assessed the cost-effectiveness of treatments for *BRCA*m breast cancer or TNBC, or for olaparib in *BRCA*m, HER2-, high risk eBC. Thus, in the absence of any HER2- eBC evaluations, the most relevant previous NICE evaluations in HER2+ eBC (TA632,[133] TA612,[134] and TA569,[135]) were used to inform the model development for olaparib in the specific population of interest. Learnings from these evaluations are presented in each of the subsequent sections.

B.3.2 *Economic analysis*

As no published economic studies were identified which considered olaparib in the indication relevant to this submission, a *de novo* model was developed to assess the cost-effectiveness of olaparib in patients with *BRCA*m, HER2-, high risk, eBC. The model reflects the disease pathway for eBC in England, as described in Section B.1.3.2, and is aligned with the NICE reference case. Its structure is consistent with the cost-effectiveness (CE) models used in TA632,[133] TA612,[134] and TA569,[135] yet builds upon the learnings from these evaluations based on the respective feedback given by the ERG and appraisal committees. A description of the model and key features of the analysis are presented in the subsequent sections.

[a] HER2-negative status was not always reported and/or the study included HER2-positive and HER2-negative patients with HR+ disease

B.3.2.1 Patient population

The economic analysis is consistent with the NICE final scope and evaluates olaparib within its anticipated marketing authorisation:[136]

[redacted]

This population is aligned with the ITT population in the pivotal OlympiA trial,[13] which is used to inform the economic model.

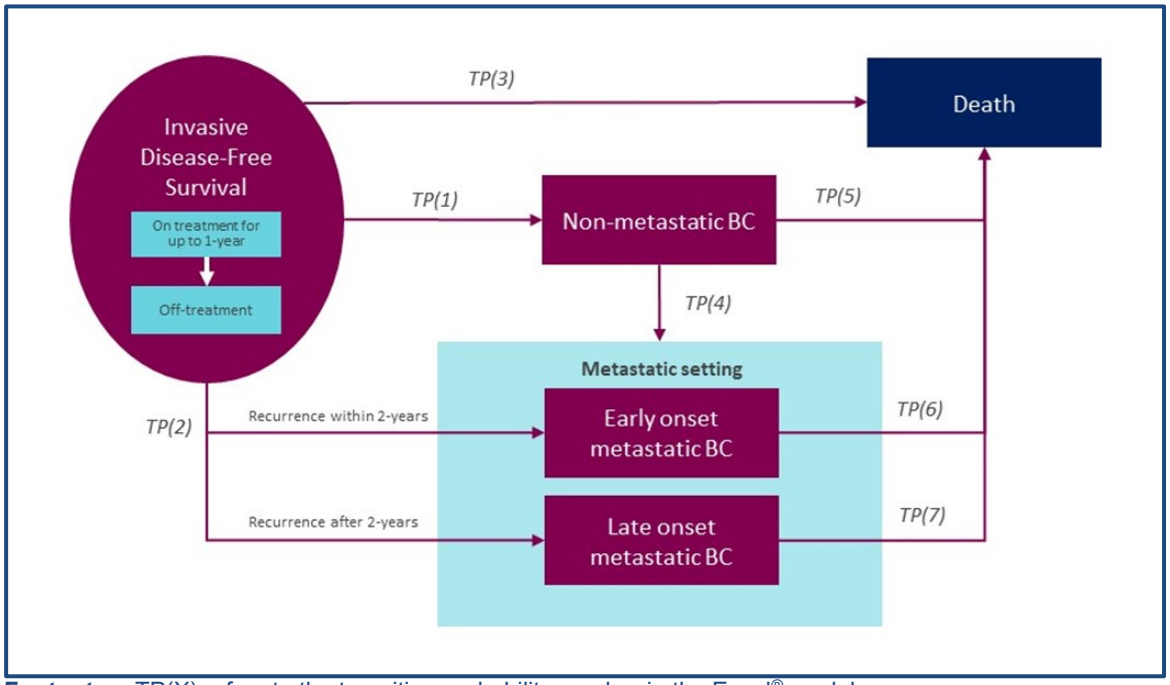
As described in Section B.1.3.2, although olaparib showed a statistically significant clinical benefit versus placebo in the full ITT population of the OlympiA trial, there are important differences in patients' underlying prognosis depending on their cancer's histological subtype that need to be considered and reflected in the economic analysis. For patients with TNBC, studies have shown that their risk of recurrence is highest during the first five years after becoming disease-free, with the risk decreasing and then plateauing at a low level over subsequent decades. In contrast, patients with HR+/HER2- disease have been shown to remain at a relatively constant risk of recurrence for at least 20 years after diagnosis (Figure 5). Although there was no statistically significant difference in the treatment effect observed between these two sub-groups in OlympiA (p=0.536, Section B.2.7),[13] when modelled this difference in baseline risk of recurrence between the subgroups is expected to impact on the absolute long-term costs and health outcomes of adjuvant treatment, which warrants their consideration as separate subgroups in the economic analysis. As such, cost-effectiveness results of adjuvant olaparib treatment in patients with *BRCA*m, HER2-, high risk eBC are presented for both subgroups of the OlympiA ITT population: TNBC and HR+/HER2- disease.

Modelling these subgroups separately allows for greater flexibility in capturing their respective patterns of long-term disease recurrence, as well as differences in available treatment options. As described in Section B.1.3.2, almost all patients with HR+/HER2- eBC will be offered endocrine therapy alongside (neo)adjuvant systemic chemotherapy, with most continuing endocrine therapy once their disease progresses. In the metastatic setting, eligible patients with TNBC may receive a PD-L1 inhibitor (atezolizumab) in the UK,[137] whereas patients with HR+/HER2- disease may be treated with a CDK4/6 inhibitor (abemaciclib,[138] palbociclib,[139] and ribociclib[140]). Further information on the initial and subsequent treatments in each respective subgroup can be found in Section B.3.5.

B.3.2.2 Model structure

A five-state semi-Markov state transition model was developed in Microsoft Excel®. The model is 'semi-Markov' as the transition probabilities between states can vary based on the time spent in each health state; this is modelled using 'tunnel' states that track the time spent in each state over time. The five health states represent key stages of disease in eBC and have been validated by clinical experts as representing the appropriate course of the disease: 'disease free', 'non-metastatic recurrence', 'early onset metastatic recurrence', 'late onset metastatic recurrence' and 'death'.[8, 9] A schematic of the model state structure is presented in Figure 15 below.

Figure 15: Schematic of the model structure



Footnotes: TP(X) refers to the transition probability number in the Excel® model.
Abbreviations: BC: breast cancer; TP: transition probability

B.3.2.2.1 Rationale for selected modelling approach

In line with NICE Decision Support Unit (DSU) guidance, the model structure was selected and developed considering a wide range of factors, including (1) the ability to capture the important aspects of the clinical and treatment pathway, (2) accepted model structures and appraisal committee feedback from previous NICE submissions in eBC, (3) structural assumptions associated with different modelling approaches, and (4) the availability and maturity of the OlympiA data.

As described above, a five-state model structure was adopted as it represents the key stages of disease in HER2- eBC. This structure is also broadly consistent with CE models which were considered appropriate for decision making in previous eBC NICE evaluations (TA632,[133] TA612,[134] and TA569[135]). A full comparison of the model structure in previous HER2+ eBC NICE evaluations vs. the economic analysis as presented in this submission is given in Table 25.

The Markov state transition method was chosen over alternative approaches, such as partitioned survival modelling, due to its ability to explicitly model the relationship between each health state. By doing so, it allows for important assumptions to be explored that are relevant to patients with *BRCA*m, HER2-, high risk eBC, such as the evolution in their risk of recurrence over time, the difference in post-progression survival outcomes for those patients who experience locoregional vs. metastatic recurrence, and the impact of time to recurrence on post-progression survival outcomes. Furthermore, it allows for external data sources to be used to inform post-progression survival as it explicitly models the relationship between disease progression and survival outcomes. Adapting a Markov model for this economic analysis therefore enables factors that influence the risk of each event to be explicitly modelled and provides more flexibility in conducting scenario analyses.

Finally, as noted in the NICE technical support document (TSD) 19, the state-transition method "… *improves transparency around the mechanisms and processes underpinning results generated using extrapolation*" by modelling survival as a product of transitions between states.[141] In doing so, the method avoids the uncertain direct extrapolation of the immature OS data from the OlympiA study.

As it was possible to include the required functionality to vary the transition rates dependent on when patients entered each relevant health state within the Markov modelling approach, alternative approaches such as patient level simulation models were judged to add additional complexity without adding any meaningful additional value and were thus not adopted.

B.3.2.2.2 Health states

The five health states as shown in Figure 15 are defined as follows:

- **iDFS – invasive disease-free survival:** Patients are free of disease recurrence (metastatic or non-metastatic disease) having previously completed local treatment and adjuvant or neoadjuvant chemotherapy.
- **Non-metastatic breast cancer:** Patients have experienced local or regional ipsilateral recurrence or have contralateral invasive breast cancer. Patients are assumed to undergo further surgery, radiotherapy and/or drug therapy to treat the recurrence of disease.
- **Early onset mBC:** Patients have experienced distant recurrence during the first 2 years after completing local treatment (i.e., during the first 2 years of the time horizon). Following the definition of dDFS in the OlympiA trial, this includes new primary non-breast invasive malignancies and both central nervous system (CNS) and non-CNS distant mBC.[13] As mBC is considered incurable, all patients that enter this state are assumed to receive palliative surgery, radiotherapy and/or drug therapy.
- **Late onset mBC:** Patients have experienced a distant recurrence event beyond the first 2 years after completing local treatment (i.e., after the first 2 years of the time horizon). As with early onset mBC, patients that enter the late onset state are assumed to receive palliative surgery, radiotherapy and/or drug therapy.
- **Death:** Absorbing state for deaths from any cause.

The model classifications of non-metastatic and metastatic recurrence closely follow the endpoint definitions of iDFS (primary) and dDFS (secondary) in the pivotal OlympiA trial. These endpoints were based on the standardised definitions for DFS and dDFS as outlined in the STEEP criteria.[13] The events leading to the non-metastatic and metastatic states are considered to incur similar treatment and management costs, and result in similar levels of HRQoL and survival. This is consistent with approaches taken in past NICE evaluations for HER2+ disease (TA632,[133] TA569[101]). Finally, the transitions to mBC have been split by <2 and >2 years, as the survival outcomes are expected to be conditional on the time within which a patient experiences disease recurrence. Further detail on this is given in the subsequent sections.

In total, there are seven possible transitions between each of the health states in the model, which are described according to the modelled treatment pathway below. Full details on the technical derivation of the transition probabilities (TPs) can be found in Appendix N.

Disease-free survival (DFS)

All patients enter the model in the iDFS health state having completed local treatment and neoadjuvant or adjuvant chemotherapy. In the intervention arm, patients immediately initiate a 12-month treatment plan with adjuvant olaparib. After discontinuation or completion of treatment, patients that remain disease free undergo 'watch and wait', comprising of routine follow-up and screening for recurrence. In the comparator arm, patients undergo 'watch and wait' from model entry to disease recurrence or death. As mentioned in Section B.1.3.2, patients with HR+/HER2- disease may also receive adjuvant endocrine therapy alongside olaparib or 'watch and wait', until disease recurrence, death or for a fixed maximum duration.

From the iDFS state, patients may experience one of three events:

1. **TP1:** develop a locoregional recurrence or contralateral breast cancer and enter the non-mBC state
2. **TP2:** develop a distant metastatic recurrence or second primary non-breast invasive malignancy and enter the disease states for mBC
3. **TP3:** experience death from any cause prior to a non-metastatic or metastatic disease recurrence

These events cover the breadth of outcomes considered in the primary endpoint of iDFS in the OlympiA trial. Both recurrence events and death are modelled as an irreversible process such that patients are unable to return to the iDFS state.

Metastatic recurrence pathway

Patients that develop a distant metastatic recurrence from either the disease-free or non-metastatic state in the first 2 years of the time horizon are assumed to enter the 'early onset mBC' state. After 2 years, patients that develop a distant metastatic recurrence enter the 'late onset metastatic recurrence state'. From both the metastatic states, patients can transition to the death state.

The risk of death after metastatic cancer was assumed to differ based on the timing of recurrence, defined as 'early' (TP6) and 'late' (TP7) onset. This is to reflect clinical expert advice that patients with early recurrence tend to have more aggressive disease that is less sensitive to subsequent palliative treatment than patients who experience late recurrence and are likely to have more indolent disease.[8] This is consistent with the approach taken in past economic models in HER2+ disease (TA632,[133] TA569,[135] and TA424[142]), which also stratified disease recurrence according to the timing of relapse following recommendations from clinical experts. For example, in TA632, 'early' vs. 'late' relapse was based on an 18-month timepoint, which was supported by data from the HERA study (trastuzumab in HER2+ breast cancer), which showed a clear difference in post-progression survival between patients who progressed before and after 18 months.[133]

For this economic analysis, the timing of early and late recurrence was set to 2 years for both patients with triple negative and HR+/HER2- disease. This 2-year time point was selected following UK clinical expert advice and is supported by literature showing consistently poor post-recurrence survival in patients that recur within 2 years (Table 24).[8] For example, the UK

'Prospective study of Outcomes in Sporadic versus Hereditary breast cancer' or 'POSH' study, which investigates the effect of a g*BRCA*m on breast cancer outcomes in UK patients with young-onset breast cancer, shows a clear difference in post-recurrence survival for patients who recur before 2 years (25% 2-year survival) versus patients who relapse after two years (>43% 2 year survival).[143] Although the POSH study does not specifically incorporate patients with high-risk disease, it includes patients highly comparable to the OlympiA population (*BRCA*m, early-stage disease at a young age) who are treated under UK clinical guidelines for eBC. It thus presents a relevant and credible data source to validate the 2-year recurrence time point chosen in the base case economic analysis. Alternative time points (1–3 years) for both subgroups were considered in sensitivity analyses. It should be noted that the model results are relatively insensitive to changes in the chosen timepoint.

For both 'early' and 'late' onset mBC, the costs and health outcomes of patients were captured within one health state given the limited data available from either OlympiA or the published literature to inform transitions between multiple progressed disease states. Furthermore, the inclusion of additional health states of progression-free and progressed metastatic disease was considered unlikely to materially impact results, as the prognosis of patients with *BRCA*m, high-risk mBC is poor (median post-recurrence survival of 7–12 months in OlympiA).[13] Instead, a one-off subsequent treatment cost, which captures up to two lines of therapy, is applied as patients transition to the metastatic disease state. This is in line with previously accepted economic models in HER2+ disease (TA632[133] and TA569[135]).

Table 24: Summary of literature evidence on the impact of time to recurrence on post-progression survival outcomes

Study	Country	Population	Definition: early vs late	Post-recurrence survival for early vs late
McKenzie et al. (2020)[143]	UK (POSH study)	Young women aged <40 years (n=3,021) with initially localized invasive breast cancer diagnosed between 2000–2008	Recurrence time: • <24 months • 24–60 months • >60 months plus	2-year post-recurrence survival: • <24 months: 25% • 24–60 months: 43% • >60 months: 49%
Lobbezoo et al. (2015)[144]	Netherlands	Consecutive patients diagnosed with mBC in 2007–2009 from 8 Southeast Dutch hospitals	Metastatic free interval: • <2 years • >2 years	Median survival: • <2 years: 9.1 months • >2 years: 27.9 months
Dawood et al. (2010)[145]	United States	Female patients diagnosed between 1992–2007 with either de novo stage IV or relapsed breast cancer at the Department of Breast Medical Oncology of The University of Texas M. D. Anderson Cancer Centre	Disease-free interval: • <6 months • 6–24 months • 2–5 years • >5 years	Median OS: • <6 months: 17.4 months • 6–24 months: 17.3 months • 2–5 years: 30.4 months • >5 years: 47.4 months

Abbreviations: OS: overall survival; POSH: The Prospective study of Outcomes in Sporadic versus Hereditary breast cancer; UK: United Kingdom.

Non-metastatic recurrence pathway

Patients that enter the non-mBC health state remain in this state until the onset of distant mBC (TP4) or death (TP5). As described above, patients that develop a distant metastatic recurrence in the first 2 years of the time horizon will enter the 'early onset' mBC state and those that have recurrence after 2 years enter the 'late onset' state, in the same manner as those who transition straight from iDFS to metastatic disease. All patients that enter the non-metastatic recurrence state are assumed to be at risk of distant recurrence or death immediately upon entering the state.

When compared to previous NICE evaluations in HER2+ disease,[133-135] the OlympiA model adopts a simplified approach to the modelling of the non-metastatic recurrence pathway by using a single state for non-mBC. In past models, non-metastatic recurrence was represented by two health states of 'locoregional recurrence' and 'remission'. The locoregional state comprised a

series of tunnel states to reflect 12 months of adjuvant therapy. During this time, few patients were expected to experience disease recurrence or death. Patients that completed adjuvant therapy then entered the state of remission. From this state, patients were at risk of mBC or death. These models therefore assumed that patients had no risk of recurrence during the first 12 months after non-metastatic recurrence and that they were subject to the mortality risk of the aged-matched general population.

In OlympiA, the [redacted].[13] This is further supported by insights from UK clinical experts, who confirmed that there was no clear definition of remission after locoregional recurrence in patients with HER2- disease, and that in general, remission after locoregional recurrence for patients with HER2-, high-risk disease is highly unlikely.[9] Based on these insights, the OlympiA model excludes the state of remission and allows for the development of distant metastatic disease upon entering the non-metastatic disease state. Although there may be the potential for a very small proportion of patients with non-metastatic disease to achieve long-term remission, it was considered that the distributions fitted to estimate the long-term transition probabilities were adequately able to capture this without the need for an additional health state (Section B.3.3.4).

B.3.2.3 Features of the economic analysis

In the base case analysis, cost and health outcomes are modelled over a lifetime horizon (assumed to be 57 years) and discounted at an annualised rate of 3.5%, as per the NICE reference case. However, given the potential for olaparib to significantly increase the proportion of patients who achieve long-term remission and achieve good long-term survival outcomes, a scenario is presented applying a discount rate of 1.5%.

A monthly cycle length was applied, consistent with previous evaluations in HER2+ eBC,[133-135] as this was determined to be sufficiently short enough to accurately capture cost and QALY outcomes in each cycle. Half-cycle correction was applied to account for the fact that events can occur at any point during each cycle, with the exception being the cost of adjuvant olaparib as this was directly estimated from the time on treatment data from OlympiA. A complete overview of the features of the economic analysis and comparisons with previous NICE evaluations in eBC is given in Table 25 below.

Table 25: Features of the economic analysis and comparisons with previous NICE evaluations in HER2+ eBC

Features	Previous evaluations			Current evaluation	
	TA632[133] – Trastuzumab emtansine for adjuvant treatment of HER2+ eBC	TA612[134] – Neratinib for extended adjuvant treatment of HR+, HER2+ eBC after adj. trastuzumab	TA569[135] – Pertuzumab for adj. treatment of HER2+ eBC	Value used for submission	Justification
Modelling approach/structure	Seven-state Markov model	Five-state Markov model	Seven-state Markov model	Five-state Markov model	Consistent with approaches that have been accepted in past eBC NICE evaluations;[133-135] model structure represents the primary stages of disease in eBC. Choice of model structure also reflects NICE DSU guidance.[141]
Timing of early vs. late recurrence	18 months	12 months	18 months	24 months	UK clinical expert advice and literature data shows consistently poor post-recurrence survival in patients similar to the OlympiA population that recur within 2 years.[8, 143]
Time horizon	52 years (lifetime)	55 years (lifetime)	52 years (lifetime)	57 years (lifetime)	The NICE reference case stipulates that the time should be sufficiently long to reflect any differences in costs or outcomes between the

Features	Previous evaluations			Current evaluation	
	TA632[133] – Trastuzumab emtansine for adjuvant treatment of HER2+ eBC	TA612[134] – Neratinib for extended adjuvant treatment of HR+, HER2+ eBC after adj. trastuzumab	TA569[135] – Pertuzumab for adj. treatment of HER2+ eBC	Value used for submission	Justification
					technologies being compared.
Cycle length	1 month	1 month	1 month	1 month	A monthly cycle length is applied consistent with the previous submissions[133-135] as it is considered short enough to accurately capture relevant costs and QALY outcomes.
Source of utilities	eBC health states: EQ-5D data from the KATHERINE trial mBC health states: Lloyd et al. (2006)[146]	EQ-5D data collected during the ExteNET trial and published literature	eBC health states: EQ-5D data from the APHINITY trial mBC health states: Lloyd et al. (2006) [146]	eBC (& LR) health states: mapped HSUs from OlympiA EORTC QLQ-C30 mBC health state: Lidgren et al. (2007)[147]	In accordance with the NICE reference case.
Source of costs	Published literature and clinical expert opinion	NHS reference costs, BNF, published literature, and clinical expert opinion	Published literature and clinical expert opinion	NHS reference costs, eMiT, Unit Costs of Health and Social Care (PSSRU), published literature and UK clinical expert opinion	In accordance with the NICE reference case.

Abbreviations: BNF: British National Formulary; eBC: early breast cancer; eMIT: drugs and pharmaceutical electronic market information tool; EQ-5D: standardised measure of health-related quality of life; HER2: human epidermal growth factor receptor 2; HR: hormone receptor; HSU: health state utility; LR: locoregional; mBC: metastatic breast cancer; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; PSS: personal social services; TA: technology appraisal; QALY: quality adjusted life year.

B.3.2.4 Intervention technology and comparators

B.3.2.4.1 Intervention

The intervention is the tablet formulation (taken orally) of olaparib at the recommended dose of 300 mg (two 150 mg tablets) taken twice daily. Patients can continue treatment until recurrence of disease, diagnosis of a second primary malignancy, treatment discontinuation or treatment completion. Treatment duration is up to a maximum of 12 months.[136]

The dosage of olaparib is aligned to the anticipated MHRA marketing authorisation for olaparib in this indication, and the treatment duration is aligned to the approach taken in the OlympiA study.[13]

B.3.2.4.2 Comparator

As described in Section B.1.3.2, there are currently no recommended or evidence-based treatment options which represent standard of care in the UK for people with *BRCA*m, HER2-, high risk eBC in the extended adjuvant setting after completing treatment with neoadjuvant or adjuvant chemotherapy. The comparator in the economic analysis is therefore 'watch and wait', which comprises of routine follow-up and screening for recurrence, and is consistent with the NICE final scope and guidance.

B.3.3 *Clinical parameters and variables*

Primary clinical data were obtained from the pivotal Phase III OlympiA trial and are based on patient-level data analysed from the early primary analysis (DCO: 27 March 2020).[13]

In addition to the OlympiA clinical trial data, the economic model uses data from external Phase III studies in *BRCA*m HER2- mBC, including data from the Phase III OlympiAD (olaparib vs. single chemotherapy) trial,[126, 148] a real-world study of CDK4/6 inhibitor treatment[149] and the Phase III IMpassion130 trial of atezolizumab in metastatic TNBC,[150] to inform the modelling of survival from the 'late onset' mBC state. These data sets provide longer-term data for outcomes in the late-onset metastatic disease state and therefore help reduce the uncertainty in the long-term extrapolations of post-progression survival.

To ensure the clinical plausibility of the long-term model extrapolations, the model utilises all-cause mortality data from the Office for National Statistics (ONS) life tables to constrain the risk of death from any state to be greater than or equal to the background risk of death by age.[151] The background mortality risk is matched on the age and gender characteristics of the OlympiA trial population. The mortality risk is further adjusted to capture the lifetime excess mortality risk from other illnesses that may lead to shortened life expectancy in persons with g*BRCA*m.[152] Details on this mortality risk-adjustment are provided in Section B.3.3.3.

B.3.3.1 Modelling of subgroup outcomes

As described in Section B.3.2.1, in order to capture differences in baseline risk of recurrence and treatment options between triple-negative and HR+/HER2- disease, the model splits these subgroups into two separate analyses. Although subgroup data from OlympiA on non-metastatic

and distant metastatic recurrence is available, most transition probabilities outlined in the sections below are estimated based on data from the ITT population or external sources (Table 27). An exception to this approach is the modelling of iDFS (TP1 and TP2). In this case the TNBC-specific iDFS data were used for the analysis of the TNBC subgroup, which is sufficiently mature and provides the most robust dataset for this analysis, while ITT data were used for the HR+/HER2- subgroup. This approach of using the ITT data as a proxy for the HR+/HER2- subgroup is justified on the following grounds:

- At the primary iDFS analysis of OlympiA, it was not possible to reliably estimate the survival of patients with HR+/HER2- disease using conventional subgroup survival analysis due to the limited number of iDFS events observed in this subgroup ([redacted] for olaparib versus [redacted] for placebo).[13, 105] This relatively small number of observed events greatly prohibits the scope of the statistical analysis for iDFS and post-recurrence survival for input to the economic model. The small number of events is due to the history of the OlympiA trial described in Section B.2.12.2, whereby the enrolment of HR+/HER2- patients began several years after the enrolment of TNBC patients. This has resulted in the HR+/HER2- subgroup being both smaller (only 17.7% of the OlympiA patients) and less mature than the TNBC cohort at the time of the early primary analysis (DCO: 27 March 2020).
- In OlympiA, there was no statistical evidence of a differential treatment effect by HER2- subgroup, with the benefit of olaparib being observed irrespective of HR status.[105] This finding is consistent with other Phase III clinical trials of PARPi treatments in *BRCA*m mBC, which also show that the comparative efficacy of PARPi treatment (including olaparib) versus chemotherapy was observed across both TNBC and HR+/HER2- subgroups.[153] Furthermore, clinical experts noted that there are no biological or clinical reasons to expect differential efficacy for olaparib by HER2- subgroup given the selection of treatment based on a patient's *BRCA* status.[129] In the absence of more mature HR+/HER2- subgroup data, these aspects support the use of the primary ITT iDFS analysis to model the relative efficacy of olaparib in the HR+/HER2- population.
- Finally, the baseline survival rates (i.e., in the placebo arm) for iDFS (and OS) in the HR+/HER2- and TNBC subgroups of OlympiA are similar across the duration of study follow-up, as shown in Table 26 below. These data further support the use of the primary ITT analysis as a proxy to model the baseline efficacy of placebo in the HR+/HER2- subgroup.

The use of the primary ITT data to model TP1/TP2 in the HR+/HER2- patient population is therefore considered the most robust approach given the limitations of the current available subgroup data for this group. For all the other transition probabilities the best available data to reflect long-term outcomes has been used for each population, as described in Table 27.

Table 26: Comparison of landmark iDFS and OS for HR+/HER2- and TNBC patients in the placebo arm of OlympiA

Time point, years	iDFS in patients randomised to placebo		OS in patients randomised to placebo	
	TNBC (N=758)	HER2-/HR+ (N=157)	TNBC (N=758)	HER2-/HR+ (N=157)
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: HER2: human epidermal growth factor receptor 2; HR: hormone receptor; iDFS: invasive disease-free survival; OS: overall survival; TNBC: triple negative breast cancer.
Source: AstraZeneca Data on File (OlympiA CSR).[13]

B.3.3.2 General approach to survival analysis and state transition modelling

The state transition probabilities were estimated following the guidance on multi-state modelling described in the NICE DSU guidance TSD19, and further outlined in the tutorial of Putter et al. (2007).[141, 154] This involved fitting a series of parametric survival models (exponential, log-normal, Weibull, log-logistic, generalised gamma, and Gompertz) to patient-level data for all transitions in the model. These survival models are used to predict outcomes during the follow-up of the OlympiA trial, and up to a lifetime horizon.

It should be noted that the cause-specific hazards for TP1 and TP2 (iDFS to distant or non-distant recurrence) were modelled assuming that the proportion of events leading to non-distant (or distant) recurrence were approximately constant over time. This was estimated by fitting parametric survival models to the primary iDFS endpoint of OlympiA, which is a composite endpoint of non-distant (TP1), distant (TP2) recurrence and death without recurrence (TP3). The cause-specific hazards for TP1 and TP2 were then estimated by apportioning the *overall* hazard rate for iDFS to the *cause-specific* hazard rates of distant and non-distant recurrence, under the assumption that the conditional probability that failure is a non-distant recurrence is constant over time. This is consistent with the approaches used in past economic models in HER2-positive disease (TA632, TA569). A complete overview of the technical derivation of the transition probabilities can be found in Appendix N.

Table 27: Description of transitions and data sources used in the economic model

ID	Transition description	Data source	ITT or subgroup data	Justification
TP1, TP2	iDFS → 'non-metastatic recurrence' or 'metastatic recurrence'	OlympiA, DCO1[13]	TNBC data for TNBC and ITT data as a proxy for HR+/HER2-	Differing number of iDFS events observed in each subgroup.
TP3	iDFS → death	UK general population mortality (ONS, 2021)[151] Adjusted for excess mortality risk in *BRCA*m patients using data from Mai et al. (2009)[152]	N/A	- Mortality data from OlympiA, evidence from the literature, and UK clinical expert feedback highlight that patients who remain in the DF state have good long-term survival outcomes similar to the age-matched general population. - This assumption is further supported by the low event numbers in the trial.
TP4, TP5	'non-metastatic recurrence' → 'mBC' & 'non-metastatic recurrence' → death	OlympiA DCO1[13]	ITT	- Risk of metastatic recurrence and death were pooled respectively across subgroups and treatment arms to maximise the sample size given the limited event numbers. - Assumption made that risk is not meaningfully impacted by HR status based on an assessment of the subgroup data from OlympiA and feedback from UK clinical experts.
TP6	'early onset mBC' → death	OlympiA DCO1[13]	ITT	
TP7	'late onset mBC' → death	Single chemotherapy: OlympiAD study (clinical trial)[126, 148] CDK4/6 inhibitor plus endocrine therapy: Collins et al. (2021) (Flatiron Health RWE study)[149] Atezolizumab plus paclitaxel: *BRCA*m biomarker subgroup of IMpassion 130 study (clinical trial)[150]	N/A	- Reflect the breadth of potential treatment options and associated outcomes after 'late onset metastatic breast cancer'. - As there are different treatment options available for triple negative vs. HR+/HER2- patients in the metastatic setting, the choice of the external Phase III studies survival curve splits to model TP7 differs by subgroup.

Abbreviations: *BRCA*: breast cancer susceptibility gene; CDK4/6 inhibitor: cyclin-dependent kinase 4/6; DCO: data cut-off; HER2: human epidermal growth factor receptor; HR: hormone receptor; iDFS: invasive disease-free survival; ITT: intention-to-treat; OS: overall survival; TNBC: triple negative breast cancer; TP: transition probability.

Following NICE DSU guidance TSD14,[155] the parametric survival analysis included:

- An assessment of the proportional hazards (PH) assumption to determine the suitability of using independent models fitted to each arm or joint models that are fitted to a data set containing both arms with a covariate for treatment group
- Generation of statistical goodness of fit measures such as Akaike and Bayesian information criteria
- Visual inspection of model fit to the trial data
- An assessment of how the conditional survival probability changes over time
- An assessment of the clinical plausibility of extrapolations

The choice of preferred model focused mainly on the models' fit to the data and the clinical plausibility and external validation of the extrapolations. Following DSU guidance, the same model was preferred in both arms.[155]

B.3.3.3 Modelling of iDFS

In contrast to simply fitting parametric survival curves to model iDFS over the time horizon of the model, this approach was not deemed sufficient on its own to accurately capture the long-term outcomes for patients with *BRCA*m, HER2-, high risk eBC for the following reasons:

- Standard parametric curves are unable to capture the significant drop and plateauing of the risk of recurrence that TNBC patients experience, as described in Section B.3.2.1;
- There was a need to split patients by distant (metastatic) and non-distant (locoregional) recurrence, as this represents the key stages of disease in HER2- eBC and;
- A robust extrapolation of the number of deaths in the iDFS health state could not be conducted given the limited number of these events in OlympiA.[13] External generalised population mortality data therefore needed to be applied to capture the long-term mortality risk in a manner that was consistent with UK clinical expert opinion.

As a result, the modelling of iDFS was conducted in four stages:

1. Fitting parametric survival models to the primary endpoint of iDFS of OlympiA;
2. Adjusting the long-term rate of recurrence to reflect the difference in baseline risk of recurrence between triple negative and HR+/HER2- disease (TP1 and TP2);
3. Apportioning the hazard rate for iDFS to the cause-specific hazards of distant (TP1) and non-distant recurrences (TP2) using a constant conditional probability of developing a non-distant recurrence;
4. Modelling of deaths without recurrence (TP3) using the *BRCA*-inflated age- and gender-matched background mortality.

An elaboration on the derivation of the clinical parameters for TP1, TP2 and TP3 is given in the following sections.

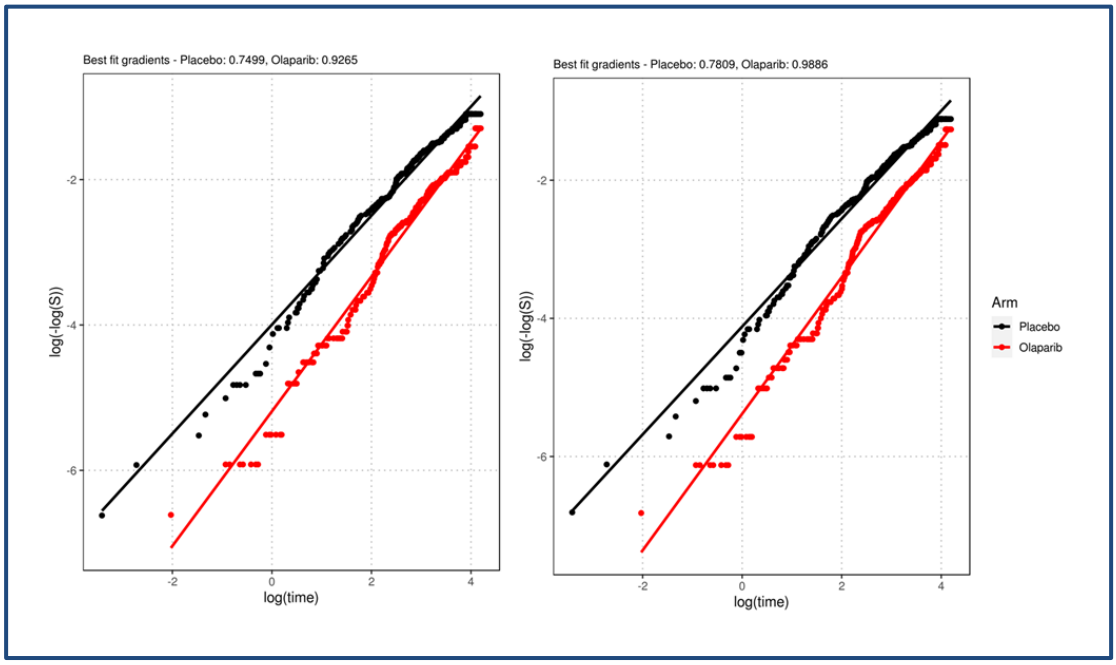
B.3.3.3.1 Derivation of the clinical parameters for TP1, TP2 & TP3

Step one: Parametric survival analysis for iDFS (TP1 and TP2)

For the primary endpoint of iDFS, an assessment of proportional hazards (PH) was conducted as part of the planned statistical analysis of the OlympiA trial. The results of this analysis are reported in the CSR.[13]

In brief, the PH assumption was assessed by visual inspection of the log-cumulative hazards plots and using the Grambsch–Therneau (G-T) test. Under PH, the log-cumulative hazards plot will show approximately parallel lines by arm, and the G-T test is not statistically significant (p>0.05). In the ITT population of OlympiA, the G-T test result was p=0.02 (i.e., statistically significant) and the log-cumulative plots (right panel, Figure 16) showed minor departures from parallel lines, indicating that the PH assumption may not hold for this endpoint. The same trends were observed for the TNBC population (left panel, Figure 16).

Figure 16: Log-cumulative hazards versus log-time plot of iDFS for the placebo and olaparib arms of OlympiA (TNBC, left panel, ITT used as a proxy for HR+/HER2-, right panel)



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.

Therefore, given that the evidence on the PH assumption is inconclusive and mature iDFS data for both treatment arms is available, it was considered more appropriate to independently fit parametric curves to the patient-level iDFS data from each arm of OlympiA (see the respective iDFS KM curves in Figure 9).

The parametric distributions were then assessed for goodness of fit to the observed data using the Akaike Information Criteria (AIC) and Bayesian Information Criteria (BIC) scores, where a lower score indicates a better fit (Table 28 and Table 29). For TNBC, the best fitting distribution based on the AIC and BIC statistics was the lognormal for both the placebo and olaparib arms.

For the HR+/HER2- group using the ITT data as a proxy, the AIC and BIC scores favoured the Gompertz for the placebo arm, and the lognormal for the olaparib arm. However, as distributions with an AIC/BIC score within 5 are considered to have similar goodness of statistical fit, all the other curves with the exception of the exponential also showed good data fits for both the TNBC and HR+/HER2- groups.

Finally, in addition to the goodness-of-fit statistics, the different parametric models were assessed for visual fit to the KM plot for iDFS (Figure 17). Considering that the risk of recurrence for the TNBC subgroup significantly decreases and plateaus after five years, it is specifically important to select a parametric model which extrapolations provide the best visual (and statistical) fit to the observed data. This is different for the HR+/HER2- group, as patients with HR+/HER2- disease have been shown to remain at a relatively constant risk of recurrence for at least 20 years after diagnosis. For this subgroup analysis, more consideration therefore needs to be given to the clinical plausibility of the long-term extrapolations and assumed change in the hazard over time, as discussed below and in Section B.3.3.3.

For the olaparib arm across both subgroup analyses, all models accurately predicted the KM probabilities for iDFS up to the end of study follow-up (~60 months). For the placebo arm, the majority of models accurately predicted the KM for iDFS, with the exception of the exponential which overestimated the survival probabilities for iDFS in the first 2 years and underestimated iDFS at later time points in both analyses, and the Gompertz model, which highly overestimated long-term iDFS after 5 years in the HR+/HER2- analysis, eventually crossing with the olaparib arm. These projections lack clinical plausibility given the consistent benefit observed with adjuvant olaparib throughout the follow-up of OlympiA.

Figure 17: Fit of the parametric survival models to the KM data for iDFS in OlympiA (TNBC, left; ITT used as a proxy for HR+/HER2, right)

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.

In summary, based on the visual fit of the models to the trial data and guided by the goodness-of-fit statistics, the lognormal model appears to be the best fitting function across both treatment arms in the TNBC and HR+/HER2- (using ITT data as a proxy) analyses, whereas the exponential and Gompertz do not seem to be appropriate options for extrapolating long-term iDFS. This can be further supported by assessing the hazard plots of either model; for example, the exponential function assumes a constant hazard over time which, based on the evidence presented in Section B.1.3.2 on long-term risk of recurrence, is not a realistic assumption to make for patients with either triple negative or HR+/HER2- early disease. Instead, considering that the OlympiA population covers eBC patients with a high risk of recurrence, their risk of death is expected to be high in the first few years after diagnosis, but then decreases and potentially even plateaus over time. This is consistent with 10-year data on BC recurrence rates from a population-based study in the Netherlands by Van Maaren et al. (2018), which showed that the hazards on recurrences in the 10 years after diagnosis for TNBC and 'luminal B' disease[b] increase in the first two years and then decrease over time, although the drop is more profound for patients with triple negative disease.[110] Out of the lognormal and Gompertz models, this initial upward and then downward trend in the hazard is most appropriately reflected in the lognormal model, whereas the Gompertz model simply assumes a monotonical decrease in hazard over time.

Collectively, the aforementioned aspects highlight that the lognormal model presents the most appropriate function for both the TNBC and HR+/HER2- analyses. However, the final choice of preferred survival model will additionally focus on the plausibility of model extrapolations, which requires integration of model assumptions surrounding the long-term risk of recurrence in TNBC and HR+/HER2-, data on the conditional probability of a non-distant recurrence and the risk of all-cause mortality (TP3). Further details on these aspects are provided in the sections below.

Step two: modelling the long-term risk of recurrence in TNBC and HER2-/HR+ (TP1 and TP2)

As outlined in Section B.3.2.1, the long-term baseline risk of recurrence in patients with TNBC and HER2-/HR+ is expected to differ significantly, with TNBC patients experiencing a steep decrease and ultimate plateauing of the recurrence rate after ~5 years post-diagnosis and HR+/HER2- patients remaining at a constant risk of recurrence for at least 20 years after diagnosis.[8]

To capture these differences, the baseline risk of recurrence for patients with TNBC was assumed to be equal to zero from year 5 of the model's time horizon. When implemented, the economic model assumes that any patient occupying the iDFS state at five years is no longer at risk of recurrence but remains at risk of death from other causes (all-cause mortality inflated for excess mortality risks from *BRCA*m). This is consistent with feedback provided by UK clinical experts and data from long-term studies in eBC. Both of these assumptions were tested in sensitivity analyses using alternative time points of 3, 7 and 10 years and setting the risk of

[b] In the study by Van Maaren et al. (2018), 'luminal A' BC is defined as grade 1/2 (tumour) HR+/HER2- disease, whereas 'luminal B' BC is defined as either HR+/HER2+ or grade 3 (tumour) HR+/HER2- disease. Considering that OlympiA covers HR+/HER2- patients with a high-risk of recurrence, the data on 'luminal B' disease provides a more suitable proxy for these patients than the data on 'luminal A' disease as grade 3 tumours tend to grow more rapidly and spread faster than tumors with a lower grade, i.e., indicating a potential higher risk of disease recurrence.

recurrence to 5% over 10 years instead of 0. This 10-year probability of recurrence in TNBC patients was reported in a study by Reddy et al. (2017), which investigated the long-term survival outcomes of TNBC survivors who are disease free at 5 years and found that 5% of these survivors will have a breast cancer recurrence within the subsequent 10 years.[156] For patients with HR+/HER2- disease, the risk of recurrence was assumed to remain throughout the lifetime horizon of the model.

Step three: Conditional probability of a non-distant recurrence (TP1 and TP2)

For both the TNBC and HR+/HER2- analyses, the conditional probability of developing a non-distant recurrence as part of an iDFS event was estimated from the summary of first iDFS event types in the OlympiA ITT population.[13, 105] These data show that of the patients who experience an iDFS event in the olaparib arm (106 patients, representing 11.5% of the total cohort), and placebo arm (178 patients, representing 19.5% of the total cohort), 21 and 37 patients experienced a non-distant recurrence respectively. Non-distant recurrence was defined by either a regional or local recurrence, or a contralateral invasive breast cancer event. The conditional probability of an iDFS event being a non-distant recurrence was therefore estimated at 19.8% (21 divided by 106) for the olaparib arm, and 20.8% (37 divided by 178) for the placebo arm. For the economic analysis, the conditional probability of non-distant recurrence was assumed the same across arms given the lack of evidence that olaparib treatment has any impact on the type of event experienced (difference between event probabilities between the olaparib vs. placebo arm of <1%).

When validating the conditional probabilities with UK clinical experts, almost all physicians considered the ~20% conditional probability of an iDFS event being an isolated non-distant recurrence for HER2- high-risk eBC patients to be reasonable, particularly given the *BRCA*m nature of the disease.[8] Although some physicians mentioned it is likely slightly lower for HER2- eBC patients in real-life practice, it was hypothesized that in *BRCA*m patients you may find a greater proportion of locoregional recurrences as patients frequently opt for a follow-up contralateral mastectomy after initial resection, which could result in earlier detection of contralateral locoregional recurrence before it develops a metastatic component and thus a higher percentage of locoregional recurrence. For this reason, in the base case economic analysis, the conditional probability for a non-distant recurrence is set at 20.4% for the TNBC and HR+/HER2- groups respectively. The corresponding conditional probability of a distant recurrence is therefore 79.6%.

Step four: Modelling of transitions from iDFS to death (TP3)

The cause-specific hazard rate for the transition of iDFS to death was modelled using all-cause mortality data from the ONS life tables (2018-20), which was matched on the baseline age (43 years) and the gender (100% female in a simplifying assumption) profile of the OlympiA population.[13, 151] The annual rates were converted to monthly rates and assumed to be constant over each year.

The age- and gender-matched life table mortality rates were further adjusted to reflect the excess mortality associated with a g*BRCA*m versus the general population. This adjustment was performed using the standardised mortality ratio (SMR=1.46, 95% CI: 0.50–2.82) from a study on the effect of *BRCA*m on mortality risk by Mai et al. (2009), which captures excess mortality for

persons with a g*BRCA*m and aged <50 years old.[152] The SMR was used to capture the lifetime excess mortality risks from other illnesses that may lead to shortened life expectancy in persons with g*BRCA*m and was assumed constant over time. This SMR and adjustment is in line with approaches accepted in previous NICE evaluations for olaparib (TA598).[157] The impact of varying the SMR on results is assessed in sensitivity analysis.

B.3.3.3.2 Overall model fit and plausibility of the extrapolation of iDFS

Table 28 and Table 29 summarise the landmark survival probabilities for iDFS for both arms in TNBC and HR+/HER2- patients, as predicted by the economic model. These estimates were obtained using the parametric survival models for iDFS (step 1) with adjustment for the long-term rate of recurrence (step 2), imputing the conditional probability of non-distant recurrence (step 3) and the modelling of death without recurrence (step four).

In order to select the most appropriate parametric survival model for the base case economic analysis, the predicted survival probabilities for iDFS in TNBC and HR+/HER2- patients are compared with the respective observed iDFS in OlympiA, relevant empirical data and RWE, and validated by UK clinical experts. A description of this validation process is outlined below:

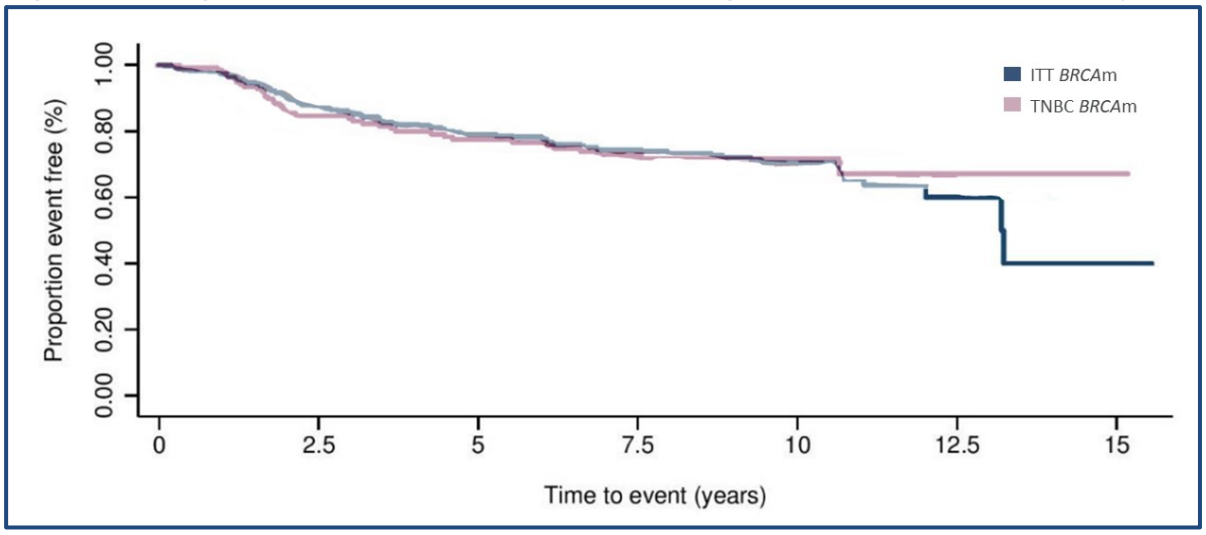
- A targeted literature search was performed in January 2022 to identify any published clinical outcome data in patients with *BRCA*m, HER2-, high risk eBC. Nine studies were found which reported on long-term disease-free survival, dDFS, recurrence-free survival (RFS) or OS in eBC (Appendix N).[49, 50, 110, 158-162]
- However, very few studies were identified that assessed the clinical outcome of patients treated for early high-risk (*BRCA*m) TNBC (with the exception of one retrospective study conducted in China[c]).[158] Furthermore, although some studies presented clinical outcome data in patients with luminal A (defined in the respective studies as HR+/HER2-) and/or luminal B (defined in the respective studies as HR+/HER2+ or HER2-) disease, none reported specific long-term survival in early (*BRCA*m) HR+/HER2- patients with a high-risk of recurrence.[110, 160, 163]
- When considering the reported DFS of these studies, it is clear that many overpredict short- and long-term iDFS for patients with high-risk HR+ disease. For example, the Dutch population-based study by Seferina et al. (2017) reported 1-, 2- and 3-year recurrence-free survival rates for patients with luminal B disease of 98.5%, 95.0% and 91.5% respectively, whereas the 3-year rate for HR+/HER2- patients on SoC in OlympiA is only [redacted]. This finding was also validated by UK clinical experts, who highlighted that the patient populations in these studies are not generalisable to the specific population studied in OlympiA who have *BRCA*m, HER2-, high-risk eBC and are expected to have significantly worse long-term outcomes than in a population unselected for high-risk characteristics.[9]
- Given these limitations in the empirical literature and the lack of published data specific to the *BRCA*m, HER2-, high-risk population relevant to the OlympiA indication, most of the studies identified through the targeted search are not considered to provide a realistic and appropriate reference to validate the predicted survival probabilities for iDFS in TNBC and HR+/HER2- patients. UK clinical experts also highlighted the lack of alternate high-quality data sources for

[c] Although the study by Chen et al. (2013) included high-risk TNBC patients, it was conducted in China and primarily assessed the effect of post-mastectomy radiotherapy on locoregional recurrence-free survival and iDFS. The study was therefore found not to be fully reflective of expected clinical outcomes of OlympiA patients in the UK.

this specific patient population and commented that the 3-year OlympiA KM data on iDFS is the best data currently available in a high-risk, HER2-, g*BRCA*m eBC population.[9]

- Instead, the most relevant study to validate the choice of the preferred parametric model for the iDFS extrapolations is the UK POSH study, which investigates the effect of a g*BRCA*m on breast cancer outcomes in patients with young-onset breast cancer.[50] The study recruited 2,733 female patients from 127 hospitals in the UK from 2000–2008 aged <40 years at first diagnosis of invasive breast cancer. The primary outcome was OS at 2, 5 and 10 years after diagnosis, and dDFS data were also reported. A TNBC subgroup analysis was also conducted for both the OS and dDFS outcomes.
- Although the POSH study does not specifically incorporate patients with high-risk disease, it includes patients who (1) have a g*BRCA*m, (2) are diagnosed aged <40 years (average age in OlympiA was 43 years), (3) have early-stage disease (almost all patients included in the POSH study [~99%] had stage 0–III disease) and (4) are treated under UK clinical guidelines for eBC.[12, 50] It therefore represents the most relevant and UK-specific data source for this economic analysis on olaparib in the 'OlympiA' indication to date.
- An overview of the reported long-term dDFS data from the POSH study, which in the absence of direct iDFS data provides a good proxy for validating the landmark iDFS estimates from the OlympiA economic model, is given in Figure 18 below and Table 28. Please note that specific data on patients with HR+/HER2- disease are not available. Instead, even though POSH includes a mix of patients with HR+/HER- and HR-/HER2+ disease, the ITT data provides an indicative trend in what can be expected in patients with *BRCA*m 'non-TNBC' disease. For example, it is clear in Figure 18 that the ITT and TNBC curves cross over time, which is aligned with the different long-term risk of recurrence between triple-negative and HR+/HER2- disease and the ultimate worse long-term prognosis for HR+/HER2- patients as described in Section B.1.3.2.

Figure 18: Long-term distant disease-free survival for gBRCAm from the POSH study



Abbreviations: dDFS: distant disease-free survival; ITT: intention-to-treat; *BRCA*: breast cancer susceptibility gene; TNBC: triple-negative breast cancer.
Source: Copson et al. (2018).[50]

TNBC

- When comparing the long-term iDFS rates from the POSH study with the estimates from the placebo arm from the five best-fitting parametric models (Table 28), it is clear that the Gompertz model predicts a relatively similar 10-year TNBC iDFS rate ([redacted]) to the POSH study (70.6%), whereas all other models give a slightly lower 10 year iDFS estimate ([redacted]). Considering that the POSH study does not specifically include patients with high-risk disease, the respective long-term iDFS rates are likely an overestimate of what should be expected in OlympiA. As such, a similar conclusion to the statistical and visual fits can be made that the Gompertz overpredicts long-term iDFS after 5 years, whereas the lognormal and generalised gamma models present more realistic estimates for patients with *BRCA*m, high-risk, eBC.
- UK medical oncologists who reviewed the extrapolated data also noted that a [redacted] iDFS rate or below at 10 years is likely reflective of current clinical practice and that the 5-, 10- and 20-year iDFS estimates across the lognormal and generalised gamma models seemed reasonable. They also commented that the long-term estimations with the exponential model (second best fitting for the olaparib arm) seemed too low for patients currently on SoC and ruled this out as an appropriate option.[8]
- Therefore, the lognormal model, which has the best statistical fit according to the AIC/BIC values, shows good consistency with the observed KM data, and produces the most plausible long-term iDFS rates on standard of care was chosen in the base-case analysis for the TNBC population. The loglogistic, Weibull and generalised gamma models were considered in scenario analyses to test the impact of alternative survival model choices.

HR+/HER2-

- For the HR+/HER2- analysis using the ITT iDFS data as a proxy, when comparing the long-term estimates from the best fitting models for the placebo arm with the data from the UK POSH study, the Gompertz model (first best fitting for the placebo arm) produces the most comparable estimates. However, as mentioned previously, the POSH study was not conducted in patients with high-risk disease, and thus the long-term dDFS rates do not accurately reflect the expected iDFS of patients with *BRCA*m, HR+/HER2-, high-risk disease.
- Instead, one study that was identified in the targeted literature search that provides another useful reference for validation is the 2005 report by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG), which assessed the 10- and 15-year effects of various systemic adjuvant therapies on breast cancer recurrence and survival based on 194 RCTs in breast cancer.[161] Their results show that for patients with HR+ disease and who have gone through ovarian ablation or suppression, the 10- and 15-year recurrence-free survival is 59.5% and 52.7% respectively.
- These data provide a good reference for validating the landmark iDFS estimates for the HR+/HER2- population, as the study potentially selects for a high-risk cohort due to the prior use of ovarian ablation or suppression. UK clinical experts highlighted that use of such treatments in the UK is generally targeted at pre-menopausal HR+ patients with high-risk disease as a way to induce early menopause and thereby improve outcomes. Use is generally limited to this high-risk group due to the side effects of these treatments and the resulting risk-benefit considerations.[9] This targeted approach is also reflected in NICE clinical guideline

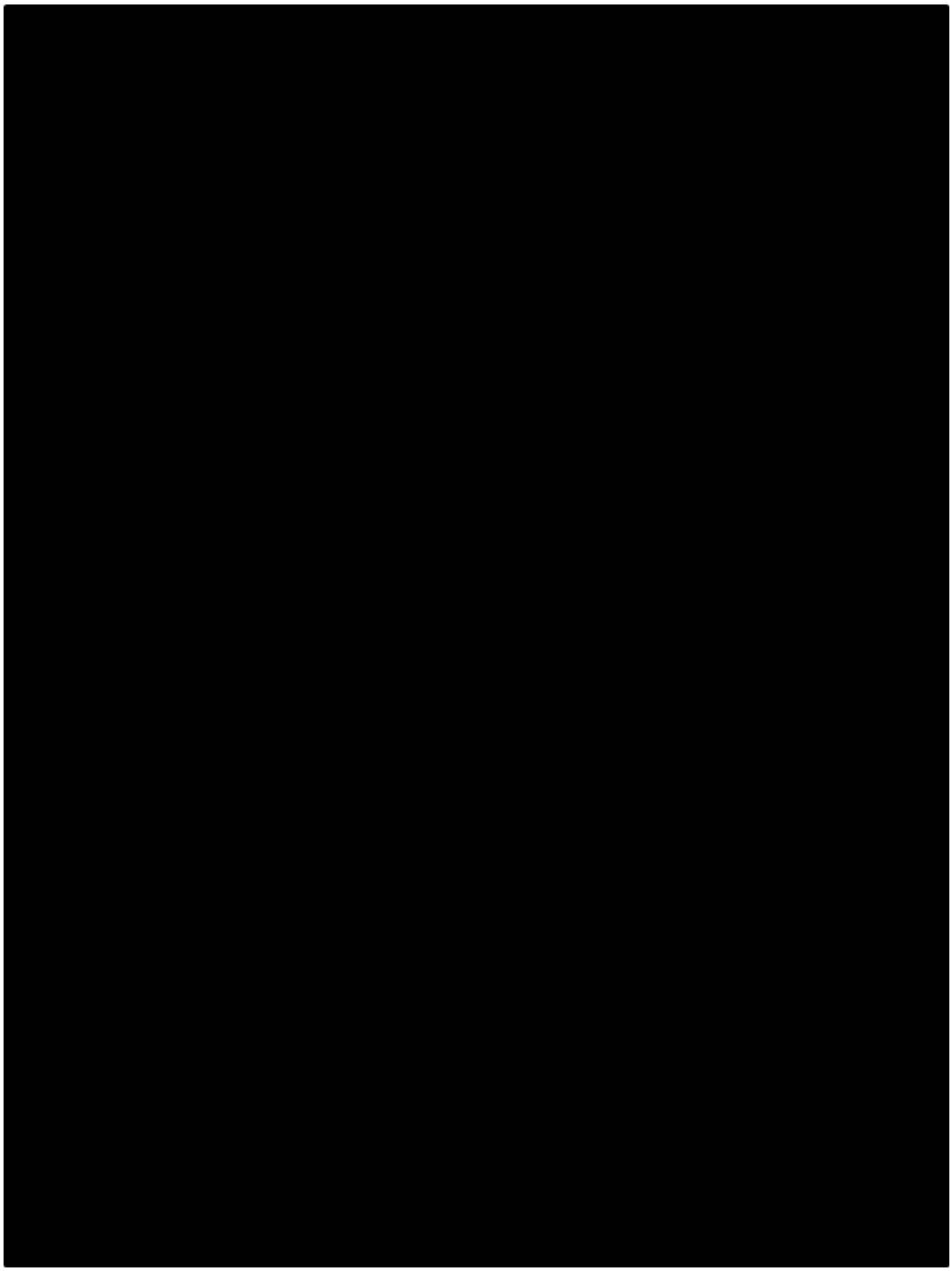
NG101.[23] Based on these insights, the lognormal and generalised gamma models provide more realistic long-term estimates than the Gompertz model.

- UK medical oncologists who reviewed the extrapolated data also confirmed that long-term iDFS estimates from the lognormal model for the SoC arm seemed most reflective of current clinical practice. Furthermore, it was mentioned that as the risk of recurrence of patients with HR+/HER2- and triple negative high-risk disease will eventually cross, HR+/HER2- patients will ultimately experience worse long-term prognosis.[8] This is reflected in the 20-year iDFS estimates from the lognormal ([redacted]) and generalised gamma ([redacted]) models, which are lower than those estimated by the lognormal model ([redacted]) model in the TNBC population analysis.
- Finally, physicians univocally commented that the exponential model produces highly unrealistic estimates ([redacted] of patients respectively disease-free at 20 years).[8] Although patients with high-risk disease generally perform worse than those with no higher risk of recurrence, as well as the fact that patients with HR+/HER2- experience a lifelong risk of recurrence, all empirical literature on HR+ disease shows that long-term disease- or RFS is >40%.[49, 110, 161] It is thus unreasonable to assume that only ~15–30% of HR+/HER2- patients would remain disease-free at twenty years post-diagnosis.
- Therefore, the lognormal model, which has the best statistical fit for the olaparib arm and the second-best fit for the placebo arm, shows good consistency with the observed KM data, and produces the most plausible long-term iDFS rates on standard of care was chosen in the base-case analysis for the HR+/HER2- population. The generalised gamma model was considered in scenario analysis to test the impact of alternative survival model choices.

Final iDFS extrapolations as per the base case economic analysis

The final iDFS extrapolations as per the model's base case for the TNBC population (lognormal parametric model, assuming a zero risk of recurrence from year 5 of the model's time horizon) and the HR+/HER2- population (lognormal parametric model, assuming a lifetime risk of recurrence) are presented in Figure 19 below.

Figure 19: Base case iDFS extrapolation for the TNBC population (top) and the HR+/HER2- population (bottom)



Footnotes: 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: iDFS: invasive disease-free survival; HER2: human epidermal growth factor receptor; HR: hormone receptor; TNBC: triple negative breast cancer.

Table 28: AIC and BIC values for the parametric survival models fitted to the OlympiA iDFS data, their respective long-term predicted survival and a comparison with empirical data (independent, TNBC)

	Placebo						Empirical data	Olaparib					
	Weibull	Gompertz	Log-logistic	Log-normal	Gen. gamma	Exp.	POSH study[50]	Weibull	Gompertz	Log-logistic	Log-normal	Gen. gamma	Exp.
Statistical fit													
AIC	1779.69	1774.92	1777.39	**1774.75**	1776.68	1799.00	–	1125.76	1124.27	1125.10	**1124.21**	1126.00	1124.91
Rank	5	2	4	**1**	3	6		5	2	4	**1**	6	3
BIC	1788.95	1784.18	1786.66	**1784.01**	1790.57	1803.63		1135.00	1133.51	1134.34	**1133.45**	1139.68	1129.53
Rank	4	2	3	**1**	5	6		5	3	4	**2**	6	1
Predicted survival per timepoint*													
% at 2 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	85.0%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% at 5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	76.5%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% at 10 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	70.6%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% at 20 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	–	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: iDFS extrapolations incorporate no long-term risk of recurrence after 5 years and all other adjustments as described in Section B.3.3.3.
Abbreviations: iDFS: invasive disease-free survival; KM: Kaplan-Meier; LY: life year; TNBC: triple-negative breast cancer.

Table 29: AIC and BIC values for the parametric survival models fitted to the OlympiA iDFS data, their respective long-term predicted survival and a comparison with empirical data (independent, ITT as a proxy for HR+/HER2-)

	Placebo						Empirical data	Olaparib					
	Weibull	Gompertz	Log-logistic	Log-normal	Gen. gamma	Exp.	EBCTCG (2005)[a,161]	Weibull	Gompertz	Log-logistic	Log-normal	Gen. gamma	Exp.
Statistical fit													
AIC	2078.53	2071.70	2075.77	2072.21	2074.17	2096.22	-	1367.40	1366.27	1366.63	**1365.66**	1367.33	1365.67
Rank	5	1	4	**2**	3	6		6	3	4	**1**	5	2
BIC	2088.16	2081.34	2085.40	2081.85	2088.63	2101.04		1377.05	1375.92	1376.28	**1375.31**	1381.81	1370.50
Rank	4	1	3	**2**	5	6		5	3	4	**2**	6	1
Predicted survival per timepoint*													
% at 2 yrs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	88.5%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% at 5 yrs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	73.3%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% at 10 yrs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	59.5%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% at 20 yrs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	52.7% (15 yrs)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: iDFS extrapolations assume a lifetime risk of recurrence and all other adjustments as described in Section B.3.3.3; [a]Ovarian ablation/suppression subgroup.
Abbreviations: HR: hormone receptor; HER2: human epidermal growth factor 2; iDFS: invasive disease-free survival; KM: Kaplan-Meier; LY: life year.

B.3.3.4 Modelling of non-metastatic recurrence

The transition probabilities for non-metastatic to mBC (TP4) and non-mBC to death (without metastatic diagnosis) (TP5) were modelled using data from the OlympiA trial.[13]

For TP4, the cause-specific hazard was estimated by fitting parametric survival models to data on the time from non-metastatic recurrence (i.e., locoregional or contralateral breast cancer) to distant metastatic recurrence (i.e., distant recurrence, new primary non-breast cancer) with deaths without recurrence treated as a censoring event. Similarly, for TP5, the cause-specific hazard was estimated using parametric survival models fitted to data on the time from non-metastatic recurrence to death, with distant metastatic recurrence treated as a censoring event. Only patients that had a non-distant recurrence event during the follow-up of OlympiA were included in the analysis.

TP4 and TP5 were estimated from a pooled dataset containing data from both the olaparib and placebo arms, and the resulting transition probabilities were applied to both arms of the model. This approach was taken because there were too few events to estimate TP4 and TP5 for each arm separately, and because there was no evidence of a clear difference in risk of non-metastatic recurrence between the two arms.

Parametric survival analysis for non-metastatic breast cancer (TP4 and TP5)

A series of parametric survival models were fitted to the cause-specific time to event data for TP4 and TP5. The AIC and BIC statistics for each of the parametric models are shown in Table 30 below. For TP4, the AIC and BIC scores favoured the lognormal (1st for AIC) and exponential (1st for BIC). For TP5, the lognormal was the best fitting model according to both AIC and BIC. However, as distributions with AIC/BIC scores within 5 are considered to have similar goodness of statistical fit, all curves demonstrated reasonably good statistical fits to the data.

Table 30: AIC and BIC values for the parametric survival models fitted to data on the time from non-distant metastatic recurrence to distant metastatic and the time from non-distant metastatic recurrence to death

Model	[redacted]	
	AIC	BIC
Time from non-metastatic recurrence to distant metastatic recurrence [TP4]		
Exponential	111.33 (2)	**113.26 (1)**
Weibull	112.79 (5)	116.66 (4)
Loglogistic	112.16 (3)	116.02 (3)
Lognormal	**111.14 (1)**	115.00 (2)
Gompertz	113.31 (6)	117.18 (5)
Generalized gamma	112.24 (4)	118.04 (6)
Time from non-metastatic recurrence to death [TP5]		
Exponential	39.76 (2)	45.56 (6)
Weibull	41.49 (5)	45.36 (4)
Loglogistic	41.00 (3)	44.86 (2)

Lognormal	**39.61 (1)**	**41.54 (1)**
Gompertz	41.58 (6)	45.45 (5)
Generalized gamma	41.06 (4)	44.92 (3)

Footnotes: (X): rank on lowest AIC/BIC by arm.

The fit of the models to the Kaplan-Meier probabilities for non-metastatic to metastatic recurrence (TP4) and for non-metastatic to death (TP5) are shown in Figure 20. These graphs provide an indication of model fit but should be viewed with caution given that the KM plots of competing risks, such as TP4 and TP5, are biased by informative censoring.

For TP4, the majority of survival models accurately predict the KM probabilities for non-metastatic to metastatic recurrence, with the exception of the generalised gamma which appeared to underestimate the recurrence rate towards the end of the follow-up. All other models produce similar predictions of survival from disease recurrence, which are broadly consistent with literature estimates of 5-year DFS after locoregional recurrence of 27.8% to 38%[d].[164, 165] The KM plots that accompany these literature estimates suggest that the rate of recurrence decreases over time, consistent with the patterns typically associated with lognormal and loglogistic models. Guided by the goodness of fit statistics, the lognormal model was thus selected as the preferred model for TP4. The impact of using the loglogistic model for TP4 on base case results was considered in sensitivity analysis; it should however be noted that the choice of the parametric model for extrapolating TP4 only has a minor impact on results.

For TP5, all models yielded a reasonable fit to the KM probabilities for non-metastatic recurrence to death. At the end of the follow-up, models such as the Gompertz or generalised gamma tended to predict a plateauing of the risk of death without subsequent metastatic recurrence, whilst all other models predicted a continuous and ongoing risk of death. The trend towards a reduction in the risk of death prior to recurrence is highly uncertain given the very low number of events in the analysis ([redacted]). Further, the estimation of multi-parameter models, such as the lognormal or Weibull, on limited data potentially increases the chance of inappropriate extrapolations. Therefore, for TP5, the exponential model was selected for the base case analysis. The impact of using other models (lognormal, loglogistic) for TP5 on the base case results was considered in sensitivity analysis.

[d] Both references are in triple-negative disease, as no clinical outcome data after locoregional recurrence was found for HR+/HER2- patients only.

Figure 20: Fit of the parametric survival models to the ITT OlympiA KM data for non-metastatic to metastatic recurrence (left) and for non-metastatic to death (right) in OlympiA, pooled arms

Abbreviations: ITT: intention-to-treat; KM: Kaplan Meier

B.3.3.5 Modelling of metastatic recurrence

B.3.3.5.1 Early onset mBC

The transition probabilities for 'early onset' mBC to death (TP6) were modelled using data on the post-distant metastatic recurrence survival in the OlympiA trial.[13] These data represent the survival outcomes of patients who had distant recurrence during the approximate 2.5-year median follow-up of OlympiA (DCO: 27 March 2020).

At the primary iDFS analysis of OlympiA, [redacted] in the placebo arm had a distant metastatic recurrence. This included patients whose first iDFS event was a distant recurrence ([redacted]), and patients that experienced a distant recurrence after first experiencing a locoregional or contralateral invasive breast cancer ([redacted]). In total, there were [redacted] after metastatic recurrence in the olaparib arm, and [redacted] after metastatic recurrence in the placebo arm. The median time to death was [redacted] in the olaparib arm vs. [redacted] in the placebo arm. The KM plot for post-distant metastatic recurrence survival by arm is shown in Figure 21.

Figure 21: KM plot of post-distant metastatic recurrence survival by arm in OlympiA

Source: AstraZeneca Data on File (OlympiA CSR).[13]

It is acknowledged that the median survival after distant recurrence in the olaparib arm ( ) was than for placebo ( ). This difference in post-recurrence survival can be attributed to several factors, including differences in the treatments administered after recurrence and imbalances in the characteristics and prognosis of patients with distant recurrence after olaparib and placebo:

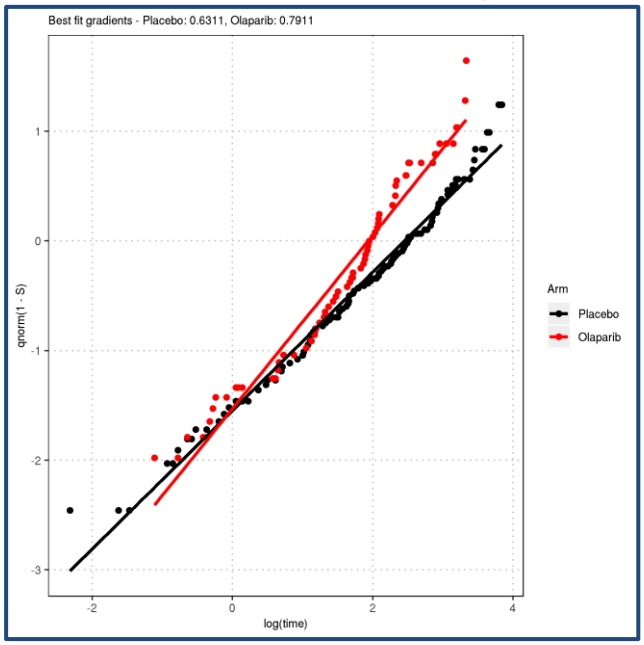
- The after metastatic recurrence in the placebo versus the olaparib arm ( ) is expected to have improved the survival of placebo versus olaparib patients, likely positively biasing the results in favour of placebo. Several Phase III randomised trials have demonstrated a median OS improvement with PARPi versus chemotherapy in *BRCA*m breast cancer.[126, 153]
- Clinical experts also highlighted that those patients who experience an "early" distant recurrence in spite of active treatment with olaparib may constitute a group with particularly treatment-insensitive disease.[8] As such, these patients may also be less responsive to subsequent treatments that they receive in the metastatic setting. In contrast, those patients experiencing early distant recurrence in the placebo arm are likely to represent a more mixed cohort in terms of treatment-sensitivity and would thus be expected to have more favourable post-distant-recurrence survival.

In line with the OlympiA data on the post-distant metastatic recurrence survival, the base case economic analysis applies transition probabilities independently by arm. However, the impact of assuming the same survival after 'early onset mBC' across arms is tested in the sensitivity analysis. When implemented, the transition probabilities for the olaparib arm are then modelled using the survival rates estimated from the placebo arm of OlympiA.

Parametric survival analysis for mBC (TP6)

A series of parametric survival models were fitted to the time to event data for TP6. Due to evidence of non-proportional hazards from the overlapping of Kaplan-Meier probabilities across study arms at the beginning of the survival curve for TP6 (Figure 21), the survival models were fitted independently to each arm of the study. This is supported by the log cumulative hazards plot for TP6, which showed lack of proportionality in the survival curves (Figure 22).

Figure 22: Log-cumulative hazards versus log-time plot of post-metastatic recurrence for the placebo and olaparib arms of OlympiA



The AIC and BIC statistics for the fitted models are shown in Table 31. For the olaparib arm, the loglogistic and exponential models were the best fitting according to AIC and BIC, respectively. For the placebo arm, the exponential was best fitting on both AIC and BIC. The fit of the models to the KM probabilities for TP6 are shown in Figure 23.

Table 31: AIC and BIC values for the parametric survival models fitted to data on the time from metastatic recurrence to death

Model	Olaparib (N=87)		Placebo (N=149)	
	AIC	BIC	AIC	BIC
Exponential	371.61 (2)	373.98 (1)	641.27 (1)	644.24 (1)
Weibull	373.49 (6)	378.23 (5)	642.10 (4)	648.04 (4)
Loglogistic	370.96 (1)	375.70 (2)	641.87 (3)	647.81 (3)
Lognormal	372.33 (4)	377.07 (4)	642.30 (5)	648.24 (5)
Gompertz	372.22 (3)	376.95 (3)	641.65 (2)	647.58 (2)
Generalized gamma	372.49 (5)	379.60 (6)	642.48 (6)	651.39 (6)

Footnotes: (X): rank on lowest AIC/BIC by arm.

Figure 23: Fit of parametric survival models to the KM data for metastatic to death by arm in OlympiA

Abbreviations: KM: Kaplan Meier, mBC: metastatic breast cancer

For the placebo arm, all of the models yielded similar and reasonable predictions of survival up to around 2-years. After this time point, there was greater variability in the fit of the models to the KM data. The loglogistic model tended to predict higher estimates of survivorship towards the end of the study, whilst the exponential gave lower estimates. Under extrapolation, the probabilities of survival at 5- and 10-years after 'early onset mBC' was estimated at [redacted] for loglogistic and [redacted] for exponential, respectively. The survival estimate for the exponential model was judged to provide the most plausible prediction when compared to literature estimates of the post-distant recurrence survival of patients with 'early onset mBC' (<24 months since diagnosis; 5.4% at 5-years and ~0% at 10 years).[143] This was also confirmed with UK clinical oncologists, who commented that generally, survival for high-risk BC patients who relapse quickly after completing adjuvant treatment is very poor.[8]

For the olaparib arm, all of the models yielded similar and reasonable predictions of survival up to around 2 years and showed relatively similar statistical fits. The extrapolated probabilities of survival at 5- and 10-years after 'early onset mBC' were approximately [redacted] for loglogistic and [redacted] for exponential, respectively. For consistency with the placebo arm, the exponential model was used in the base case for the modelling of TP6 for olaparib. Alternative modelling options were explored in scenario analyses.

B.3.3.5.2 Late onset mBC

As described in Section B.3.3, the transition probabilities for 'late onset' mBC to death (TP7) are modelled using data external to the OlympiA trial. To reflect the breadth of potential treatment options and associated outcomes after 'late onset mBC', the transition probabilities for TP7 were modelled as a 'weighted-average' of survival probabilities (S(t)) for first-line treatments of *BRCA*m

mBC. Following UK clinical guidelines and input from UK medical oncologists, the first-line treatment options available to patients with *BRCA*m mBC are:[8, 9, 13, 105, 149, 150]

- Single chemotherapy regimens
- CDK4/6 inhibitor plus endocrine therapy (HR+/HER2- patients only)
- Atezolizumab plus paclitaxel (TNBC and PD-L1 positive patients only)

The transition probabilities for each treatment regimen were modelled using data from three studies that reported on the OS of patients with *BRCA* mutations in a first line mBC setting, of which a summary is given in Table 32:

1. Single chemotherapy: OlympiAD study (clinical trial)[126, 148]
2. CDK4/6 inhibitor plus endocrine therapy: Collins et al. (2021) (Flatiron Health RWE study)[149]
3. Atezolizumab plus paclitaxel: *BRCA*m biomarker subgroup of IMpassion 130 study (clinical trial)[150]

The OlympiAD and Collins et al. (2021) studies were identified from a previous systematic literature review of randomised clinical trials in germline *BRCA*m mBC, and from previous AstraZeneca real world studies.[166] Both studies were selected based on their relevance and generalisability to the OlympiA population (*BRCA*m, HER2- mBC and treated at a first-line) and the availability of subject-level survival data for analysis. The IMpassion 130 study was identified from clinical guidelines.[167] An overview of the key information and clinical characteristics of all three studies is provided in Table 32 below. It should be noted that baseline data are only available for the full study population (N=85, n=36 are 1st line patients) of the Flatiron study. Baseline data were not available for the *BRCA*m-positive subgroup of IMpassion 130.

Due to paucity of data, adjustment or matching to the OlympiA population was not performed. Considering that only baseline characteristics from OlympiA are available for patients who entered the study but therefore had not progressed to metastatic disease, it was not considered appropriate to match the patient characteristics of the three trials mentioned above in metastatic disease with a trial investigating patients in an iDFS state. In both the OlympiAD and Collins et al. (2021) studies, there was also insufficient baseline data on the surgical outcomes of patients at primary diagnosis to match to the high-risk status of OlympiA. Furthermore, the first-line subgroup data of OlympiAD was pooled across TNBC and HR+ groups, and was thus assumed to apply to both populations. This ensured an adequate sample size and event numbers to provide robust estimates of survival for TP7. Although it is acknowledged that this is a simplified approach and might lead to a small yet likely insignificant impact on the outcomes, these studies were considered the 'best evidence' available to inform the survival estimates for 'late onset' *BRCA*m mBC for this economic analysis. Furthermore, it should be noted that that the economic model is relatively insensitive to changes in long-term survival estimates as is demonstrated in scenario analyses when testing a range of extrapolations.

Table 32: Summary of study information and clinical characteristics for OlympiAD, Flatiron health database study & IMpassion 130

Study	OlympiAD[13, 105]		Collins et al. (2021)[149]	IMpassion 130[150]
Study type	Randomised, open-label, phase 3 trial of olaparib vs. TPC (capecitabine, vinorelbine, Eribulin)		Retrospective study of the patterns and effectiveness of CDK4/6 inhibitor treatment using data from the Flatiron Health database (2013-2018)	Phase 3 randomised, double-blind, study of first-line treatment with atezolizumab plus nab-paclitaxel vs. nab-paclitaxel
Patient population	Patients with g*BRCA*m HER2-negative mBC who had received ≤2 lines of chemotherapy for mBC		Patients with HR+/HER2-, g*BRCA*m mBC	902 patients with metastatic TNBC
Patient group used to transition probabilities	Individual subject-level data of patients who had not previously received chemotherapy for mBC and were therefore undergoing 1st line treatment for mBC		Individual subject-level data from patients who received a CDK4/6 inhibitor in 1st line (36 out of 85 patients)	Patients who were both *BRCA*m (89 of 612 patients tested) and PD-L1 positive (45 out of 89 *BRCA*m patients) and thus eligible for atezolizumab treatment based on its EMA
Treatment group (n)	Olaparib (n=59)	TPC (n=28)	CDK4/6 inhibitor (n=36)	Atezolizumab (n=45)
Number of events, n (%)	30 (51%)	21 (75%)	13 (36%)[a]	N/A[b]
Hormone receptor positive (%)	39.0%	42.9%	100%[a]	0%[b]
Triple-negative (%)	61.0%	57.1%	0%[a]	100%[b]
Time from diagnosis (mean)	4.8 years (ITT population)	4.7 years (ITT population)	4.5 years (1,641 days / 365.25 days per year)[a]	18-month follow-up[b]
ECOG performance status 0 (normal activity), %	79.7%	60.7%	60.4% (29/48 pts with known ECOG status)[a]	58.3%[b]

Footnotes: [a]Based on the full dataset (N=85); 1st line specific clinical characteristics data not available. [b]Based on ITT data; baseline data were not available for the BRCAm-positive subgroup of IMpassion 130. **Abbreviations:** CDK4/6 inhibitor: cyclin-dependent kinase 4/6 (CDK4/6) inhibitor; ECOG: Eastern Cooperative Oncology Group; EMA: European Marketing Authorisation; N/A: not available; ITT: intention-to-treat; TPC: treatment of physician's choice.

Estimating the weighted-average survival probabilities

The cumulative survival probabilities for chemotherapy and CDK4/6 inhibitor treatment of 'late onset' mBC were modelled using parametric survival models fitted to individual subject data from the OlympiAD and Collins et al. (2021) studies. [126, 148, 149] As individual subject-level data were not available for IMpassion 130, the efficacy of atezolizumab was modelled by combining the survival estimates for chemotherapy treatment from OlympiAD with the OS hazard ratio (0.55) of atezolizumab plus nab-paclitaxel versus nab-paclitaxel alone from IMpassion 130.[126, 148, 150]

The individual treatment survival probabilities were then combined as a weighted-average of survival probabilities based on an assumed case mix of treatment for 'late onset mBC' using the following equation:

$$S(t) = \sum \pi_i \times \hat{S}(t)_i$$

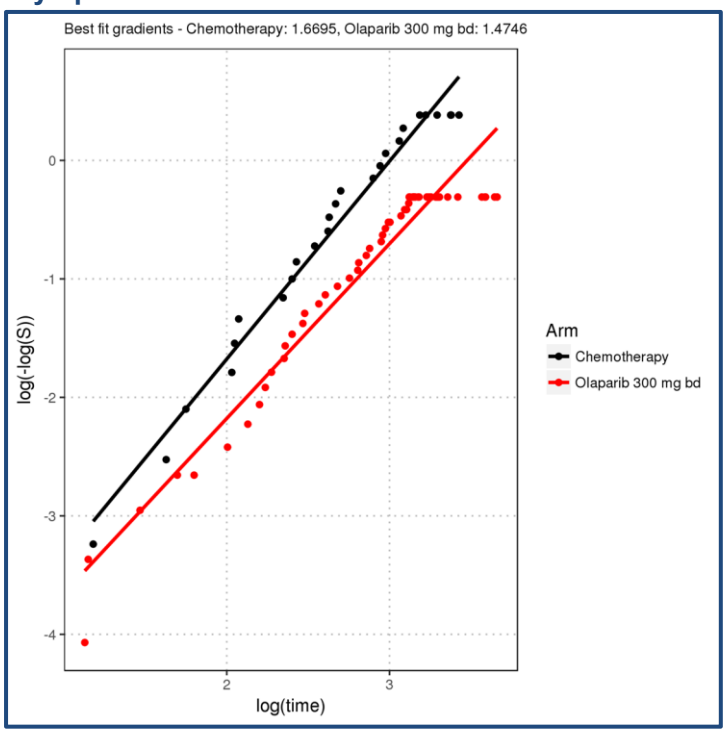
Where π_i is the case weight used for treatment i, and $\hat{S}(t)_i$ is the associated survival probability.

The following sections provide further details on the fitting of parametric survival models to the subject-level data from OlympiAD and Collins et al. (2021),[126, 148, 149] the derivation of case weights for estimating the weighted-average survival probabilities, and a summary of the weighted-average survival probabilities for TP7 in the base case analysis.

Parametric survival analysis for 'early onset' mBC (TP7)

A series of parametric survival models were fitted to the time to event data from OlympiAD and Collins et al. (2021).[126, 148, 149] For OlympiAD, the event time was defined as the time from randomisation to death from any cause. Following DSU guidance, the PH assumption for the first-line subgroup of OlympiAD was assessed by visual inspection of the log-cumulative hazards plot (Figure 24).[155] The lack of proportionality in the curves for olaparib and TPC supported the fitting of independent curves to each arm of the study population.

Figure 24: Log-cumulative hazards versus log-time plot for first-line subgroup of OlympiAD



Abbreviations: bd: twice daily.

For the Flatiron health RWE data, the event time was defined as time from the start date of first line CDK4/6 inhibitor treatment to death from any cause. The PH assumption was not considered for the Flatiron study given that only one study population was analysed, i.e., first-line g*BRCA*m patients treated with CDK4/6 inhibitors.[149]

The AIC and BIC statistics for the models fitted independently to each treatment group of OlympiAD and Collins et al. (2021) are shown in Table 33. For the TPC arm of OlympiAD, the lognormal was the best fitting model according to both AIC and BIC, with the loglogistic model having the second-best fit on both scores. For the CDK4/6 inhibitor group of Collins et al. (2021), the loglogistic was the best fitting according to AIC and BIC, and the lognormal model was second best.

Table 33: AIC and BIC values for the parametric survival models fitted to data on the time from metastatic recurrence to death in OlympiAD and Collins et al. (2021)

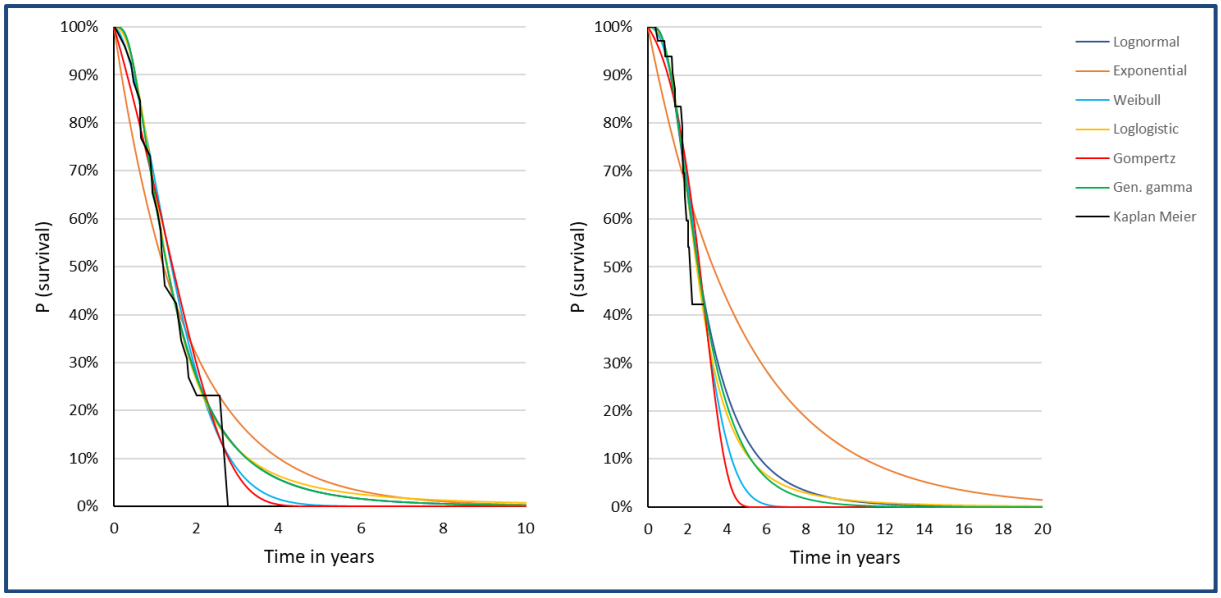
Model	OlympiAD: olaparib (N=59), placebo (N=28)[126, 148] Flatiron health RWE data: CDK4/6 inhibitor treatment (N=36)[149]	
	AIC	BIC
Time from metastatic recurrence to death – TPC arm of 1st line OlympiAD group [TP7]		
Exponential	171.69 (6)	173.02 (6)
Weibull	166.64 (3)	169.30 (3)
Loglogistic	165.32 (2)	167.98 (2)

Model	OlympiAD: olaparib (N=59), placebo (N=28)[126, 148] Flatiron health RWE data: CDK4/6 inhibitor treatment (N=36)[149]	
	AIC	BIC
Lognormal	**164.95 (1)**	**167.61 (1)**
Gompertz	169.53 (5)	172.20 (5)
Generalized gamma	166.95 (4)	170.94 (4)
Time from metastatic recurrence to death – 1st line CDK4/6 inhibitor treatment in Flatiron study [TP7]		
Exponential	133.26 (6)	134.84 (6)
Weibull	125.04 (3)	128.20 (3)
Loglogistic	**123.74 (1)**	**126.91 (1)**
Lognormal	124.15 (2)	127.32 (2)
Gompertz	128.19 (5)	131.36 (5)
Generalized gamma	126.09 (4)	130.84 (4)

Footnotes: (X): rank on lowest AIC/BIC by arm.
Abbreviations: CDK4/6 inhibitor: cyclin-dependent kinase 4/6 (CDK4/6) inhibitor; TP: transition probability; TPC: treatment of physician's choice; RWE: real world evidence.

The fit of the models to the Kaplan-Meier probabilities for TP7 are shown in Figure 25 below.

Figure 25: Fit of parametric survival models to the Kaplan-Meier data for metastatic to death by arm in the 1st line TPC chemotherapy subgroup of OlympiAD (left) and for the 1st line CDK4/6 inhibitor treatment subgroup of Collins et al. (2021) (right)



Abbreviations: CDK4/6 inhibitor: cyclin-dependent kinase 4/6 (CDK4/6) inhibitor; p: probability; TPC: treatment of physician's choice

For the TPC arm of OlympiAD, the majority of models provided a robust fit to the Kaplan-Meier data. The exponential model had a poor overall fit to the trial data, underestimating survival in the initial period and overestimating survival towards the end of follow-up. The best fitting models according to AIC and BIC (lognormal and loglogistic) provided similar levels of fit to the trial data

and had consistent predictions under extrapolation. Therefore, for the base case, the lognormal (best on AIC and BIC) was used to model the outcomes of single chemotherapy treatment on TP7.

For the 1st line CDK4/6 inhibitor population of Collins et al. (2021), most models provided a reasonable fit to the Kaplan-Meier data up to approximately 21 months of follow-up. The exponential model had a poor overall fit to the trial data, underestimating survival in the initial period and overestimating survival at the tail. From month 21, all of the models tended to poorly fit the tail of the Kaplan-Meier curve. The tail of the *observed* Kaplan-Meier curve for Collins et al. (2021) is highly uncertain due to the limited numbers at risk after this time point: 16 patients at month 21, declining to 12 and 7 by months 24 and 30, respectively. For the base case, the loglogistic (best on AIC and BIC) was therefore used to model the outcomes of CDK4/6 inhibitor treatment on TP7. Alternative choices of survival models are considered in the sensitivity analysis.

Case weights for modelling outcomes in late onset mBC

A summary of the weights used to derive the 'weighted-average' survival probabilities for TP7 is provided in Table 34 below.

- For TNBC, the population was assumed to receive a case mix of single chemotherapy and atezolizumab plus paclitaxel in line with UK clinical guidelines.[137] The percentage use of atezolizumab plus paclitaxel was based on insights from UK physicians reflecting on their current clinical practice and the proportion of *BRCA*m patients that would be eligible for treatment having tested PD-L1 positive.[8, 168] All remaining patients were assumed to receive single chemotherapy at first line.
- For HR+/HER2-, a case mix of single-agent chemotherapy and CDK4/6 inhibitor plus endocrine therapy use was assumed, which is aligned with UK clinical guidelines.[138-140] Similar to determining the case mix for TNBC patients, the use of CDK4/6 inhibitor plus endocrine treatment in first line for patients with HR+/HER2- disease was informed by insights from UK medical oncologists, who commented that generally 90% of patients will receive either abemaciclib, palbociclib or ribociclib in first-line.[8] All remaining patients were assumed to receive single chemotherapy (10%).

The same case mix of treatment was applied across both arms in the model. This is justified on the basis that PARP inhibitor treatments are not currently available in a mBC setting in the UK, and hence the same types of treatments would be available to patients on either arm.[169]

Table 34: Case mix of treatment in the 'late onset' mBC state

	Olaparib	Placebo	Efficacy data source
TNBC			
Single chemotherapy	70%	70%	TPC arm of the 1st line subgroup of OlympiAD
CDK4/6 inhibitor plus endocrine therapy	0%	0%	N/A; not approved for TNBC patients in the UK

Atezolizumab plus paclitaxel	30%	30%	TPC arm of the 1st line subgroup of OlympiAD, adjusted for the OS hazard ratio benefit of atezolizumab from IMpassion 130 (0.55)
HR+/HER2-			
Single chemotherapy	10%	10%	TPC arm of the 1st line subgroup of OlympiAD
CDK4/6 inhibitor plus endocrine therapy	90%	90%	Real world effectiveness study of CDK4/6 inhibitors in g*BRCA*m mBC
Atezolizumab plus paclitaxel	0%	0%	N/A; not recommended for HR+/HER2- patients in the UK

Abbreviations: CDK4/6 inhibitor: cyclin-dependent kinase 4/6; HER2: human epidermal growth factor receptor 2; HR: hormone receptor; mBC: metastatic breast cancer; N/A: not applicable; PD-L1 inhibitor: checkpoint inhibitor anticancer drugs; TNBC: triple negative breast cancer; TPC: treatment of physician's choice; UK: United Kingdom.

Weighted-average survival for TP7

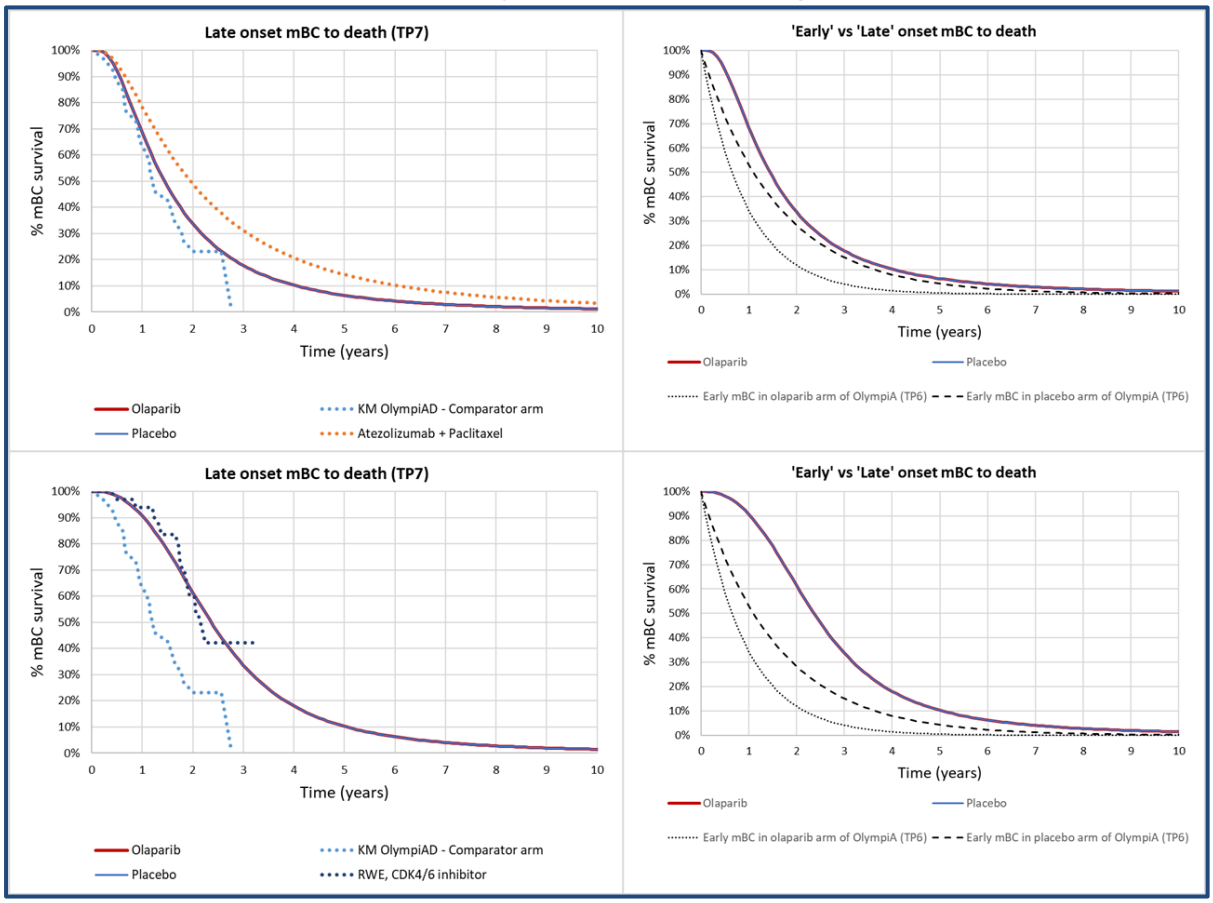
- The weighted-average survival probabilities for TP7 were modelled using the base case choices of survival models to model chemotherapy and CDK4/6 inhibitor treatment, the hazard ratio of OS for atezolizumab from IMpassion130 (0.55 [95% CI: 0.21–1.41]), and the case mix probabilities from Table 34.[150]

Figure 26 shows the weighted-average survival probabilities for TP7 in TNBC and HER2-/HR+. The modelled probabilities are compared to the KM data of OlympiAD and Collins et al. (2021) and to the survival probabilities for TP6 ('early onset mBC').[126, 148, 149] As the same case weights are applied to both arms, the corresponding survival probabilities for TP7 are the same across arms.

- For TNBC, TP7 is modelled using a case mix of survival probabilities for single chemotherapy (OlympiAD) and atezolizumab plus paclitaxel. The median survival for TP7 is approximately 1.5 years, with ~6% of patients predicted to be alive at 5-years after diagnosis of 'late onset' metastatic TNBC. This is consistent with feedback from UK clinical experts, who commented that most TNBC patients do not tend to survive more than 2 years after developing metastatic disease.[8] When compared to the survival probabilities for 'early onset' mBC (TP6), the model predicts improved median survival for those with 'late' versus 'early' onset disease. This is consistent with the post-recurrence survival reported in the UK POSH study by McKenzie et al. (2020) (Table 24).[143]
- For HR+/HER2-, TP7 is modelled using a case mix of survival probabilities for the TPC arm of OlympiAD and CDK4/6 inhibitor treatment. The resulting weighted-average survival probabilities for TP7 fall between the Kaplan-Meier estimates for each respective study. The median survival for TP7 is approximately 2.5 years with just over 10% of patients alive at 5-years after diagnosis of 'late onset' HR+ mBC. The model predicts longer survival for patients with 'late onset' HR+ mBC when compared to those with TNBC. This is plausible in view of the availability of new and effective treatment options for HR+ mBC, including CDK4/6 inhibitors,

and again aligned with feedback from UK clinical experts, who commented that survival for HR+ patients in the metastatic setting is generally longer than for TNBC patients.[8]

Figure 26: Weighted-average survival probabilities for 'late onset mBC' (TP7) in TNBC (upper) and HR+/HER2- (lower) vs. survival data/extrapolations of the OlympiAD study (TPC), CDK4/6 inhibitor use (Collins et al. (2021)) and atezolizumab plus paclitaxel (left) and the survival probabilities for 'early onset mBC' (TP6) (right)

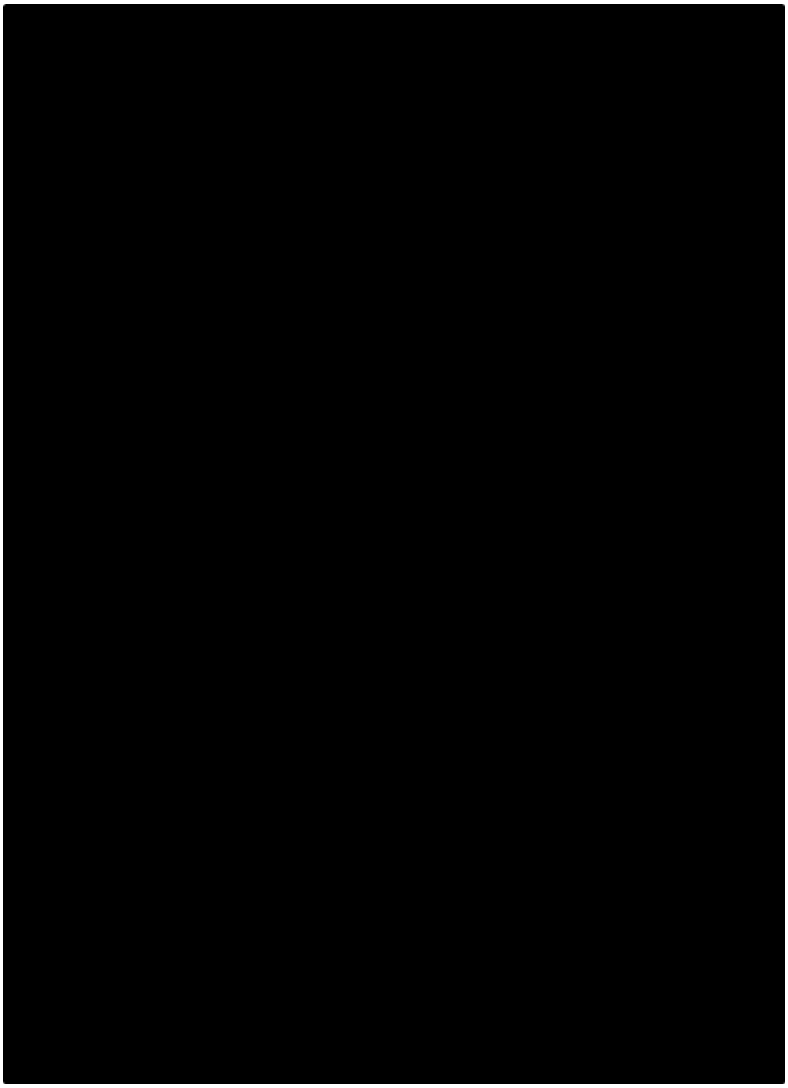


Abbreviations: mBC: metastatic breast cancer; TNBC: triple-negative breast cancer; TPC: treatment of physician's choice

B.3.3.6 Modelling of OS

The aggregated OS curves produced by the extrapolation analyses and the OS KM data for the TNBC (left) and HR+/HER2- (right) populations are presented in Figure 27. Considering there is limited external data in high-risk, *BRCA*m, HER2- eBC (as described in Section B.3.3.3) to appropriately validate the long-term OS extrapolations, the OS curves were presented to UK clinical experts to better understand their validity in relation to current UK practice. All of the experts commented that the landmark survival probabilities for OS in both TNBC and HR+/HER2- patients seemed plausible, particularly the high-risk nature of their disease. They also noted that the eventual crossing of the HR+/HER2- and TNBC long-term OS estimates would be expected in clinical practice, considering the respective differences in patterns of long-term disease recurrence between the two subgroups.[8]

Figure 27: Fit of the aggregated OS to the Kaplan-Meier data in OlympiA (TNBC, top; HR+/HER2 using ITT data, bottom)



Abbreviations: HER2: Human epidermal growth factor receptor-2; HR: hormone receptor; ITT: intent-to-treat; OS: overall survival; TNBC: triple-negative breast cancer.

B.3.4 *Measurement and valuation of health effects*

B.3.4.1 Health-related quality-of-life data from clinical trials

As described in Section B.2.6.3, in OlympiA health-related quality of life (HRQoL) was assessed using the FACIT-Fatigue and EORTC QLQ-C30 questionnaires. No EQ-5D-3L or EQ-5D-5L data were collected in the study. The FACIT-Fatigue and EORTC QLQ-C30 were completed at baseline (prior to randomisation) and every 6 months for a period of 2-years. For both instruments, compliance rates were high at baseline ([redacted] in both arms) and remained above [redacted] at all visits. Overall, there was no clinically meaningful change in HRQoL across the study follow-up and no meaningful difference in HRQoL between arms. These findings suggest no detrimental impact of treatment with olaparib on HRQoL.

In the absence of EQ-5D-3L or 5L data, health state utility (HSU) values for the OlympiA trial were estimated by mapping from the EORTC QLQ-C30 data using published algorithms. These data were considered the most robust and applicable source of HSU data for the iDFS state in the economic model given they are based on HRQoL data collected in patients with high-risk, *BRCA*m eBC. As data were only routinely collected every 6 months up to recurrence or for a maximum of 2 years in OlympiA, the HSUs for AEs, metastatic and non-metastatic BC had to be sourced from external data sources, including past NICE evaluations and empirical literature.

A summary of the mapping analysis is provided in Section B.3.4.2 below. The findings of the systematic literature review that was used to identify HSUs for metastatic and non-metastatic BC is provided in Section B.3.4.3. Further detail on the mapping analysis and literature review is provided in the Appendices.

B.3.4.2 Mapping

Published mapping algorithms were identified from the online HERC mapping database (accessed December 2021). In line with the NICE reference case, only algorithms with HSUs derived from the UK value set were considered in the analysis. For each algorithm, the characteristics of the mapping population were compared against the target population (i.e., OlympiA) to determine suitability for use in the mapping. Two relevant published algorithms were identified:

1. Crott and Briggs (2010),[170] who reported direct mapping of the QLQ-C30 to UK EQ-5D-3L HSUs and;
2. Longworth et al. (2014),[171] who reported indirect mapping of the QLQ-C30 to the domains of the EQ-5D-3L.

The algorithm by Crott and Briggs (2010) was selected for use in the base case analysis as the included patient population (locally advanced BC vs. a mix of cancer types in Longworth et al., 2014) was most relevant to OlympiA, and has been used in a previous NICE evaluation for HER2- mBC (TA423).[172] HSUs based on the mapping by Longworth et al. (2014) were considered in sensitivity analysis.[171] Further details on the two mapping analyses are available in

Appendix N. A summary of the HSUs based on the Crott and Briggs (2010) mapping is provided in Table 35 below.

Table 35: Summary statistics for the mapped HSU values using the Crott and Briggs (2010) algorithm (capped at 1) by arm and study period

	Treatment	N	Mean	SD	Median	Min	Max
Baseline	Olaparib 300mg bd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Study follow-up and recurrence-free	Olaparib 300mg bd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Study follow-up and post-recurrence	Olaparib 300mg bd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: bd: twice daily; HSU: health state utility; SD: standard deviation.

As in the primary analysis of EORTC QLQ-C30 in OlympiA, there was [redacted] in mean HSU across visits ([redacted] for baseline vs. follow-up visits) or [redacted] for olaparib and placebo, respectively).[14] Relatively few HSU values were collected after recurrence in OlympiA as the study did not require HRQoL data collection during the post-recurrence survival follow-up.[13, 14] Any data collected during this period are outside the planned scheduled visits of the study and may therefore be subject to selection bias.

Overall, the mean HSUs for Olympia at baseline (approximately 0.87) fall within the range of HSUs for the UK population norms of women aged 35-55 years (mean HSU of 0.85 to 0.91). When compared to general population norms data for EORTC QLQ-C30, the baseline QLQ-C30 scores of the OlympiA population are generally similar to those reported for women aged 40-45 years (see Appendix N). The consistency between the QLQ-C30 scores of OlympiA and the general population supports the results of the mapping analysis in showing similar HSUs for OlympiA vs. the age- and gender-matched UK general population.

The results of the regression analysis are summarised in Table 36. The results suggest [redacted] (at a 5% significance level) or [redacted] between the arms of OlympiA (olaparib vs. placebo = [redacted]). These results support the use of the same HSU for iDFS across the olaparib and placebo arms of the model. The least squares mean estimate of the HSU for iDFS (i.e., recurrence-free), averaged across arms, was 0.869 (95% CI: 0.865–0.873). This value was used to model the HSU of iDFS in the economic model, as is outlined in Section B.3.4.4.

In the regression analysis, there was also [redacted] (at a 5% significance level) or [redacted] in HSU comparing post versus pre-recurrence scores [redacted], [redacted] The absence of an effect of recurrence on HSU is likely due to the limited data collected after recurrence, as described previously. The data collected after recurrence are therefore not

considered in the economic model. Alternative data are obtained from the published literature as described in the following sections.

Additional regression analyses were performed to assess the impact of hormone receptor status on HSU. There was no [redacted] of HR+ vs. TNBC status on HSU [redacted]. Furthermore, there was [redacted] on the HSU of post vs. pre-recurrence (interaction term [redacted]). For these reasons, the HSU from the ITT population of OlympiA was used to model the HSU of iDFS in both the TNBC and HR+/HER2- populations in order to maximise the available sample size of utility data.

Table 36: Results of linear regression analysis on mapped HSUs from OlympiA using Crott and Briggs algorithm

Fixed effects	Estimate	95% CI and *p*-value
Intercept	[redacted]	[redacted]
Olaparib vs. placebo	[redacted]	[redacted]
Baseline HSU; mean (baseline)	[redacted]	[redacted]
Recurrence (vs. recurrence-free)	[redacted]	[redacted]

Footnotes: [redacted]
Abbreviations: CI: confidence interval; HSU: health state utility.

B.3.4.3 Health-related quality-of-life studies

Published estimates of the HSU of patients with eBC were identified via an SLR, which was initially conducted in December 2020 and subsequently updated in January 2022. The evidence retrieved by this review was supplemented by an overview of HSU values used in past NICE evaluations, which were identified by an additional SLR of economic evaluations conducted alongside the HSU review. Both reviews are described in full detail in Appendix G and H. A summary of the HSU data relevant to the economic analysis presented in this submission is given below.

SLR of health state utilities in eBC

In total, the literature review of HSU values in eBC identified 5 studies that met the requirements of the NICE reference case (EQ-5D-3L or EQ-5D-5L HSU estimated using the UK value set). A summary of the HSU values extracted from these studies is provided in Appendix H; a short description is given below:

- The studies by Conner-Spady et al. (2001) reported HSU values collected from a prospective longitudinal study of HRQoL in 52 BC patients receiving high dose chemotherapy with autologous blood stem cell transplantation at the Tom Baker Cancer centre in Calgary (Canada) from 1995 to 1998.[173, 174] HSUs were summarised according to treatment status during follow-up. These studies had a relatively small sample size and seem not to have been used to inform cost-effectiveness evaluations in past technology evaluations.
- The study by Lidgren et al. (2007) reported HSU from 361 consecutive BC patients attending an outpatient clinic at the Karolinska University hospital in Stockholm, Sweden, between April and May 2005.[147] The study was cross-sectional and reported HSUs according to diagnosis

status, including patients in the first year after primary BC, and in the years after locoregional or metastatic recurrence. Whilst the study was conducted in Sweden, the reported HSUs were evaluated using the UK social tariff for the EQ-5D-3L, and hence is considered applicable to the NICE reference case.

- The multinational study by Criscitiello et al. (2021) investigated the HRQoL among patients with HR+/HER2- eBC and used the EQ-5D-5L to measure HRQoL and a crosswalk UK societal tariff by van Hout et al (2012) to value health states, which means it meets the requirements of the NICE reference case.[175, 176]
- Finally, the real-world UK study by Verrill et al. (2020) aimed to assess how living in each stage of HER2+ BC treatment (patients with eBC currently receiving adjuvant treatment; patients with eBC who have completed adjuvant parenteral therapy; and patients with mBC) impacts directly on patients' HRQoL and productivity.[177] Similar to the study by Criscitiello et al. (2021), Verrill et al. (2020) also meets the requirements of the NICE reference case as the authors used EQ-5D-5L to measure HRQoL and valued health states using van Hout et al (2012).[176]
- It should however be noted that none of the identified studies reported HSU values that could be considered representative of the specific OlympiA population eligible for adjuvant olaparib as all studies lacked information on *BRCA* mutation status or risk of recurrence status. In terms of health status, Lidgren et al. (2007),[147] Criscitiello et al. (2021)[175] and Verrill et al. (2020)[177] provided values that may be relevant to the state structure of the model. However, in the context of the DF health state, the mapped HSU values from OlympiA are considered more appropriate given they more closely represent the health status of patients eligible for adjuvant olaparib in the OlympiA indication (*BRCA*m, HER2-, high risk, early disease).

Overview of health state utilities used in past evaluations for eBC

The literature review of economic evaluations in eBC identified 5 past NICE evaluations that reported HSU values relevant to the early and post-recurrence settings of the economic model (TA632,[133] TA612,[134] TA569,[135] TA501,[178] TA424[142]). Four of the five evaluations were for HER2-positive disease[133-135, 142] and one was for radiotherapy in eBC.[178] None of the included evaluations reported HSU in *BRCA*m or HER2- disease.

- In the recent NICE evaluations of trastuzumab emtansine (TA632),[133] neratinib (TA612),[134] and pertuzumab (TA569),[135] HSU values for iDFS were derived from the EQ-5D data collected in their respective clinical studies (KATHERINE for TA632,[133] ExteNET for neratinib and APHINITY for pertuzumab). The HSU values for iDFS ranged from 0.756 to 0.837. In all previous evaluations, trial-based HSU data were only available up to recurrence.
- In all past NICE evaluations, the HSU values for non-metastatic and metastatic recurrence were estimated from the literature or based on assumptions. For the metastatic disease setting, the most commonly used data sources for HSU values were the vignette study by Lloyd et al. (2006)[146] and the EQ-5D-3L study by Lidgren et al. (2007);[147] the latter of which was also identified in the literature review of HSUs in eBC.
- The study by Lloyd et al. (2006) has been the manufacturer's preferred source across numerous past evaluations; however, its use of the standard gamble technique to elicit HSUs from 100 members of the general population has been criticised as not reflecting the NICE

reference case.[146] In the most recent NICE evaluation of trastuzumab emtansine (TA632),[133] the evidence review group argued that the HSU value for patients with mBC should be based on Lidgren et al. (2007) as these data correspond more closely to the NICE reference case than Lloyd et al. (2006).[146, 147] This approach was ultimately adopted by the manufacturer and accepted in the final committee meeting.

- Due to data paucity, the HSU for non-metastatic disease was frequently assumed equal to the HSU for iDFS. This assumption asserts that patients who experience non-metastatic disease recurrence have no worsening in HRQoL versus those who are disease-free. This was justified based on data from Lidgren et al. (2007) that reports similar mean HSU values between patients with primary (i.e., iDFS) and non-mBC.[147]

In the base case analysis, the HSUs for 'early' and 'late' onset mBC were based on data from Lidgren et al. (2007).[147] This is justified based on the relevance of the data to the state structure, and its acceptance in past NICE evaluations. The mBC HSU values from Lloyd et al. (2006) were used in sensitivity analysis.[146]

B.3.4.4 Health-related quality-of-life data used in the economic analysis

A summary of the HSU values used in the base case and the sensitivity analysis are presented in Table 37 below.

Table 37: Base case and scenario analysis health state utility values used in the economic model

Health state	Base case value (95% CI)	Sensitivity analysis scenarios		
		1. using the Longworth et al. (2014)[171] mapping algorithm	2. using HSUV from Lloyd et al. (2006)[146] for the mBC states	3. using HSUV from Lidgren et al. (2007)[147] for all health states
DF	0.869 (0.865, 0.873)	0.802 (0.797, 0.807)	0.869 (0.865, 0.873)	0.779 (0.700; 0.849)
Non-metastatic recurrence	0.869 (0.865, 0.873)	0.802 (0.745; 0.811)	0.869 (0.745; 0.811)	0.779 (0.745; 0.811)
Early and late onset metastatic recurrence	0.685 (0.620, 0.735)	0.685 (0.620, 0.735)	0.521 (0.052)	0.685 (0.620; 0.735)
Sources	**DF:** OlympiA[13, 14] (Crott & Briggs mapping)[170] **Non-mBC:** assumption **mBC:** Lidgren et al. (2007)[147]	**DF:** OlympiA[13, 14] (Longworth et al., 2014 mapping)[171] **Non-mBC:** assumption **mBC:** Lidgren et al. (2007)[147]	**DF:** OlympiA[13, 14] (Longworth et al., 2014 mapping)[171] **Non-mBC:** assumption **mBC:** Lloyd et al. (2006)[146]	**All states:** Lidgren et al. (2007)[147]

Abbreviations: CI: confidence interval; DF: disease-free; HSUV: health state utility value; mBC: metastatic breast cancer.

None of the studies identified in the literature reported HSU or HRQoL for mBC based on the timing of recurrence. It should however be noted that the mBC HSUV from Lidgren et al. (2007) and Lloyd et al. (2006) are estimated based on questionnaires from patients with metastatic disease regardless of how quickly they experienced recurrence.[146, 147] The utility values therefore capture patients with both early and late recurrence patients, which supports the use of applying these values across the broader mBC health state. Following approaches accepted in past NICE evaluations (TA632,[133] TA569[135]), the HSUV for the non-mBC state was assumed equal to the HSUV for iDFS. Although it is acknowledged this might be a slightly optimistic assumption; imputing a HSUV for non-mBC equal or slightly lower than the DF state in the economic analysis has no major impact on the outcomes.

Finally, it is acknowledged that the HSUV for the DF state (0.869) from the OlympiA mapping analysis using the Crott & Briggs (2010) algorithm is slightly higher than the disease-free HSUVs observed and/or included in previous NICE appraisals in HER+ disease. However, there has been increasing evidence from empirical literature that patient reported HRQoL amongst patients with eBC who are and remain disease-free over time is generally high, with reported scores comparable to general population scores.[175, 177, 179, 180] For example, a recent meta-analysis of health utility values across different stages of breast cancer by Kaur et al. (2022) reported that HUVs in patients with early-stage BC can be as high as 0.9, especially when patients are off active treatment.[181] Furthermore, a recent 2021 multinational study by Criscitiello et al. (2021), which characterized HRQoL among patients with HR+/HER2- eBC who either receive adjuvant treatment or are under post-adjuvant surveillance, showed an overall cross-country mean EQ-5D index score of 0.868, and a UK-specific score of 0.872, both of which are almost identical to the mapped DF HSUV from OlympiA.[175]

A possible critique of the relevance of this UK-specific score to OlympiA patients could be that the mean age of the included UK population in the study was 61.5 years, which is not reflective of an average OlympiA patient (43 years) and might also not incorporate the impact on patients' QoL of inducing an early menopause, something which is often done for pre-menopausal HR+ patients with high-risk disease.[13, 23] However, in the Criscitiello et al. (2021) study,[175] the mean EQ-VAS score remained above 0.87 for any age group under 65 years, and there was no significant difference in mean EQ-VAS score between pre- and post-menopausal status groups (0.870 vs. 0.868). This not only indicates that younger BC patients who are disease-free generally do not experience reduced HRQoL, but also that adverse events from currently available adjuvant treatments such as endocrine therapies may not have had a negative impact sufficient to outweigh the potential benefits of successful treatment. This finding was also confirmed during interviews with UK clinical oncologists, who unanimously commented that the QoL of eBC patients will become similar to an age-matched general population over time.[8] The mapped DF HSUV of 0.869 from OlympiA thus represents a realistic estimate for disease-free, HER2-, high-risk eBC patients in the UK and is therefore used in the base case economic analysis.

Although the Criscitiello et al. (2021) study was in HR+/HER2- patients only, it is reasonable to make similar inferences on DF utility for patients with triple-negative disease. UK clinical oncologists commented that TNBC patients who are and remain disease-free generally are in better health than those with HR+/HER2- disease, simply because they do not receive long-term

endocrine therapy which may impact their QoL.[8] The DF HSUV of 0.869 is therefore equally as representative for patients with triple-negative disease as in HR+/HER2- patients. This also aligns with the outcomes from the regression analysis which showed no [redacted] of HR+ vs. TNBC status on HSU [redacted].

Finally, comments from UK clinical experts highlighted that patients with *BRCA*m disease might experience slightly more anxiety and stress around their cancer returning than patients who are not *BRCA* carriers.[8] However, based on a 2013 NICE report on Familial Breast Cancer which only reported a utility decrement of 0.005 associated with a positive *BRCA* testing result vs. individuals who do not have BC, it is assumed that this impact on patients' overall HRQoL is minimal and already reflected in the mapped HSUV of 0.869.[22, 182] This does however highlight the need for effective adjuvant treatments such as olaparib, which aim to reduce the risk of recurrence and thereby can have a positive effect on the anxiety of recurrence experienced by patients.

Age adjustment

Age-related utility decrements are included in the model's base case analysis to account for the natural decline in quality of life associated with age. The economic model includes an adjustment of all health state utilities (base case and scenario analyses) over the time horizon to reflect the modelled patient's age, and as such, prevents the health state utilities exceeding those of the age-matched UK population. The adjustment is modelled using the general population HSU norm equation from Ara & Brazier (2010).[183]

B.3.4.5 Adverse reactions

A one-off QALY adjustment for adverse events (AEs) was modelled based on each AE respective disutility (loss of utility) multiplied by its assumed duration. The economic analysis only includes AEs that were:

- ≥ Grade 3: AEs were included if they were classified as CTCAE Grade 3 or above. The costs of Grade 1 and 2 events are assumed to be negligible and therefore omitted from the analysis.
- ≥2% of patients: to ensure that key events were captured while ensuring the list of included events was manageable.

A summary of the AEs included in the economic analysis, their associated disutilities, durations and sources is presented in Table 38 below.

Table 38: Disutility values associated with AEs, and assumed duration of events

Adverse event	Disutility value	Source	Duration (days)	Source
Anaemia	-0.119	TA563[184]	[redacted]	OlympiA CSR[13] (median duration)
Neutropenia	-0.090	Nafees et al. (2008)[185]	[redacted]	

Abbreviations: AE: adverse event; ERG: Evidence Review Group; TA: technology appraisal.

B.3.5 *Cost and healthcare resource use identification, measurement and valuation*

In accordance with the NICE reference case, an SLR was conducted in December 2020 and updated in January 2022 to identify published literature of resource use and cost data associated with the treatment and management of patients with high-risk, *BRCA*m, HER2- eBC. Please refer to Appendix I for full details of how cost and resource use data were identified.

In total, the SLR identified 55 full publications reporting cost or resource use data that were eligible for final inclusion in the economic evaluation review. Details of all included studies and those excluded at full-text review are provided in Appendix I. Of the 41 studies which were fully extracted, none provided relevant UK-specific cost and/or resource data for use in the OlympiA economic model. It was therefore considered most appropriate to derive unit costs for the base case economic analysis from the most recent NHS reference costs, drugs and pharmaceutical electronic market information tool (eMIT), Unit Costs of Health and Social Care (PSSRU), and the British National Formulary (BNF).

The modelled costs and healthcare resource use associated with the lifetime treatment and management of patients with *BRCA*m, high-risk, HER2-, eBC comprised of the following:

- Treatment-related costs
- Drug acquisition costs (including endocrine and subsequent therapies)
- Drug administration and monitoring costs
- Disease management costs
- AE costs
- End of life care costs

B.3.5.1 Intervention and comparator costs and resource use

This section provides a summary of the intervention and comparator treatment costs in the economic model and the costs of treatments for non-metastatic and metastatic BC.

For patients with TNBC, the intervention in the model is 1 year adjuvant treatment with olaparib tablets at a dose of 300 mg twice daily. As per the OlympiA clinical study protocol,[35] treatment is administered until recurrence of disease, tolerability, or adverse events or until completion of the 1 year treatment period. After discontinuation or completion of treatment, patients are assumed to undergo watch and wait until recurrence. The comparator, '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. Further detail on these costs is provided in Section B.3.5.1 below.

For patients with HR+/HER2- disease, the intervention in the model is 1-year adjuvant treatment with olaparib tablets alongside a background regimen of adjuvant endocrine therapy, as indicated. The comparator is 'watch and wait' plus background endocrine therapy.

B.3.5.1.1 Adjuvant therapies

Olaparib

Olaparib is available in 150 mg and 100 mg film-coated tablet formulations and comes in pack sizes of 56 tablets or a multipack containing 112 film coated tablets (2 packs of 56). The 100 mg tablet is available for dose reduction.[21] The list price cost for 28 days of treatment with olaparib is £4,635.00, and the cost per model cycle (monthly [30.44 days]) is £5,038.90.[28] A confidential patient access scheme (PAS) for olaparib is in place and the results presented in this submission include this PAS. A summary of olaparib drug acquisition and administration costs are presented in Table 39 below.

Table 39: Summary of olaparib drug related costs

Items	Olaparib	Rationale
Dosing per administration	300 mg (2x 150 mg tablets)	Draft SmPC
Frequency of administration	Twice daily	Draft SmPC
Treatment cost: 150 mg (56 film coated tablet pack)	[redacted]	Confidential PAS price
Treatment cost: 100 mg (56 film coated tablet pack)	[redacted]	Confidential PAS price
4-weekly treatment cost	[redacted]	–
Monthly (30.44 days) treatment cost	[redacted]	–

Abbreviations: PAS: patient access scheme; SmPC: summary of product characteristics.

In the base-case economic analysis, acquisition costs are applied in line with how treatment was received in the OlympiA study, using the percentage of patients that remained on study drug in the olaparib arm of the OlympiA trial. This was estimated from the Kaplan-Meier probabilities for the time from randomisation to discontinuation of study drug from any cause (see Figure 28 below), as these were fully complete and thus the best source of data available. These data appropriately reflect the observed duration of treatment in the OlympiA trial by including the impact of disease recurrence, as well as tolerability and adverse events on the duration of treatment.

In OlympiA, although [redacted],[13] which can be attributed to interruptions in the treatment course. Therefore, in the economic model, the total duration of treatment is limited to 12 months, which is in line with the actual duration (excluding time with dose interruptions) in OlympiA and the recommend duration of adjuvant olaparib in the OlympiA indication.

Figure 28: Time to treatment discontinuation from OlympiA

Abbreviations: HER2: human epidermal growth factor 2; HR: hormone receptor; ITT: intention to treat; TNBC: triple negative breast cancer.

In the economic model, the monthly cycle cost of adjuvant olaparib is applied to the proportion of patients on the drug at the start of each month of the 12 cycles of treatment: from month 0 to month 11 of the fixed 1-year treatment. As outlined previously, this is to ensure that the model captures the costs of unused tablets in patients that discontinue treatment between each monthly cycle of the model time horizon.

Endocrine therapies (HR+/HER2- only)

In the economic model, patients with HR+/HER2- disease were assumed to receive adjuvant endocrine therapy until disease recurrence, death or for a maximum number of years. The costs of adjuvant endocrine therapy were modelled based on the numbers occupying the iDFS state over time. The model assumes that 90% of the HR+/HER2- patients receive adjuvant endocrine therapy, for a maximum duration of 10 years. These inputs were validated by UK clinical experts and are aligned with the recommendations on extended (>5 years) endocrine therapy in the NICE NG101 guidelines.[8, 23] Alternative scenarios on duration were considered in sensitivity analysis.

In the base case analysis, of the HR+/HER2- patients who receive endocrine therapy, it is assumed that 90% receive aromatase inhibitors (split equally between letrozole and anastrozole) and 10% receive tamoxifen.[8] The healthcare resource utilisation for the monitoring and administration of endocrine therapies were assumed to be captured by the routine disease management costs assigned to the iDFS state, and thus the cost of administration and monitoring for ET is set to zero. Based on this distribution a weighted average was calculated based on the respective treatment costs per cycle for each of the three treatments, equating to a per cycle (monthly; 30.44 days) cost of adjuvant endocrine therapy of £5.13.

Table 40: Split of HR+/HER2- patients receiving endocrine therapies in the DF state

Therapy	% of patients receiving the ET	Daily dose of ET	Pack size	Cost per pack[186]	Monthly acq. costs[a]
Letrozole	45%	2.5 mg	28 x 2.5mg tabs	£1.63	£1.77
Anastrozole	45%	1 mg	28 x 1 mg tabs	£0.98	£1.07
Tamoxifen	10%	20 mg	30 x 10 mg tabs	£4.20	£8.56

Abbreviations: acq.: acquisition; DF: disease-free; ET: endocrine therapy; HR: hormone receptor; HER2: human epidermal growth factor 2; tabs: tablets.
Notes: [a]Monthly cost based on 30.44 days

B.3.5.1.2 Treatment of non-metastatic and metastatic recurrence

Patients that experience recurrence in the model are assumed to receive additional treatments, including surgical intervention (either with curative or palliative intent), radiotherapy and drug-based interventions. The uptake of different treatments depends on numerous factors, including stage of disease (non-metastatic or metastatic), timing of progression ('early' vs. 'late') and the hormone receptor status (HR+ or TNBC) of patients.

Drug-based interventions

The systemic drug treatment of patients with advanced (non-metastatic or metastatic) breast cancer is highly complex. The availability of multiple chemotherapy regimens leads to many potential options for single or combination treatment of (non-)mBC.[187] The list of options relevant to the UK clinical setting was therefore derived from various sources, including drug labels and local chemotherapy protocols, and further validated with inputs from UK clinical experts.[8] An overview of the recommended treatment options for *BRCA*m patients with non-mBC or mBC and their respective costs as included in the economic model is presented in Table 41 below. It should be noted that for treatment options with multiple available vial/pack sizes, the formulation with the lowest cost/mg was selected for the model. Furthermore, in the base case analysis, the inclusion of the costs of wastage from intravenous/subcutaneous drugs in terms of unused vials is included.

In the economic model, the costs of treatment for non-metastatic and metastatic BC are modelled as a weighted average of costs, and then applied as a one-off cost accrued upon entering the recurrence states. This approach to subsequent treatment costs has been applied and accepted in numerous past evaluations in oncology (TA632,[133] TA569[135] etc.). This approach was preferred to the alternative approach whereby drug costs are modelled according to time spent in state, as it was not possible to accurately track the treatment status of patients occupying the metastatic or non-metastatic states (i.e., in terms of line of treatment or progression status).

Table 41: Drug acquisition costs (subsequent treatments)

Drug	Dose per tablet/vial (mg)	Pack size/vial	Cost per pack/vial	Source
Endocrine therapy				
Letrozole (tablet)	2.5	28	£1.63	eMiT (June 2021)[186]
Anastrozole (tablet)	1.0	28	£0.98	
Fulvestrant (IV)	250	2	£124.51	
Tamoxifen (tablet)	10	30	£4.20	
Exemestane (tablet)	25	30	£4.76	
Platinum chemotherapy				
Cisplatin (IV)	100	1	£8.97	eMiT (June 2021)[186]
Carboplatin (IV)	450	1	£13.51	
Cytotoxic chemotherapy				
Cyclophosphamide (IV)	1000	1	£13.55	eMiT (June 2021)[186]
Capecitabine (tablet)	300	60	£7.77	
Paclitaxel (IV)	300	1	£15.97	
Docetaxel (IV)	160	1	£17.38	
Doxorubicin (IV)	200	1	£20.02	
Epirubicin (IV)	200	1	£35.42	
CDK4/6 inhibitors				
Abemaciclib (tablet)	150	56	£2,950.00	BNF NICE (April 2022)[188-190]
Palbociclib (tablet)	125	63	£8,850.00	
Ribociclib (tablet)	200	63	£2,950.00	
PD-L1 inhibitor				
Atezolizumab (IV)	840	1	£2,665.38	BNF NICE (April 2022)[191]
mTOR inhibitor				
Everolimus (tablet)	10	30	£2,673.00	BNF NICE (April 2022)[191]

Footnotes: The formulation for each treatment with the lowest cost/mg has a 100% utilisation in the economic model.
Abbreviations: CDK4/6 inhibitor: cyclin-dependent kinase 4/6 (CDK4/6) inhibitor; eMIT: drugs and pharmaceutical electronic market information tool; IV: intravenous; PD-L1 inhibitor: checkpoint inhibitor anticancer drug; SC: subcutaneous.

To more accurately reflect the difference in therapy options patients receive in earlier and later lines of treatment for metastatic disease, two treatment lines are being modelled for costs in the

'early' and 'late onset' metastatic recurrence states: first line and second line and beyond. This approach to modelling subsequent treatment costs for metastatic recurrence is consistent with past NICE evaluations (TA612[134] and TA569[135]). The total costs of these subsequent lines of treatment are calculated as a weighted average based on current market shares in the UK. Table 42 details the market shares, and the average treatment duration in each health state. The quoted market shares have been primarily ascertained through interviews with UK clinical experts.[8] The data on treatment duration has primarily been taken from other clinical trials and UK treatment protocols and/or guidelines, which are referenced in the table below.

Table 42: Subsequent treatment durations and market shares

Treatment regimen	# monthly cycles*	Source of tx duration	Share TNBC	Share HR+/HER2-
Locoregional disease (non-metastatic)				
Anthracycline + taxane	6.0	Assumed the same as the TAC regimen	5%	-
Carboplatin + paclitaxel	6.0	NHS chemotherapy protocol for carboplatin in triple negative or *BRCA*m mBC[192]	50%	25%
Capecitabine	7.1	Mean number of 21-day chemotherapy cycles from the OlympiAD study[126]	30%	10%
Cyclophosphamide + anthracycline + taxane	6.0	NHS chemotherapy protocol for the TAC regimen[193]	15%	50%
Letrozole	14.7	Assumed the same as anastrozole	-	45%
Anastrozole	14.7	Mean exposure to anastrozole in the FALCON study[194]	-	45%
Tamoxifen	14.7	Assumed the same as anastrozole	-	10%
1L 'early onset' distant recurrence (metastatic)				
Capecitabine (mono)	7.1	Mean number of 21-day chemotherapy cycles from the OlympiAD study[126]	30%	-
Carboplatin (mono)	6.0	NHS chemotherapy protocol for carboplatin in triple negative or *BRCA*m mBC[192]	20%	-
Paclitaxel (mono)	6.0	NHS chemotherapy protocol for paclitaxel in mBC[195]	20%	10%

Docetaxel (mono)	6.0	NHS chemotherapy protocol for docetaxel in mBC[196]	10%	-
Atezolizumab + paclitaxel	7.0	Median administrations in the IMPassion130 study[150, 168]	20%	-
Abemaciclib +/- letrozole or fulvestrant	16.0	Median number of cycles in the MONARCH3 study[197]	-	15%
Palbociclib +/- letrozole or fulvestrant	15.9	Median time to first therapy in the RWE study by Collins et al. (2021), converted to mean number of cycles[149]	-	55%
Ribociclib +/- letrozole or fulvestrant	16.0	Assumed the same as abemaciclib	-	20%
1L 'late onset' distant recurrence (metastatic)				
Capecitabine (mono)	7.1	Same sources as above	25%	-
Carboplatin (mono)	6.0		20%	-
Paclitaxel (mono)	6.0		15%	10%
Docetaxel (mono)	6.0		10%	-
Atezolizumab + paclitaxel	7.0		30%	-
Abemaciclib +/- letrozole or fulvestrant	16.0		-	15%
Palbociclib +/- letrozole or fulvestrant	15.9		-	55%
Ribociclib +/- letrozole or fulvestrant	16.0		-	20%
2L+ distant recurrence (metastatic)				
Capecitabine (mono)	7.1	Same sources as above	30%	80%
Carboplatin (mono)	6.0		30%	-
Paclitaxel (mono)	6.0		30%	10%
Eribulin	6.0	NHS chemotherapy protocol for Eribulin in mBC	10%	-
Fulvestrant	16.2	Mean exposure to fulvestrant in the FALCON study[194]	-	5%
Everolimus + exemestane	6.0	NHS chemotherapy protocol for E+E in metastatic HR+ BC[198]	-	5%

Abbreviations: 1L: first line; 2L: second line; *BRCA*: breast cancer susceptibility gene; HER2: human epidermal growth factor 2; HR: hormone receptor; mBC: metastatic breast cancer; NHS: National Health Service; RWE: real world evidence; TAC: docetaxel (Taxotere), doxorubicin hydrochloride (Adriamycin) and cyclophosphamide; TNBC: triple negative breast cancer; tx: treatment
Notes: * based on the economic model's monthly cycles

Key assumptions on subsequent treatments (based on feedback from UK clinical experts)[8, 9]

- For patients with an isolated locoregional recurrence, the choice of treatment regimen is often similar to the treatment options given in the early disease setting but is guided by what regimen the patient received as primary (neo-)adjuvant therapy, and for how long.

- Generally, feedback from physicians indicates that most patients with triple negative disease will likely receive a combination of a platinum-based chemotherapy with a taxane, or a combined taxane/anthracycline/cyclophosphamide regimen. For those patients who received an anthracycline, taxane or platinum chemotherapy in the early disease setting, clinicians often consider capecitabine as a treatment for locoregional disease.

- Similar insights on treatment choices were given for patients with HR+/HER2- disease, although more patients in this group will likely receive a combination of a taxane, anthracycline and cyclophosphamide than solely carboplatin and paclitaxel. All physicians also commented that almost 90–100% of HR+ patients would be recommended additional hormone therapy in parallel to their other systemic treatments, or that their existing hormone therapy may be altered. A similar share of letrozole, anastrozole and tamoxifen as in the early disease setting (45%, 45% and 10% respectively) has thus been assumed for HR+ patients with locoregional disease in the economic model.

- In the metastatic setting, all physicians commented that 1st line treatments differ significantly based on whether patients have triple negative or HR+/HER2- disease. For patients with TNBC, those who are PD-L1-positive would be eligible to receive atezolizumab as a 1st line therapy option. Physicians on average noted a 20-30% utilisation of atezolizumab in the 1st line setting, stating that the proportion of eligible patients in clinical practice is less than the 40.9% which was seen in the IMpassion130 trial, especially as patients who have had a recurrence within 1 year of completing chemotherapy are not eligible. To reflect this insight in the model, a smaller percentage share of atezolizumab has been assumed in the 'early' (20%) vs. 'late' (30%) recurrence metastatic states. For those patients with TNBC who do not receive atezolizumab, clinicians commented that they mostly prescribe single-agent chemotherapy such as capecitabine, carboplatin or paclitaxel (docetaxel was generally not preferred due to toxicities).

- For patients with metastatic HR+/HER2- disease, physicians agreed that CDK4/6 inhibitors would be used in almost all patients (90%, excluding those in visceral crisis). There were some discrepancies in which CDK4/6 inhibitor was preferred, but overall, most physicians described a high use of palbociclib given prescriber familiarity with this option as it has been available the longest. It should be noted that in the economic model, patients who have an 'early' (<2 years) recurrence will receive fulvestrant in combination with a CDK4/6 inhibitor instead of letrozole, as they will likely be resistant to

aromatase inhibitors if they progressed so quickly. For those patients who do not receive a CDK4/6 inhibitor in first-line, physicians mainly give single-agent paclitaxel.

- Finally, when considering further lines of therapy (2L+), physicians agreed that the treatment options become much more variable and individualised to the patient, as they are dependent on prior treatments received (and how well they were tolerated), and the time to recurrence.

- In TNBC patients, physicians state that most patients would receive whichever chemotherapy regimen (many physicians mentioned capecitabine, taxanes, and carboplatin) they have not previously received in 2L, and that a smaller proportion may also receive Eribulin, especially in the 3L setting.

- In the HR+/HER2-negative group, physicians noted that many patients (~95%) lose their hormone sensitivity. Those who remain hormone responsive may receive fulvestrant or exemestane + Everolimus, while those who lose their hormone sensitivity are likely to receive capecitabine, and some paclitaxel.

To estimate the costs for subsequent treatments in the non-metastatic and metastatic recurrence health states, the mean treatment duration – expressed in model cycles – was used, multiplied by the per cycle cost and proportion of patients receiving each of the treatment regimens, giving a total subsequent treatment cost for each health state. The mean treatment duration for each treatment regimen is presented in Table 42 above. In the non-metastatic recurrence state, treatment is limited to a single line of therapy on the assumption that second-line treatment would only be required upon further progression or recurrence of disease. Patients that have a subsequent recurrence after non-mBC are assumed to enter one of the mBC states ('early' or 'late' recurrence) and accrue the costs of treatment from this state. In the 'early onset' and 'late onset' metastatic recurrence states, all patients are assumed to receive at least one round of treatment, and a fixed proportion (75% and 90% for the two metastatic recurrence states respectively) will receive 2nd or later lines of treatment, which was informed by UK clinicians.[8] Patients who continue onto 2L+ treatment will incur treatment costs for 1.7 lines of treatment, which is the mean number of subsequent treatment lines patients in the TPC arm go through after completing 1st line treatment in OlympiAD.[126]

As mentioned previously, it is important to note that the market shares and costings of subsequent therapies are not a major driver of the cost-effectiveness results. The impact of these assumptions should therefore not be overemphasised.

Radiotherapy and surgery

In addition to drug treatment, some patients who experience disease recurrence will also receive surgical intervention (either curative or palliative intent) and/or radiotherapy:

- In OlympiA, radiotherapy was used to treat both non-mBC and mBC and was reported in [redacted] olaparib patients and [redacted] placebo patients with any recurrence event (DCO1 ITT population). Information on the dose of radiotherapy used in OlympiA was not available.[13]

- At the time of DCO1 of OlympiA, post-recurrence surgery had been reported in [redacted] olaparib patients and [redacted] placebo patients with any recurrence event (ITT population). These included surgeries that were performed after recurrence for non-mBC and during the treatment of mBC.[13] For patients with locoregional recurrence (non-mBC), this would likely involve re-attempting the complete resection of the tumour.[199] In patients with mBC, surgery combined with stereotactic radiotherapy is often only used to manage the complications of brain or bone metastases.[200] The type of surgery administered is therefore likely to differ by health state in the model. To reflect this, the economic model includes separate relevant UK-specific input parameters for the costs of surgery in non-mBC and mBC.
- The unit costs of radiotherapy and surgery for patients with non-mBC was based on the diagnosis and procedure, and radiotherapy costs of stage IIIa BC patients from an English study by Sun et al. (2020), which assessed the costs of early invasive BC in England using national patient-level data.[79] These costs were inflated to 2020 levels using relevant health care inflation indices from the PSSRU. As a simplifying assumption, the costs of radiotherapy were assumed to be the same across health states in the model. The unit cost of surgery in the mBC was taken from the 2019-20 NHS reference costs (stereotactic intracranial radiosurgery).[201] The costs of surgery and radiotherapy are assumed to be the same across receptor populations on the justification that receptor status is not known to impact on the decision to undergo either procedure.

Finally, the proportions of patients receiving radiotherapy and surgery in non-mBC and mBC were informed by UK medical oncologists.[8] The impact of using the respective proportions obtained from the post-event summaries of OlympiA is explored in sensitivity analysis. An overview of the proportion of patients receiving surgery and/or radiotherapy in each health state and the associated costs is given in Table 43 below.

Table 43: Subsequent radiotherapy and surgery (shares & costs)

Treatment	Costs		Proportion of patients (%)		
	Input	Source	Non-met BC	'Early onset' met BC	'Late onset' met BC
Radiotherapy	£3,115.03	Sun et al. (2020)[79], stage IIIa radiotherapy cost, inflated to 2021 costs using PSSRU 2021 NHSCII price index[202]	[redacted][a]	20.00%	25.00%
Surgery for non-met BC	£5,383.44	Sun et al. (2020)[79], stage IIIa diagnosis and procedure cost, inflated to 2021 costs using PSSRU 2021 NHSCII price index[202]	[redacted][a]	-	-
Surgery for met BC (both early and late recurrence)	£2,121.80	NHS reference costs (2019/20)[201]: AA71B; Stereotactic Intracranial Radiosurgery, for Neoplasms or Other	-	10.00%	15.00%

		Neurological Conditions, with CC Score 0-3 & 4+ (total HRG costs)			

Abbreviations: BC: breast cancer; met: metastatic; PSSRU: Personal Social Services Research Unit.
Notes: [a]As the feedback from UK clinical experts on the proportion of patients who receive radiotherapy and surgery in locoregional disease was almost identical to the OlympiA post-event summaries, the proportion of patients from OlympiA was kept as an input.

B.3.5.2 Drug administration & monitoring costs

Drug administration

Administration costs were included for all therapies. However, for oral therapies, no costs were assumed, with the exception of including a pharmacy cost to account for the pharmacist's time during the prescription and preparation of treatments, which was included for all therapies. Administration costs were sourced from the latest NHS reference costs (2019-20) and the latest PSSRU report (2021)[201, 202]; an overview of the administration costs used in the economic model are presented in Table 44 below.

Table 44: Administration costs

Chemotherapy admin type	Cost	Source
IV simple	£281.28	SB12Z - Deliver Simple Parenteral Chemotherapy at First Attendance - Total HRG costs
IV complex	£475.67	SB13Z - Deliver more Complex Parenteral Chemotherapy at First Attendance - Total HRG costs
IV complex - prolonged infusion	£403.84	SB14Z - Deliver Complex Chemotherapy, including Prolonged Infusion Treatment, at First Attendance - Total HRG costs
IV (subsequent doses)	£339.46	SB15Z - Deliver Subsequent Elements of a Chemotherapy Cycle - Total HRG costs
SC (nurse administration)	£25.50	Jones & Burns (PSSRU, 2021)[202] - 30-minute band 6 hospital-based nurse appointment (cost per working hour = £51)
Pharmacy dispensing	£8.80	NICE TA639;[137] 12 minutes of pharmacist time

Abbreviations: HRG: healthcare resource group; IV: intravenous; PSSRU: Unit Costs of Health and Social Care; SC: subcutaneous.

Monitoring costs

Monitoring costs (complete blood count) associated with both adjuvant olaparib treatment and treatments used in the (non-) metastatic states have been incorporated as part of health state resource use as described in Table 45 below.

B.3.5.3 Health-state unit costs and resource use

Consistent with previous NICE appraisals in HER2+ eBC, health state costs have been applied cyclically and irrespective of treatment arm throughout the duration of the model time horizon, with the exception of monthly complete blood counts for olaparib in the 12 months of adjuvant treatment. The resource use and costs required in each health state are outlined in Table 45 and Table 46 below respectively. The supportive care regimens and assumptions used are aligned to those in past HER2+ NICE evaluations and have been validated by UK clinical experts.[201] Furthermore, similar to TA424,[142] TA569[135] and TA632,[133] the resource use and supportive care regimens are expected to differ depending on how long a patient has remained in the disease-free health state. Specific supportive care costs are therefore derived and applied in three distinct time periods: (1) first 12 months (Y<1), (2) months 12 to 60 (Y1-5) and (3) any time from year 5 onwards (Y5+).

Table 45: Resource use by health state

	Frequency (per year)				
Resource item	**DF (Y<1)**	**DF (Y1-5)**	**DF (Y5+)**	**LR**	**mBC**
Oncology visit	2	0	0	4	12
GP visit to monitor and manage long-term treatment for breast cancer	1	1	1	2	4
Clinical nurse specialist	0	0	0	4	12
Mammogram	1	1	0	1	0
CT scan	0	0	0	4	4
Complete blood count	12/1[a]	1	1	12	12

Footnotes: [a]12 CDCs for patients on olaparib treatment, 1 for patients on "watch & wait"
Abbreviations: CT: computerized tomography; DF: disease-free; GP: general practitioner; LR: locoregional; mBC: metastatic breast cancer; Y: year.

Table 46: Resource use costs

Resource item	Cost	Source
Oncology visit	£200.20	NHS Reference Costs 2019/20[201]: WF01A - Non-Admitted Face-to-Face Attendance, Follow-up – consultant led - 370, medical oncology
GP visit to monitor and manage long-term treatment for breast cancer	£39.23	Jones & Burns (PSSRU, 2021)[202] - per surgery consultation lasting 9.22 minutes, with qualification and direct staff costs, Table 10.3b

Resource item	Cost	Source
Clinical nurse specialist	£31.00	Jones & Burns (PSSRU, 2021)[202] - per hour for band 7 nurse in line with Macmillan costing fact sheet,[203] assuming 30-minute appointment time, Table 13
Mammogram	£32.65	NHS Reference Costs 2019/20[201]: DAPF, direct access plain film - directly accessed diagnostic services
CT scan	£105.12	NHS Reference Costs 2019/20[201]: RD20A, RD21A, RD22Z-RD27Z - Computerised Tomography Scans 19 years and over, with or without contrast, one to three or more areas, average cost estimated
Complete blood count	£2.56	NHS Reference Costs 2019/20[201]: DAPS05, haematology, directly accessed pathology services

Abbreviations: CT: computerized tomography; DF: disease-free; GP: general practitioner; LR: locoregional; mBC: metastatic breast cancer; PSSRU: Unit Costs of Health and Social Care; Y: year.

B.3.5.4 Adverse reaction unit costs and resource use

The health effects of treatment-related AEs were included in the base case economic analysis and modelled via the incidence (occurring in at least 2% of the OlympiA study population) of Grade ≥ 3 AEs, as described in Section B.2.10.3. The costs associated with treating and managing AEs in the analysis are presented in Table 47 below.

Costs were sourced from the NHS reference costs 2019–2020.[201] AE costs were applied as a one-off cost in the analysis. In reality, AEs can occur at any point while a patient receives treatment. The application of the costs at this timepoint in the analysis is expected to result in an overestimation of AE costs in the analysis. Nevertheless, both treatment-related side-effect profiles are relatively mild, and the costs associated with AEs is thought to have a negligible impact on the overall cost-effectiveness results.

Table 47: Adverse event costs

Adverse event	Costs	Source
Anaemia	£532.79	NHS Reference Costs 2019/2020[201]; SA04G-SA04L - Iron Deficiency Anaemia - non-elective short stay – average cost estimated
Neutropenia	£126.99	NHS Reference Costs 2015/2016; XD25Z Neutropenia drugs band 1; uplifted to 2021 prices using the PSSRU 2021[202] NHSCII price index as XD25Z has been taken out of the current NHS Reference Costs 2019/20[201]

Abbreviations: NHS: National Health Service; PSSRU: Unit Costs of Health and Social Care; TA: technology appraisal.

B.3.5.5 Miscellaneous unit costs and resource use

B.3.5.5.1 End of life costs

The costs of end of life or terminal care are modelled as a one-off cost applied to patients who enter the death state. These costs reflect the additional care required in the months prior to death. These costs have been included in numerous previous cancer HTAs and economic models, including the recent NICE evaluation of atezolizumab for TNBC (TA639)[137]. Table 48 summarises the unit cost and resource use of end-of-life care.

Table 48: Unit cost and resource use of EoL care

Setting	Unit costs	Proportion of patients in each setting	Weighted cost
Hospital and social hospice care (combined)	£12,066.00	40%	£4,826.40
Hospice	£697.56	10%	£69.76
Home	£1,443.39	50%	£721.70

Abbreviations: EoL: end of life.
Source: Atezolizumab NICE appraisal in TNBC (TA639)[137]

In the base case analysis, it is assumed that most deaths from iDFS would be non-cancer related and that cancer-related end-of-life care would not necessarily apply to these events; EoL costs are therefore only applied to death arising from the non-mBC or mBC states. As there is a small risk that this approach could underestimate the costs of end-of-life care as *BRCA*m patients remain at a heightened risk of cancer and other illnesses, end-of-life care costs were assumed to apply to all deaths in a scenario analysis.

B.3.5.5.2 Testing costs

BRCA testing costs were considered in scenario analyses only. As described in Section B.1.3.1.3, *BRCA* testing is already well established within the breast cancer pathway, and is already available for many patients, particularly those with high-risk disease. Consistent with the UK government's ambitions to create the most advanced healthcare system in the world, and to incorporate the latest genomics advances into routine healthcare to improve outcomes, further [redacted], which will ensure that by the time that olaparib is available in the eBC setting, it will be possible to identify all eligible patients in time for treatment initiation. For example, [redacted]

For this reason, it is [redacted]. *BRCA* testing costs are thus not included in the base case analysis as this would represent an unrealistic and overly conservative assumption, plus [redacted] is independent of the treatment decision for olaparib use in breast cancer.

However, in a scenario analysis, the total cost of *BRCA* testing is estimated from the unit cost of *BRCA* testing multiplied by the number needed to test to identify one *BRCA*m patient. Although the exact cost of testing and type of *BRCA* testing strategy that will be used to identify eligible patients has not yet been confirmed at the time of writing this submission, an approximate price for *BRCA* testing currently sits at around [redacted]. The number needed to test is calculated as one divided by the prevalence of g*BRCA*m in TNBC (10.7%, 9.3 tested) and HR+/HER2- (2.7%, 37.0 tested) patients. The total cost of *BRCA* testing is applied as a one-off cost in the first cycle of the model. This cost only applies to the olaparib arm on the basis that testing is not a requirement of 'watch and wait'.

The total cost included in the economic model of *BRCA*m testing ranges from [redacted] for TNBC to [redacted] for HR+/HER2- patients. It should however be noted that this represents an upper limit on the costs of *BRCA* testing as it assumes that all HER2- eBC patients would require testing, and that none of the eligible patients would have already determined *BRCA* status based on past testing (e.g., cascade testing from familial risk). In clinical practice, testing may be targeted to those with certain risk factors and/or *BRCA* status may be known. The testing cost included for both the TNBC and HR+/HER2- analyses is therefore adjusted in the scenario analysis with the assumption that approximately ~50% of OlympiA patients are currently expected to already be eligible for *BRCA* testing in England.

B.3.6 *Summary of base-case analysis inputs and assumptions*

B.3.6.1 Summary of base-case analysis inputs

A summary of the key variables included in the economic model for both the TNBC and HR+/HER2- analyses are provided in Appendix N.

B.3.6.2 Summary of key model assumptions

A summary of the economic model's base-case assumptions is provided in Table 49 below. Please note that where assumptions differ between the TNBC and HR+/HER2- analyses, this is noted in the 'Rationale/justification' column.

Table 49: Summary of the key model assumptions and inputs

Model input	Source/assumption	Rationale/justification
Time-to-event efficacy data for transition probabilities TP1-2	iDFS data from OlympiA[13, 105] (DCO 27/3/2020), standard parametric modelling approach	• Data from the OlympiA trial is the most robust source of data. • It should be noted that TNBC-specific iDFS data were used for the analysis of the TNBC subgroup, which is sufficiently mature and provides the most robust dataset for this analysis, while ITT data were used as a proxy for the HR+/HER2- subgroup due the limited number of iDFS events

Model input	Source/assumption	Rationale/justification
		observed in this subgroup, evidence of no statistically significant differences in the treatment effect, and consistency of the outcomes between the ITT and HR+ group during the trial follow-up period.
Time-to-event efficacy data for transition probability TP3	All-cause mortality data from the ONS life tables, matched to the OlympiA patient profile[13]	• The ONS lifetables are used to inform the transition from iDFS to death, which could not be modelled using OlympiA data due to low event numbers (n=2 for olaparib and n=0 placebo). • The data is subsequently adjusted to reflect excess mortality from *BRCA* mutations using the standardized mortality ratio from Mai et al. (2009).
Time-to-event efficacy data for transition probabilities TP4-5	Data on the time from non-metastatic recurrence to distant metastatic recurrence and data on the time from non-metastatic recurrence to death from OlympiA (DCO 27/3/2020),[13] standard parametric modelling approach	• Data from the OlympiA trial is the most robust source of data. • Risk of metastatic recurrence and death were pooled respectively across subgroups and treatment arms to maximize the sample size given the limited event numbers. • Assumption made that risk is not meaningfully impacted by HR status.
Time-to-event efficacy data for TP6	Data on the post-distant metastatic recurrence survival from OlympiA (DCO 27/3/2020),[13] standard parametric modelling approach	
Time-to-event efficacy data for TP7	Data from external Phase III studies in *BRCA*m HER2-negative metastatic breast cancer[126, 148-150]	These datasets provide longer-term data for outcomes in the late-onset metastatic disease state, which was not available from OlympiA, and therefore help reduce the uncertainty in the long-term extrapolations of post-progression survival.
Long-term risk of recurrence	- TNBC: declines to zero by year 5 - HR+/HER2-: patients are at a lifetime risk of recurrence	To capture the differences in long-term baseline risk of recurrence for patients with TNBC vs. HR+/HER2- disease, which is consistent with feedback provided by UK

Model input	Source/assumption	Rationale/justification
		clinical experts and data from long-term studies in eBC.
Definition of the timing of 'early' vs. 'late' recurrence	Two-years	UK clinical expert advice and literature data shows consistently poor post-recurrence survival in patients similar to the OlympiA population that recur within 2 years.
Utility values	**eBC health states:** mapped HSUs from OlympiA EORTC QLQ-C30[13] **non-metastatic recurrence:** assumed the same as DF **mBC health state:** Lidgren et al. (2007)[147] No difference in HSUVs by treatment arm	• In accordance with the NICE reference case. • The summary statistics for the mapped HSU values for OlympiA showed no evidence of a meaningful difference in the HSUV scores of patients across treatment arms. • Following approaches accepted in past appraisals, the HSUV for the non-metastatic breast cancer state was assumed equal to the HSUV for iDFS.
Intervention (olaparib) arm cost	Aligned to existing PAS for olaparib	Reflects cost of olaparib in current UK clinical practice.
Comparator arm cost	No drug costs were assigned to patients on the comparator 'watch and wait'.	The comparator, 'watch and wait', which is in line with the NICE final scope, comprises of monitoring and surveillance for disease recurrence and is therefore not associated with any drug costs.
Administration costs	Administration costs were included for all therapies, with the exception of endocrine therapies	In accordance with the NICE reference case. Oral endocrine therapies do not require administration under supervision at first dose, so no costs (except for pharmacy dispensing costs) were assumed.
End-of-life care costs	Inclusion of end-of-life care costs	Inclusion of these costs reflects the additional care required in the months prior to death. These costs have been included in numerous previous cancer HTAs and economic models, including the recent NICE evaluation of atezolizumab for TNBC (TA639).[137]

B.3.7 *Base-case results*

B.3.7.1 TNBC: Base-case incremental cost-effectiveness analysis results

Total costs, life years gained (LYG), QALYs, and incremental cost per QALY gained (ICER) in the base case for the TNBC analysis are presented in Table 50 below. In the base case analysis, adjuvant olaparib treatment generates [redacted] incremental QALYs and £40,537 incremental costs over a lifetime time horizon compared with placebo ("watch & wait"), resulting in an ICER of £29,732 per QALY gained. It should be noted that these results are based on the current PAS price for olaparib as presented in Table 39.

Table 50: 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]	£29,732

Note: discounted outcomes
Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life year gained; QALY: quality-adjusted life year

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

B.3.7.2 HR+/HER2-: Base-case incremental cost-effectiveness analysis results

Base case results for the HR+/HER2- analysis are presented in Table 51 below. In the base case analysis, adjuvant olaparib treatment generates [redacted] incremental QALYs and £40,204 incremental costs over a lifetime time horizon compared with placebo ("watch & wait"), resulting in an ICER of £35,312 per QALY gained. It should be noted that these results are based on the current PAS price for olaparib as presented in Table 39.

Table 51: 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]	£35,312

Note: discounted outcomes
Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life year gained; QALY: quality-adjusted life year

B.3.8 *Exploring uncertainty*

B.3.8.1 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was conducted to assess the parametric uncertainty associated with the base case model results. All key parameters were assigned probability distributions and point estimates were drawn using Monte Carlo simulation techniques. Where available, known correlation between parameters was preserved.

The PSA was run for 1,000 iterations as this was found to be sufficient to produce stable results. Results from the PSA for the TNBC and HR+/HER2- analyses are presented in Table 52 and Table 53 respectively. The base case probabilistic ICER for the TNBC analysis is £30,168 per QALY gained, and **highly consistent with the ICER in the deterministic analysis** (£29,732 per QALY gained). **Similar results are shown for the HR+/HER2-**, with a base case probabilistic ICER of £36,315 vs. an ICER of £35,312 in the deterministic analysis.

Table 52: Base case results (probabilistic) (TNBC)

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]	£30,168

Note: discounted outcomes; results are based on the current PAS price for olaparib
Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life year gained; QALY: quality-adjusted life year

Table 53: Base case results (probabilistic) (HR+/HER2-)

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]	£36,315

Note: discounted outcomes; results are based on the current PAS price for olaparib
Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life year gained; QALY: quality-adjusted life year

The cost-effectiveness plane and cost-effectiveness acceptability curve for olaparib versus placebo for the TNBC analysis are presented in Figure 29 and Figure 30 and in Figure 31 and Figure 32 for the HR+/HER2- analysis. At a willingness to pay threshold of £30,000, adjuvant olaparib treatment has a [redacted] probability of being cost-effective compared with "watch & wait" in the TNBC analysis, and a [redacted] probability in the HR+/HER2- analysis.

Figure 29: Cost-effectiveness plane, olaparib vs. placebo ("watch & wait") (TNBC)

Abbreviations: QALY: quality adjusted life year; TNBC: triple negative breast cancer

Figure 30: Cost-effectiveness acceptability curve, olaparib vs. placebo ("watch & wait") (TNBC)

Abbreviations: TNBC: triple negative breast cancer

Figure 31: Cost-effectiveness plane, olaparib vs. placebo ("watch & wait") (HR+/HER2-)

Abbreviations: HER2: human epidermal growth factor 2; HR: hormone receptor; QALY: quality adjusted life year

Figure 32: Cost-effectiveness acceptability curve, olaparib vs. placebo ("watch & wait") (HR+/HER2-)

Abbreviations: HER2: human epidermal growth factor 2; HR: hormone receptor

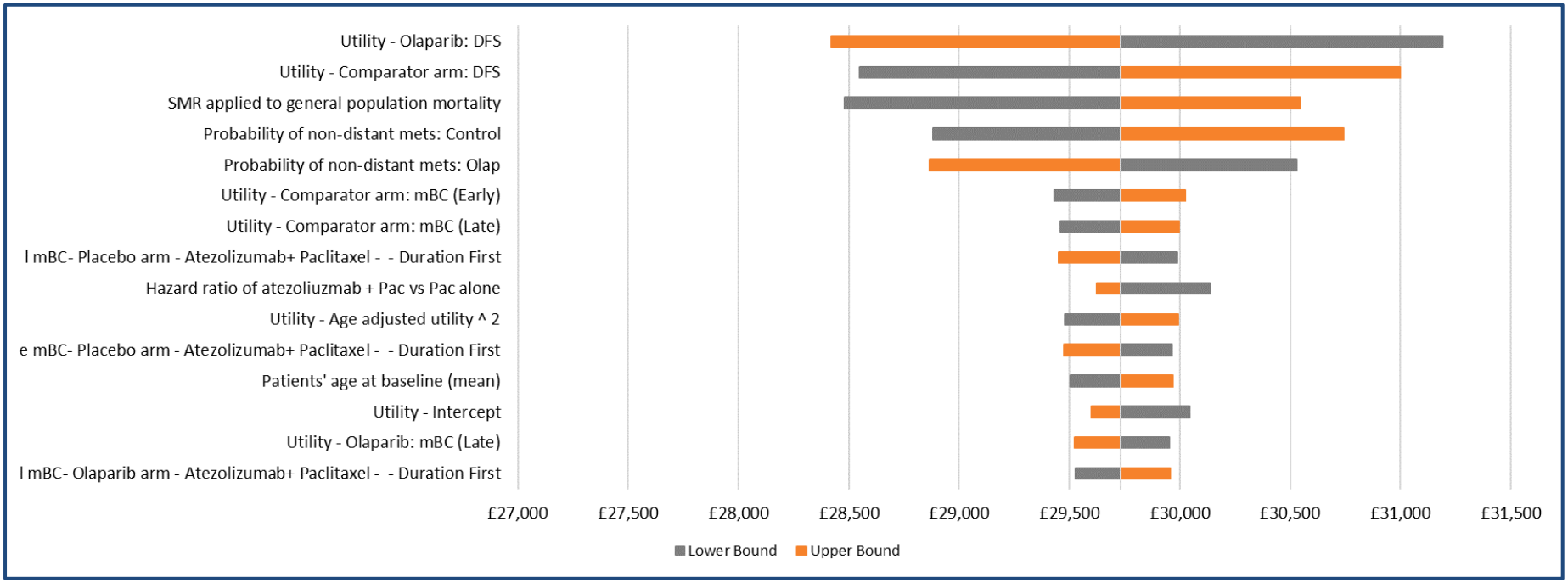
B.3.8.2 Deterministic sensitivity analysis

One-way deterministic sensitivity analysis (DSA) was performed to identify key model drivers. Parameters were varied one at a time between their upper and lower 95% confidence intervals, which were determined using standard errors when available (e.g., for utilities), or using standard errors estimated based on ±10% variation around the mean where measures of variance around the base case values were not available.

The DSA was performed on more than 150 model input parameters. This included clinical inputs such as the standardised mortality ratio and probability of an iDFS event being a non-distant recurrence, cost inputs such as duration of subsequent treatment, and the health state utility inputs. Other key model parameters such as the shape and scale parameters of the survival models are considered as part of the scenario analysis and PSA.

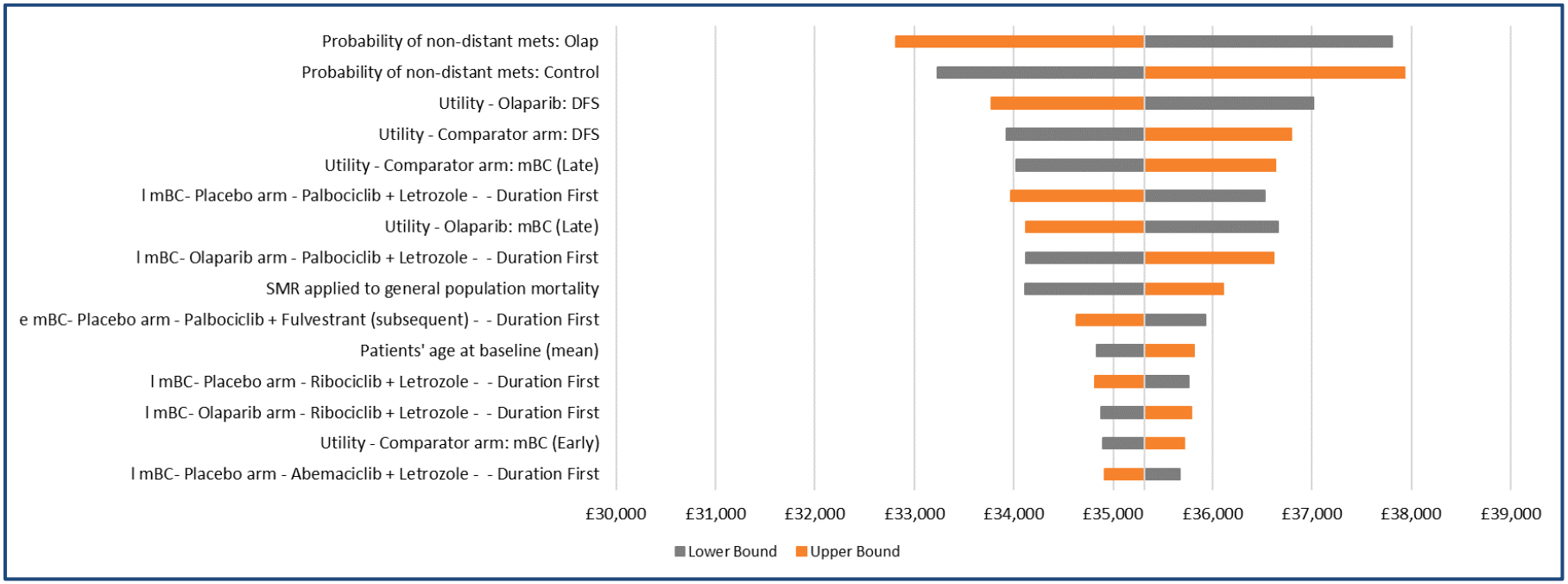
The results of the DSA for the top 15 most influential parameters on the spread of the cost-effectiveness results are shown in Figure 33 for the TNBC analysis and in Figure 34 for the HR+/HER2-. Overall, the results show the ICER is most sensitive to variation in the utility assigned to iDFS, the probability of developing a distant vs. a locoregional metastasis and the excess mortality risk associated with a *BRCA* mutation. However, for both the TNBC and HR+/HER2- analyses, the highest produced ICER is only a maximum of £2-3k above the respective ICER from the base case analysis, giving further confidence in the stability of the results.

Figure 33: Deterministic sensitivity analysis results, tornado diagram (TNBC)



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

Figure 34: Deterministic sensitivity analysis results, tornado diagram (HR+/HER2-)



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

B.3.8.3 Scenario analysis

Table 54 provides a summary of the results of the scenario analyses for both the TNBC and HR+/HER2- populations. For the TNBC analysis, the results of the scenario analysis indicate that the model is most sensitive to the length of the time horizon, the HSUV assigned to the progression free state and the inclusion of *BRCA* testing costs. However, it should be noted that in only a couple of scenarios the ICER for the TNBC analysis goes above £30k. The highest ICER (£33,562) is produced in the scenario assuming a lower HSUV for the DF state which, as described in Section B.3.4.4, is too low and not reflective of HRQoL amongst patients with eBC who are and remain disease-free over time.

For the HR+/HER2- analysis, the model is most sensitive to the same parameters as the TNBC analysis, as well as the choice of survival curve for iDFS (TP1/TP2). However, it should be noted that the generalised gamma, Weibull and loglogistic all have relatively poor fits to the observed data and generally predict conservative long-term survival estimates for olaparib, as discussed in Section B.3.3.3. These scenarios therefore present overly pessimistic ICER estimates.

The model results were insensitive (<5% change in ICER) to almost all other scenarios and parameters, including the time point for determining early vs. late recurrence, the choice of survival distribution for TP4, TP5, TP6 and TP7, the HSUV assigned to the progressed disease state and using treatment arm-specific probabilities of iDFS being a non-distant recurrence event.

Overall, the results of the scenario analysis suggest that the base case analysis for both the TNBC and HR+/HER2- populations are **robust to variations** in input parameters.

Table 54: Scenario analysis results (discounted, TNBC & HR+/HER2- analyses)

Scenario	Base case value	Scenario analysis value	ICER (£/QALY) (TNBC)	ICER (£/QALY) (HR+/HER2-)
Base case	–	–	**£29,732**	**£35,312**
Discount rate	3.5%	1.5%	£21,054	£25,817
Time horizon	57 years	40 years	£30,701	£36,119
		50 years	£29,782	£35,351
Time point for determining early vs. late recurrence	2 years	1 year	£29,456	£35,212
		3 years	£29,959	£35,495
Include wastage for IV and SC treatments	Yes	No	£29,746	£35,311
Include *BRCA* testing costs	No	Yes	£30,699	£39,902
TNBC: time point at which patients	5 years	3 years	£32,442	–
		7 years	£28,900	–
		10 years	£28,665	–

Scenario	Base case value	Scenario analysis value	ICER (£/QALY) (TNBC)	ICER (£/QALY) (HR+/HER2-)
are no longer at a risk of recurrence				
TNBC: risk of recurrence after 5 years	0%	10-year probability of recurrence of 5%	£31,511	–
Age-adjusted utilities	Yes	No	£27,390	£32,743
Apply end-of-life costs to all deaths	No	Yes	£29,855	£35,411
TP1/TP2: conditional prob. recurrence	Combined treatment arms	By individual treatment arms	£29,857	£35,660
TP1/TP2 distribution	Lognormal	Loglogistic	£28,906	£45,193
		Weibull	£28,297	£47,158
		Generalised gamma	£30,259	£47,205
TP4 distribution	Lognormal	Loglogistic	£29,698	£35,274
		Exponential	£29,642	£35,210
TP5 distribution	Exponential	Lognormal	£29,819	£35,417
		Loglogistic	£29,796	£35,389
TP6 distribution	Exponential	Loglogistic	£31,222	£37,460
		Gompertz	£30,845	£36,921
		Lognormal	£31,238	£37,486
TP6: assume the same risk of death across arms	No	Yes	£29,110	£34,404
TP7 distribution: chemotherapy	Lognormal	Loglogistic	£29,776	£35,313
		Weibull	£29,668	£35,311
		Generalised gamma	£29,730	£35,312
TP7 distribution: CDK4/6 inhibitor	Loglogistic	Lognormal	–	£35,325
		Weibull	–	£35,276
		Generalised gamma	–	£35,308
Utility values	PF: 0.869 Non-mBC: 0.869 mBC: 0.685	Scenario 1: PF: 0.802 Non-mBC: 0.802 mBC: 0.685	£32,492	£38,600
		Scenario 2: PF: 0.869 Non-mBC: 0.869 mBC: 0.521	£29,040	£34,469
		Scenario 3:	£33,562	£39,875

Scenario	Base case value	Scenario analysis value	ICER (£/QALY) (TNBC)	ICER (£/QALY) (HR+/HER2-)
		PF: 0.779 Non-mBC: 0.779 mBC: 0.685		
HR+/HER2-: Duration of adjuvant endocrine therapy	10 years	5 years	–	£35,305
		7 years	–	£35,308
Radiotherapy and surgery shares	Please refer to Table 43	Non-mBC: 13.8% RT, 55.2% surgery 'Early' mBC: 28% RT olaparib, 37% RT placebo, 23% surgery olaparib, 26% surgery placebo 'Late' mBC: 34% RT, 25% surgery	£29,659	£35,234

Abbreviations: *BRCA*: breast cancer gene; CDK4/6: cyclin-dependent kinase 4/6; HER2: human epidermal growth factor 2; HR: hormone receptor; ICER: incremental cost-effectiveness ratio; IV: intravenous; mBC: metastatic breast cancer; PF: progression-free; RT: radiotherapy; SC: subcutaneous; QALY: quality adjusted life year; TNBC: triple negative breast cancer; TP: transition probability

B.3.9 *Subgroup analysis*

Please refer to Section B.3.2.1 – cost-effectiveness results of adjuvant olaparib treatment in patients with *BRCA*m, HER2-, high risk eBC are presented for both subgroups of the OlympiA ITT population: TNBC and HR+/HER2- disease. Modelling these subgroups separately allows for greater flexibility in capturing their respective patterns of long-term disease recurrence, as well as differences in available treatment options. No additional subgroup analyses have been carried out.

B.3.10 *Validation of the cost-effectiveness analysis*

Consistency with the trial and literature

As described in Section B.3.2.2, the modelling approach and structure was selected and developed considering a wide range of factors, including (1) the ability to capture the important aspects of the clinical and treatment pathway, (2) accepted model structures and appraisal committee feedback from previous NICE submissions in eBC, (3) structural assumptions associated with different modelling approaches, and (4) the availability and maturity of the OlympiA data.

The overall approach was validated by two UK health economists in September 2021, and subsequently by another UK health economics expert (with prior experience working at an ERG), who advised on the appropriateness of the methodology implemented for decision-making from a UK perspective.

Quality control

The model was subject to extensive review and quality control prior to finalisation. This included the verification of Excel calculations by the vendor responsible for developing the model, review by four experts in health economic modelling at AstraZeneca, and a separate, external Excel review conducted by a third-party vendor. This external review included an assessment of the face validity of the model, and third-party validation of the model settings, sensitivity analyses, workings and macros, and data sources used in the model. A range of extreme value and logic tests were conducted to examine the behaviour of the model and ensure that the results were logical.

Validation and generalisability of the inputs and results

Unit costs were sourced from the most recent NHS reference costs, eMiT, Unit Costs of Health and Social Care (PSSRU), and the British National Formulary (BNF) to ensure that the results of the economic analysis are appropriate for decision-making in the UK setting. Where possible, the model has been populated with clinical input data from the OlympiA trial which, as discussed in Section B.2.12.1, can be considered generalisable to the UK population and clinical practice. To reflect the availability of different first-line treatment options available to patients with *BRCA*m mBC in the UK, three additional external studies were used to inform patients' survival in this state. Finally, clinical inputs such as subsequent treatment splits, as well as clinical outcomes predicted by the model, were compared and aligned with data from (UK) empirical literature and informed and/or validated by external clinical expert opinion through two rounds of interviews. This ensured that all input parameters and clinical outcomes were properly validated to present robust base case assumptions.[8, 9]

B.3.11 *Interpretation and conclusions of economic evidence*

A *de novo* cost utility model was developed to evaluate the cost-effectiveness of olaparib versus current standard of care ("watch & wait", placebo) as a monotherapy for the adjuvant treatment of adult patients with g*BRCA*m who have HER2-negative, high-risk eBC who have previously been treated with neoadjuvant or adjuvant chemotherapy. In order to capture differences in patterns of long-term disease recurrence and available treatment options for metastatic disease between triple-negative and HR+/HER2- BC, the model splits the subgroups into two separate analyses; cost-effectiveness results are thus presented for each subgroup.

The model mainly draws upon clinical data from the OlympiA study: a high-quality, international, Phase III, placebo-controlled trial which has demonstrated that adjuvant olaparib administered for up to one-year significantly improves the outcomes of patients with g*BRCA*m, HER2-, high-risk eBC. The baseline characteristics of the patients in OlympiA have been validated by clinical experts and can be considered generalisable to the corresponding UK population. This evaluation can therefore be considered relevant to clinical practice in England and Wales.

The base-case results of the economic analysis indicate that adjuvant treatment with olaparib **is cost-effective** at the current olaparib PAS price, with an ICER of £29,732 and £35,312 for the TNBC and HR+/HER2- populations respectively. Furthermore, compared to placebo ("watch &

wait"), olaparib also produces **considerable clinical and patient benefits**, including [redacted] and [redacted] additional life years and [redacted] and [redacted] additional discounted QALYs per patient on average for each population respectively. Running the analysis under a range of key scenarios yielded results highly consistent to the base case, suggesting that the base case ICERs for both the TNBC and HR+/HER2- populations are robust to variations in input parameters. Similar results were demonstrated with the PSA, which was consistent with the deterministic analysis with similar mean incremental costs and QALYs generated to the base case analysis for both TNBC and HR+/HER2-.

The key strength associated with the presented cost-effectiveness analysis is the use of the best available and, where possible, UK-specific evidence to inform the economic model, including clinical effectiveness and quality of life data from OlympiA, data from three external studies to inform survival in metastatic disease aligned with UK clinical practice, and costs and resource use taken from well-established UK sources and previous NICE appraisals in eBC. Furthermore, all assumptions have undergone a rigorous validation process, including a comparison with relevant (UK) empirical data and RWE and two rounds of interviews with UK clinical oncologists.

The primary limitation of this analysis is the relatively low number of events observed for the iDFS endpoint, in particular for the HR+ subgroup as described in Section B.3.3.1. Although this is not uncommon in early-stage cancer therapies it may introduce a level of uncertainty in the economic analyses. Future planned analyses of the OlympiA clinical trial could support the resolution of residual uncertainty in this subgroup. Nevertheless, it should be noted that the analyses presented using the TNBC and ITT datasets for each subgroup respectively produce robust and externally valid estimates of the long-term clinical effectiveness of olaparib in each subgroup respectively. The predicted overall survival from the model is consistent with the observed data from the OlympiA study and well-aligned with clinician expectations and available real-world evidence.

Olaparib is a highly efficacious, well-tolerated and innovative treatment option for *BRCA*m HER2-negative eBC and **represents a step-change in the treatment paradigm for patients with high-risk disease**, a patient group in which the risk of cancer returning can be unacceptably high. Results from the OlympiA trial have shown that olaparib not only **reduced the risk of recurrence but also improved OS**, highlighting the exciting demonstration of the benefits of targeting the specific *BRCA*m biology of disease for these patients. Further to these important clinical benefits of olaparib to patients, it is also a **cost-effective use of NHS resources** when compared against the thresholds commonly used in decision making in England, as is demonstrated by the results presented in this submission.

B.4 References

1. Cancer Research UK. Breast Cancer Statistics. Available at: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer (accessed 04/06/2021), 2021.
2. Cancer Research UK. The 20 Most Common Causes of Cancer Deaths, UK, 2018. 2018. Available at: https://www.cancerresearchuk.org/health-professional/cancer-statistics/mortality/common-cancers-compared#heading-Zero (accessed 11/01/2022).
3. Office for National Statistics. Cancer survival by stage at diagnosis in England. 2019. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancersurvivalratescancersurvivalinenglandadultsdiagnosed (accessed 17/03/2022).
4. Breast Cancer Care. Treating primary breast cancer. Available at: https://breastcancernow.org/sites/default/files/publications/pdf/bcc4_treating_primary_breast_cancer_2018_web.pdf (accessed 04/06/2021). 2021.
5. Yersal O, Barutca S. Biological subtypes of breast cancer: Prognostic and therapeutic implications. World journal of clinical oncology 2014;5:412-424.
6. Eliyatkın N, Yalçın E, Zengel B, et al. Molecular Classification of Breast Carcinoma: From Traditional, Old-Fashioned Way to A New Age, and A New Way. J Breast Health 2015;11:59-66.
7. Martei YM, Matro JM. Identifying patients at high risk of breast cancer recurrence: strategies to improve patient outcomes. Breast cancer (Dove Medical Press) 2015;7:337-343.
8. AstraZeneca Data on File. Early breast cancer clinical interviews March 2022 (Data on File Number: GB-35540). 2022.
9. AstraZeneca Data on File. Early breast cancer clinical interviews December 2021 (Data on File Number: GB-35535). 2022.
10. Feng Y, Spezia M, Huang S, et al. Breast cancer development and progression: Risk factors, cancer stem cells, signaling pathways, genomics, and molecular pathogenesis. Genes & diseases 2018;5:77-106.
11. Baretta Z, Mocellin S, Goldin E, et al. Effect of BRCA germline mutations on breast cancer prognosis: A systematic review and meta-analysis. Medicine (Baltimore) 2016;95:e4975.
12. Copson E, Eccles B, Maishman T, et al. Prospective Observational Study of Breast Cancer Treatment Outcomes for UK Women Aged 18–40 Years at Diagnosis: The POSH Study. JNCI: Journal of the National Cancer Institute 2013;105:978-988.
13. AstraZeneca Data on File. OlympiA Clinical Study Report. 2021.
14. Tutt A, Garber JE, Kaufman B, et al. Adjuvant Olaparib for Patients with BRCA1- or BRCA2-Mutated Breast Cancer. New England Journal of Medicine 2021;384:2394-2405.
15. NICE. Olaparib for Adjuvant Treatment of High-Risk HER2-Negative, BRCA-Positive Early Breast Cancer After Chemotherapy Final Scope. 2021. Available at: https://www.nice.org.uk/guidance/indevelopment/gid-ta10903 (accessed 13/04/2022).
16. British National Formulary. Olaparib, drug action. 2021. Available from: https://bnf.nice.org.uk/drug/olaparib.html (accessed 06/01/2022).
17. Helleday T. The underlying mechanism for the PARP and BRCA synthetic lethality: clearing up the misunderstandings. Mol Oncol 2011;5:387-93.
18. Murai J, Huang SN, Das BB, et al. Trapping of PARP1 and PARP2 by Clinical PARP Inhibitors. AACR 2012;72:5588–99.
19. Hodgson DR, Dougherty BA, Lai Z, et al. Candidate biomarkers of PARP inhibitor sensitivity in ovarian cancer beyond the BRCA genes. Br J Cancer 2018;119:1401-1409.
20. Andor N, Maley CC, Ji HP. Genomic Instability in Cancer: Teetering on the Limit of Tolerance. Cancer Res 2017;77:2179-2185.
21. EMA. Olaparib (Lynparza®) Summary of Product Characterstics. 2020.

22. NICE. Familial breast cancer: classification, care and managing breast cancer and related risks in people with a family history of breast cancer (Clinical guideline [CG164]). Available at: https://www.nice.org.uk/guidance/cg164 (accessed 06/01/2022), 2013.
23. NICE. NICE Guideline [NG101]: Early and locally advanced breast cancer: diagnosis and management. Available at: https://www.nice.org.uk/guidance/ng101 (accessed 06/01/2022). 2018.
24. England N. National Genomic Test Directory. Available at: https://www.england.nhs.uk/publication/national-genomic-test-directories/ (accessed 06/01/2022), 2021.
25. NHS. The NHS Long Term Plan. 2019.
26. NHS. Improving Outcomes Through Personalised Medicine. Available at: https://www.england.nhs.uk/wp-content/uploads/2016/09/improving-outcomes-personalised-medicine.pdf (accessed 06/03/2022). 2016.
27. UK Government. Genome UK: The Future of Healthcare. Available at: https://www.gov.uk/government/publications/genome-uk-the-future-of-healthcare (accessed 12/01/2022). 2020.
28. British National Formulary (BNF). Olaparib. Available from: https://bnf.nice.org.uk/medicinal-forms/olaparib.html.
29. Arpino G, Milano, M, De Placido, S. Features of aggressive breast cancer. Breast 2015;24:594-600.
30. Cardoso F, Kyriakides S, Ohno S, et al. Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2019;30:1194-1220.
31. NCCN. NCCN Clinical Practice Guidelines in Oncology: Breast Cancer. Version 5.2020. Available at: https://www2.tri-kobe.org/nccn/guideline/breast/english/breast.pdf (accessed 06/04/2022). 2020.
32. Jahn SW, Bösl A, Tsybrovskyy O, et al. Clinically high-risk breast cancer displays markedly discordant molecular risk predictions between the MammaPrint and EndoPredict tests. Br J Cancer 2020;122:1744-1746.
33. Ragaz J, Ariel IM. High-Risk Breast Cancer: Definition of the Risk. In: Ragaz J, Ariel IM, eds. High-Risk Breast Cancer: Diagnosis, 1989:3-23.
34. Schneeweiss A, Möbus V, Tesch H, et al. Intense dose-dense epirubicin, paclitaxel, cyclophosphamide versus weekly paclitaxel, liposomal doxorubicin (plus carboplatin in triple-negative breast cancer) for neoadjuvant treatment of high-risk early breast cancer (GeparOcto-GBG 84): A randomised phase III trial. Eur J Cancer 2019;106:181-192.
35. AstraZeneca Data on File. OlympiA Clinical Study Protocol. 2020.
36. Hess KR, Esteva FJ. Effect of HER2 status on distant recurrence in early stage breast cancer. Breast cancer research and treatment 2013;137:449-455.
37. Riggio AI, Varley KE, Welm AL. The lingering mysteries of metastatic recurrence in breast cancer. British Journal of Cancer 2021;124:13-26.
38. Holleczek B, Stegmaier C, Radosa JC, et al. Risk of loco-regional recurrence and distant metastases of patients with invasive breast cancer up to ten years after diagnosis – results from a registry-based study from Germany. BMC Cancer 2019;19:520.
39. Thomas R, Williams M, Marshall C, et al. The total hospital and community UK costs of managing patients with relapsed breast cancer. British journal of cancer 2009;100:598-600.
40. Lakhani SR, Van De Vijver MJ, Jacquemier J, et al. The pathology of familial breast cancer: predictive value of immunohistochemical markers estrogen receptor, progesterone receptor, HER-2, and p53 in patients with mutations in BRCA1 and BRCA2. J Clin Oncol 2002;20:2310-8.
41. Giuliano AE, Connolly JL, Edge SB, et al. Breast Cancer-Major changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA Cancer J Clin 2017;67:290-303.
42. AstraZeneca. Lynparza™ approved in the European Union as first-in-class treatment for advanced BRCA-mutated ovarian cancer. Available from: https://www.astrazeneca.com/media-centre/press-releases/2014/lynparza-approved-european-union-brca-mutated-ovarian-cancer-treatment-18122014.html#. 2014.

43. American Association for Cancer Research. FDA Approves First Targeted Therapeutic for BRCA-mutant Breast Cancer. Available at: https://www.aacr.org/blog/2018/01/12/fda-approves-first-targeted-therapeutic-for-brca-mutant-breast-cancer/ (accessed 09/02/2021) 2018.
44. Caulfield S, Davis CC, KF B. Olaparib: A Novel Therapy for Metastatic Breast Cancer in Patients With a BRCA1/2 Mutation. J Adv Pract Oncol 2019;10:167-174.
45. AstraZeneca. Lynparza approved in EU for the treatment of germline BRCA-mutated HER2-negative advanced breast cancer. Available at: https://www.astrazeneca.com/media-centre/press-releases/2019/lynparza-approved-in-eu-for-the-treatment-of-germline-brca-mutated-her2-negative-advanced-breast-cancer-10042019.html (accessed 09/02/2020). 2019.
46. Brewer HR, Jones ME, Schoemaker MJ, et al. Family history and risk of breast cancer: an analysis accounting for family structure. Breast Cancer Res Treat 2017;165:193-200.
47. Meyerson W, Leisman J, Navarro FCP, et al. Origins and characterization of variants shared between databases of somatic and germline human mutations. BMC Bioinformatics 2020;21:227.
48. Gorodetska I, Kozeretska I, Dubrovska A. BRCA Genes: The Role in Genome Stability, Cancer Stemness and Therapy Resistance. Journal of Cancer 2019;10:2109-2127.
49. De Talhouet S, Peron J, Vuilleumier A, et al. Clinical outcome of breast cancer in carriers of BRCA1 and BRCA2 mutations according to molecular subtypes. Scientific reports 2020;10:1-9.
50. Copson ER, Maishman TC, Tapper WJ, et al. Germline *BRCA* mutation and outcome in young-onset breast cancer (POSH): a prospective cohort study. The Lancet Oncology 2018;19:169-180.
51. GLOBOCAN. Estimated age-standardized incidence rates (World) in 2020, breast, females, all ages. Available from: https://gco.iarc.fr/today/home (accessed 12/01/2022), 2020.
52. National Cancer Institute: Surveillance Epidemiology and End Results Program. Cancer Stat Facts: Female Breast Cancer Subtypes. Available at: https://seer.cancer.gov/statfacts/html/breast.html (accessed 06/04/2022). 2020.
53. Jack RH, Davies EA, Renshaw C, et al. Differences in breast cancer hormone receptor status in ethnic groups: a London population. European Journal of Cancer 2013;49:696-702.
54. Whitaker K, Obeid E, Goldstein L, et al. Abstract P6-08-21: Prevalence of HER2 positivity in germline BRCA 1/2-associated breast cancers (gBRCA1/2-BC). Cancer Research 2020;80:P6-08-21-P6-08-21.
55. Evans DG, Lalloo F, Howell S, et al. Low prevalence of HER2 positivity amongst BRCA1 and BRCA2 mutation carriers and in primary BRCA screens. Breast Cancer Res Treat 2016;155:597-601.
56. Maynes DL, Hunt KS, Pockaj BA, et al. Are HER2-positive breast cancer and BRCA mutation-associated breast cancer mutually exclusive diseases? Evidence from the Mayo Clinic Arizona Cohort. 2010. Available at: https://ascopubs.org/doi/10.1200/jco.2010.28.15_suppl.e21075 (accessed 06/03/2022). Journal of Clinical Oncology;28:e21075-e21075.
57. Koh SJ, Ohsumi S, Takahashi M, et al. Prevalence of mutations in BRCA and homologous recombination repair genes and real-world standard of care of Asian patients with HER2-negative metastatic breast cancer starting first-line systemic cytotoxic chemotherapy: subgroup analysis of the global BREAKOUT study. Breast Cancer 2022;29:92-102.
58. O'Shaughnessy J, Brezden-Masley, C., Cazzaniga, M. et al. Prevalence of germline BRCA mutations in HER2-negative metastatic breast cancer: global results from the real-world, observational BREAKOUT study. Breast Cancer Res 2020;22.
59. Howlader N, Altekruse SF, Li CI, et al. US incidence of breast cancer subtypes defined by joint hormone receptor and HER2 status. J Natl Cancer Inst 2014;106.
60. Shao C, Wan J, Tang H, et al. A comprehensive literature review and meta-analysis on prevalence of BRCAm, HRRm and HRD+ across tumor types. Journal of Clinical Oncology 2021;39:10589-10589.

61. Office for National Statistics (ONS). Cancer survival by stage at diagnosis for England (experimental statistics): Adults diagnosed 2012, 2013 and 2014 and followed up to 2015. 2016. Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/cancersurvivalbystageatdiagnosisforenglandexperimentalstatistics/adultsdiagnosed20122013and2014andfollowedupto2015 (Accessed 19th January 2022).
62. National Health Service (NHS) Digital. Breast Screening Programme, England 2019-20. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/breast-screening-programme/england---2019-20. 2021.
63. Cancer Research UK. Breast screening. Available at: https://www.cancerresearchuk.org/about-cancer/breast-cancer/getting-diagnosed/screening/breast-screening (accessed 07/11/2021), 2020.
64. Macmillan Cancer Support. Breast Screening with a Family History of Cancer. Available from https://www.macmillan.org.uk/cancer-information-and-support/worried-about-cancer/screening/breast-cancer-family-history (accessed 20/01/2022).
65. Breast Cancer Now. Facts and statistics 2021. Available at: https://breastcancernow.org/about-us/media/facts-statistics#:~:text=Around%2055%2C000%20women%20and%20370,are%20diagnosed%20with%20breast%20cancer (accessed 07/01/2021), 2021.
66. National Health Service (NHS). Breast cancer in women. Available at: https://www.nhs.uk/conditions/breast-cancer/ (Accessed 19th January 2022).
67. Bodai BI, Tuso P. Breast cancer survivorship: a comprehensive review of long-term medical issues and lifestyle recommendations. The Permanente journal 2015;19:48-79.
68. Breast Cancer Now. Breast cancer symptoms. Available from: https://breastcancernow.org/information-support/have-i-got-breast-cancer/signs-symptoms-breast-cancer.
69. Senkus E, Kyriakides S, Penault-Llorca F, et al. Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology 2013;24:vi7-vi23.
70. West Midlands Expert Advisory Group for Breast Cancer. Clinical Guidelines for the Management of Breast Cancer. 2018. Available at: https://www.england.nhs.uk/mids-east/wp-content/uploads/sites/7/2018/02/guidelines-for-the-management-of-breast-cancer-v1.pdf (accessed 21/01/2022).
71. Forbes C, Fayter D, de Kock S, et al. A systematic review of international guidelines and recommendations for the genetic screening, diagnosis, genetic counseling, and treatment of BRCA-mutated breast cancer. Cancer Manag Res 2019;11:2321-2337.
72. Petrucelli N, Daly MB, Pal T. BRCA1- and BRCA2-Associated Hereditary Breast and Ovarian Cancer. Available at: https://www.ncbi.nlm.nih.gov/books/NBK1247/ (accessed 06/03/2022). In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Mirzaa G, Amemiya A, eds. GeneReviews(®), 1993.
73. Manchanda R, Sun L, Patel S, et al. Economic Evaluation of Population-Based BRCA1/BRCA2 Mutation Testing across Multiple Countries and Health Systems. Cancers (Basel) 2020;12.
74. NICE. NICE health technology evaluations: the manual. Available at: https://www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technology-evaluation (accessed 12/04/2022), 2022.
75. NICE. NICE health technology evaluation topic selection: the manual. Available at: https://www.nice.org.uk/process/pmg37/chapter/about-this-guide (accessed 12/04/2022), 2022.
76. NICE. DG34: Tumour profiling tests to guide adjuvant chemotherapy decisions in early breast cancer. 2018. Available from: https://www.nice.org.uk/guidance/dg34/chapter/1-Recommendations (accessed 04/03/2022).
77. Groenvold M. Health-related quality of life in early breast cancer. Dan Med Bull 2010;57:B4184.

78. Boivin MJ, Sikorskii A, Haan P, et al. Health-Related Quality of Life: Longitudinal Analysis From the Time of Breast Biopsy Into the Post-treatment Period. Frontiers in Global Women's Health 2021;2.
79. Sun L, Cromwell D, Dodwell D, et al. Costs of Early Invasive Breast Cancer in England Using National Patient-Level Data. Value in Health 2020;23:1316-1323.
80. Seferina SC, Ramaekers BLT, de Boer M, et al. Cost and cost-effectiveness of adjuvant trastuzumab in the real world setting: A study of the Southeast Netherlands Breast Cancer Consortium. Oncotarget 2017;8:79223-79233.
81. Oh S, Heflin L, Meyerowitz BE, et al. Quality of life of breast cancer survivors after a recurrence: a follow-up study. Breast Cancer Research and Treatment 2004;87:45-57.
82. Hamer J, McDonald R, Zhang L, et al. Quality of life (QOL) and symptom burden (SB) in patients with breast cancer. Support Care Cancer 2017;25:409-419.
83. Reed E, Simmonds P, Haviland J, et al. Quality of Life and Experience of Care in Women With Metastatic Breast Cancer: A Cross-Sectional Survey. Journal of Pain and Symptom Management 2012;43:747-758.
84. Rautalin M, Färkkilä N, Sintonen H, et al. Health-related quality of life in different states of breast cancer–comparing different instruments. Acta Oncologica 2018;57:622-628.
85. Foster TS, Miller JD, Boye ME, et al. The economic burden of metastatic breast cancer: a systematic review of literature from developed countries. Cancer treatment reviews 2011;37:405-415.
86. Yin W, Horblyuk R, Perkins JJ, et al. Association between breast cancer disease progression and workplace productivity in the United States. Journal of occupational and environmental medicine 2017;59:198-204.
87. Song Y, Barry WT, Seah DS, et al. Patterns of recurrence and metastasis in BRCA1/BRCA2-associated breast cancers. Cancer 2020;126:271-280.
88. Cheung EL, Olson AD, Yu TM, et al. Communication of *BRCA* Results and Family Testing in 1,103 High-Risk Women. Cancer Epidemiology, Biomarkers & Prevention 2010;19:2211-2219.
89. Koehly LM, Peters JA, Kuhn N, et al. Sisters in hereditary breast and ovarian cancer families: communal coping, social integration, and psychological well-being. Psychooncology 2008;17:812-21.
90. Laudicella M, Walsh B, Burns E, et al. Cost of care for cancer patients in England: evidence from population-based patient-level data. British journal of cancer 2016;114:1286-1292.
91. FDA. Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics: Guidance for Industry. Accessed 13/02/2022, 2018.
92. EMA. Guideline on the clinical evaluation of anticancer medicinal products. 2021. Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-evaluation-anticancer-medicinal-products-man-revision-6_en.pdf. Accessed 12.01.2022.
93. Neate C, Strasak A, Burger HU, et al. Challenges with overall survival as an endpoint for efficacy assessment in first line metastatic breast cancer randomized controlled clinical trials and the investigation of truncated overall survival as an alternative endpoint. memo - Magazine of European Medical Oncology 2014;7:162-168.
94. McCrea C, Chatzidaki I, Drane E, et al. PCN24 Disease-Free Survival (DFS) As a Surrogate Endpoint for Overall Survival (OS) in HER2 Negative (HER2–) Primary Breast Cancer (BC). Value in Health 2020;23:S425.
95. Saad ED, Squifflet P, Burzykowski T, et al. Disease-free survival as a surrogate for overall survival in patients with HER2-positive, early breast cancer in trials of adjuvant trastuzumab for up to 1 year: a systematic review and meta-analysis. The Lancet. Oncology 2019;20:361-370.
96. Savina M, Jacot W, Mathoulin-Pélissier S, et al. Surrogate endpoints for overall survival in randomized controlled trials evaluating adjuvant treatment for breast cancer: A meta-analysis. Annals of Oncology 2017;28:v48.
97. Gelmon KA, Fasching PA, Couch F, et al. Real-world clinical effectiveness and safety of olaparib monotherapy in HER2-negative gBRCA-mutated metastatic breast cancer: Phase IIIb LUCY interim analysis. Journal of Clinical Oncology 2020;38:1087-1087.

98. Cleeland CS, Mayer M, Dreyer NA, et al. Impact of symptom burden on work-related abilities in patients with locally recurrent or metastatic breast cancer: Results from a substudy of the VIRGO observational cohort study. Breast 2014;23:763-9.
99. Dent R, Valentini A, Hanna W, et al. Factors associated with breast cancer mortality after local recurrence. Current oncology (Toronto, Ont.) 2014;21:e418-e425.
100. NICE. TA632: Trastuzumab emtansine for adjuvant treatment of HER2-positive early breast cancer. 2020. Available from: https://www.nice.org.uk/guidance/ta632 (accessed 09/02/2022).
101. NICE. TA569: Pertuzumab for adjuvant treatment of HER2-positive early stage breast cancer. 2019. Available from: https://www.nice.org.uk/guidance/ta569 (accessed 09/02/2022).
102. NICE. TA612: Neratinib for extended adjuvant treatment of hormone receptor-positive, HER2-positive early stage breast cancer after adjuvant trastuzumab. 2019. Available from: https://www.nice.org.uk/guidance/ta612 (accessed 09/02/2022).
103. Voogd AC, Nielsen M, Peterse JL, et al. Differences in risk factors for local and distant recurrence after breast-conserving therapy or mastectomy for stage I and II breast cancer: pooled results of two large European randomized trials. J Clin Oncol 2001;19:1688-97.
104. Cancer Research UK. Breast cancer survival statistics. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer/survival (accessed 12/03/2022), 2021.
105. Tutt A, Garber JE, Kaufman B, et al. OlympiA: A phase III, multicenter, randomized, placebo-controlled trial of adjuvant olaparib after (neo)adjuvant chemotherapy in patients with germline BRCA1/2 mutations and high-risk HER2-negative early breast cancer. Journal of Clinical Oncology 2021;39:LBA1-LBA1.
106. Rastogi P, Toi M, Martin M, et al. Abstract OT2-02-02: MONARCH E: A phase 3 study of standard adjuvant endocrine therapy with or without abemaciclib in patients with high risk, node positive, hormone-receptor positive, human epidermal growth factor receptor 2-negative early-stage breast cancer. Cancer Research 2020;80:OT2-02-02-OT2-02-02.
107. Sheffield KM, Peachey JR, Method MW, et al. Recurrence risk in early breast cancer as defined by clinicopathologic features. Journal of Clinical Oncology 2021;39:e18581-e18581.
108. Holleczek B, Stegmaier C, Radosa JC, et al. Risk of loco-regional recurrence and distant metastases of patients with invasive breast cancer up to ten years after diagnosis - results from a registry-based study from Germany. BMC cancer 2019;19:520-520.
109. Sopik V, Sun P, Narod SA. Predictors of time to death after distant recurrence in breast cancer patients. Breast Cancer Res Treat 2018;173:465-474.
110. van Maaren MC, de Munck L, Strobbe LJA, et al. Ten-year recurrence rates for breast cancer subtypes in the Netherlands: A large population-based study. Int J Cancer 2019;144:263-272.
111. Force J P, J., Stashko, I., et al. Distinct biological signatures describe differences in BRCA mutated subgroups. American Association for Cancer Research 2018.
112. Quek R, Mardekian J, Burk C. Germline BRCA mutations (gBRCAmut) on breast cancer (BC) outcomes: A large meta-analysis. Journal of Clinical Oncology 2018;36:e12575-e12575.
113. Lal A, Ramazzotti D, Weng Z, et al. Comprehensive genomic characterization of breast tumors with BRCA1 and BRCA2 mutations. BMC Medical Genomics 2019;12:84.
114. National Institute for Health and Care Excellence. 2020. Trastuzumab emtansine for adjuvant treatment of HER2-positive early breast cancer [TA632]. Available at: https://www.nice.org.uk/guidance/ta632 (Accessed 19th January 2022).
115. NICE. TA598: Olaparib for maintenance treatment of BRCA mutation-positive advanced ovarian, fallopian tube or peritoneal cancer after response to first-line platinum-based chemotherapy. 2019. Available from: https://www.nice.org.uk/guidance/ta598 (accessed 21/01/2022).
116. NICE. TA620: Olaparib for maintenance treatment of relapsed platinum-sensitive ovarian, fallopian tube or peritoneal cancer. 2020. Available from: https://www.nice.org.uk/guidance/ta620 (accessed 21/01/2022).
117. NICE. TA693: Olaparib plus bevacizumab for maintenance treatment of advanced ovarian, fallopian tube or primary peritoneal cancer. 2021. Available from: https://www.nice.org.uk/guidance/ta693 (accessed 21/01/2022).
118. AstraZeneca Data on File. Core Data Sheet. Lynparza 100 mg, 150 mg tablets. 2018.

119. Sousa FG, Matuo R, Soares DG, et al. PARPs and the DNA damage response. Carcinogenesis 2012;33:1433-40.
120. Megnin-Chanet F, Bollet MA, Hall J. Targeting poly(ADP-ribose) polymerase activity for cancer therapy. Cell Mol Life Sci 2010;67:3649-62.
121. Sugimura K, Takebayashi S, Taguchi H, et al. PARP-1 ensures regulation of replication fork progression by homologous recombination on damaged DNA. J Cell Biol 2008;183:1203-12.
122. Tuffaha HW, Mitchell A, Ward RL, et al. Cost-effectiveness analysis of germ-line BRCA testing in women with breast cancer and cascade testing in family members of mutation carriers. Genet Med 2018;20:985-994.
123. AstraZeneca Data on File. Pharmacological Therapies In Non Metastatic, Primary, Invasive HER2-Negative Breast Cancer: Clinical Systematic Literature Review Report. 2021.
124. AstraZeneca. Lynparza reduced risk of death by 32% in the adjuvant treatment of patients with germline BRCA-mutated high-risk early breast cancer. Available at: https://www.astrazeneca.com/media-centre/press-releases/2022/lynparza-reduced-risk-of-death-by-32-percent-in-the-adjuvant-treatment-of-patients-with-germline-brca-mutated-high-risk-early-breast-cancer.html (accessed 22/03/2021), 2022.
125. Tutt A, Stephens C, Frewer P, et al. VIOLETTE: A randomized phase II study to assess the DNA damage response inhibitors AZD6738 or AZD1775 in combination with olaparib (Ola) versus Ola monotherapy in patients (pts) with metastatic, triple-negative breast cancer (TNBC). Journal of Clinical Oncology 2019;37:TPS1112-TPS1112.
126. Robson ME, Tung N, Conte P, et al. OlympiAD final overall survival and tolerability results: Olaparib versus chemotherapy treatment of physician's choice in patients with a germline BRCA mutation and HER2-negative metastatic breast cancer. Ann Oncol 2019;30:558-566.
127. Tung NM, Robson ME, Ventz S, et al. TBCRC 048: Phase II Study of Olaparib for Metastatic Breast Cancer and Mutations in Homologous Recombination-Related Genes. J Clin Oncol 2020;38:4274-4282.
128. A.N.J. Tutt JG, R.D. Gelber, K-A. Phillips, A. Eisen, O.T. Johannsson. VP1-2022: Pre-specified event driven analysis of Overall Survival (OS) in the OlympiA phase III trial of adjuvant olaparib (OL) in germline BRCA1/2 mutation (gBRCAm) associated breast cancer. ESMO Virtual Plenary 2022.
129. AstraZeneca Data on File. Global OlympiA Advisory Board Report. 2021.
130. Martinez-Delgado B, Yanowsky K, Inglada-Perez L, et al. Genetic anticipation is associated with telomere shortening in hereditary breast cancer. PLoS Genetics 2011;7:e1002182-e1002182.
131. Cortazar P, Zhang L, Untch M, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet 2014;384:164-72.
132. Zetterlund L, Celebioglu F, Hatschek T, et al. Long-term prognosis in breast cancer is associated with residual disease after neoadjuvant systemic therapy but not with initial nodal status. British Journal of Surgery 2021;108:583-589.
133. NICE. TA632: Trastuzumab emtansine for adjuvant treatment of HER2-positive early breast cancer [ID1516]. Committee Papers. 2020. Available from: https://www.nice.org.uk/guidance/ta632/evidence/committee-papers-pdf-8771187997 (accessed 16/03/2022).
134. NICE. TA612: Neratinib for extended adjuvant treatment of hormone receptor-positive, HER2-positive early stage breast cancer after adjuvant trastuzumab [ID981]. Committee Papers. 2019. Available from: https://www.nice.org.uk/guidance/ta612/evidence/appraisal-consultation-committee-papers-pdf-6967189694 (accessed 16/03/2022).
135. NICE. TA569: Pertuzumab for adjuvant treatment of HER2-positive early breast cancer [ID1192]. Committee Papers. 2018. Available from: https://www.nice.org.uk/guidance/ta569/evidence/appraisal-consultation-1-committee-papers-pdf-6720470173 (accessed 16/03/2022).
136. AstraZeneca Data on File. Draft Summary Of Product Characteristics: Olaparib 100 mg and 150 mg film-coated tablets. 2021.

137. NICE. TA639: Atezolizumab with nab-paclitaxel for untreated PD-L1-positive, locally advanced or metastatic, triple-negative breast cancer. 2020. Available from: https://www.nice.org.uk/guidance/ta639 (accessed 09/02/2022).
138. NICE. TA725: Abemaciclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy. 2021. Available from: https://www.nice.org.uk/guidance/ta725 (accessed 16/03/2022).
139. NICE. TA619: Palbociclib with fulvestrant for treating hormone receptor-positive, HER2-negative, advanced breast cancer. 2020. Available from: https://www.nice.org.uk/guidance/ta619 (accessed 16/03/2022).
140. NICE. TA687: Ribociclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy. 2021. Available from: https://www.nice.org.uk/guidance/ta687 (accessed 16/03/2022).
141. Woods BS, Sideris E, Palmer SJ, et al. NICE DSU technical support document 19: Partitioned survival analysis for decision modelling in health care: a critical review. 2017:72.
142. NICE. TA424: Pertuzumab for the neoadjuvant treatment of HER2-positive breast cancer [ID767]. Committee Papers. 2016. Available from: https://www.nice.org.uk/guidance/ta424/documents/committee-papers-2 (accessed 16/03/2022).
143. McKenzie HS, Maishman T, Simmonds P, et al. Survival and disease characteristics of de novo versus recurrent metastatic breast cancer in a cohort of young patients. Br J Cancer 2020;122:1618-1629.
144. Lobbezoo DJA, van Kampen RJW, Voogd AC, et al. Prognosis of metastatic breast cancer: are there differences between patients with de novo and recurrent metastatic breast cancer? British journal of cancer 2015;112:1445-1451.
145. Dawood S, Broglio K, Ensor J, et al. Survival differences among women with de novo stage IV and relapsed breast cancer. Ann Oncol 2010;21:2169-2174.
146. Lloyd A, Nafees B, Narewska J, et al. Health state utilities for metastatic breast cancer. Br J Cancer 2006;95:683-90.
147. Lidgren M, Wilking N, Jönsson B, et al. Health related quality of life in different states of breast cancer. Quality of life research 2007;16:1073-1081.
148. Robson ME, Ruddy KJ, Im S-A, et al. Patient-reported outcomes in patients with a germline BRCA mutation and HER2-negative metastatic breast cancer receiving olaparib versus chemotherapy in the OlympiAD trial. European journal of cancer (Oxford, England : 1990) 2019;120:20-30.
149. Collins JM, Nordstrom BL, McLaurin KK, et al. A Real-World Evidence Study of CDK4/6 Inhibitor Treatment Patterns and Outcomes in Metastatic Breast Cancer by Germline BRCA Mutation Status. Oncol Ther 2021;9:575-589.
150. Emens LA, Molinero L, Loi S, et al. Atezolizumab and nab-Paclitaxel in Advanced Triple-Negative Breast Cancer: Biomarker Evaluation of the IMpassion130 Study. J Natl Cancer Inst 2021;113:1005-1016.
151. Office for National Statistics. National life tables: UK. Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesunitedkingdomreferencetables (accessed 17/03/2022), 2021.
152. Mai PL, Chatterjee N, Hartge P, et al. Potential excess mortality in BRCA1/2 mutation carriers beyond breast, ovarian, prostate, and pancreatic cancers, and melanoma. PloS One 2009;4:e4812-e4812.
153. Taylor AM, Chan DH, Tio M, et al. PARP (Poly ADP-Ribose Polymerase) inhibitors for locally advanced or metastatic breast cancer. Cochrane Database of Systematic Reviews 2021.
154. Putter H, Fiocco M, Geskus RB. Tutorial in biostatistics: competing risks and multi-state models. Stat Med 2007;26:2389-430.
155. Latimer NR. Survival analysis for economic evaluations alongside clinical trials -- extrapolation with patient-level data: inconsistencies, limitations, and a practical guide. Med Decis Making 2013;33:743-54.

156. Reddy SM, Barcenas CH, Sinha AK, et al. Long-term survival outcomes of triple-receptor negative breast cancer survivors who are disease free at 5 years and relationship with low hormone receptor positivity. Br J Cancer 2018;118:17-23.
157. NICE. TA598: Olaparib for maintenance treatment of BRCA mutated ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy [ID1124]. Committee Papers: Available at: https://www.nice.org.uk/guidance/ta598/evidence/committee-papers-pdf-6898280077 (accessed 17/03/2022), 2019.
158. Chen X, Yu X, Chen J, et al. Radiotherapy can improve the disease-free survival rate in triple-negative breast cancer patients with T1-T2 disease and one to three positive lymph nodes after mastectomy. Oncologist 2013;18:141-7.
159. Hahnen E, Lederer B, Hauke J, et al. Germline Mutation Status, Pathological Complete Response, and Disease-Free Survival in Triple-Negative Breast Cancer: Secondary Analysis of the GeparSixto Randomized Clinical Trial. JAMA Oncology 2017;3:1378-1385.
160. Abrial C, Wang-Lopez Q, Mouret-Reynier M, et al. Long-Term Overall Survival (OS) and Disease-Free Survival (DFS) According to PCR in Breast Cancers Subtypes: Luminal A and B, Triple Negative and HER2 +, Treated by Neaodjuvant Chemotherapy (NCT). Annals of Oncology 2012;23:ix102.
161. Early Breast Cancer Trialists' Collaborative Group. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005;365:1687-1717.
162. Bayraktar S, Gutierrez-Barrera AM, Liu D, et al. Outcome of triple-negative breast cancer in patients with or without deleterious BRCA mutations. Breast Cancer Res Treat 2011;130:145-53.
163. Borges GS, Colchon PH, Staak MC, et al. Analysis of Disease-free Survival and Overall Survival in Patients with Luminal A Breast Cancer Stratified According to TNM. Klin Onkol 2014;27:178-182.
164. Anderson SJ, Wapnir I, Dignam JJ, et al. Prognosis after ipsilateral breast tumor recurrence and locoregional recurrences in patients treated by breast-conserving therapy in five National Surgical Adjuvant Breast and Bowel Project protocols of node-negative breast cancer. J Clin Oncol 2009;27:2466-73.
165. Braunstein LZ, Niemierko A, Shenouda MN, et al. Outcome following local-regional recurrence in women with early-stage breast cancer: impact of biologic subtype. Breast J 2015;21:161-7.
166. McCrea C, Hettle R, Gulati P, et al. Indirect treatment comparison of olaparib and talazoparib in germline BRCA-mutated HER2-negative metastatic breast cancer. J Comp Eff Res 2021;10:1021-1030.
167. Gennari A, André F, Barrios CH, et al. ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. Ann Oncol 2021;32:1475-1495.
168. Schmid P, Adams S, Rugo HS, et al. Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer. New England Journal of Medicine 2018;379:2108-2121.
169. NICE. TA762: Olaparib for treating BRCA mutation-positive HER2-negative metastatic breast cancer after chemotherapy (terminated appraisal). Available at: https://www.nice.org.uk/guidance/TA762 (accessed 17/03/2022). 2022.
170. Crott R, Briggs A. Mapping the QLQ-C30 quality of life cancer questionnaire to EQ-5D patient preferences. Eur J Health Econ 2010;11:427-34.
171. Longworth L, Yang Y, Young T, et al. Use of generic and condition-specific measures of health-related quality of life in NICE decision-making: a systematic review, statistical modelling and survey. Health Technol Assess 2014;18:1-224.
172. NICE. TA432: Everolimus for the second-line treatment of metastatic renal cell carcinoma (review of TA219). Committee Papers. Available at: https://www.nice.org.uk/guidance/ta432/documents/committee-papers-5 (accessed 17/03/2022). 2016.

173. Conner-Spady B, Cumming C, Nabholtz JM, et al. A longitudinal prospective study of health-related quality of life in breast cancer patients following high-dose chemotherapy with autologous blood stem cell transplantation. Bone Marrow Transplant 2005;36:251-9.
174. Conner-Spady B, Cumming C, Nabholtz JM, et al. Responsiveness of the EuroQol in breast cancer patients undergoing high dose chemotherapy. Qual Life Res 2001;10:479-86.
175. Criscitiello C, Spurden D, Piercy J, et al. Health-Related Quality of Life Among Patients With HR+/HER2- Early Breast Cancer. Clin Ther 2021;43:1228-1244.e4.
176. van Hout B, Janssen MF, Feng YS, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. Value in Health 2012;15:708-15.
177. Verrill M, Wardley AM, Retzler J, et al. Health-related quality of life and work productivity in UK patients with HER2-positive breast cancer: a cross-sectional study evaluating the relationships between disease and treatment stage. Health Qual Life Outcomes 2020;18:353.
178. NICE. TA501: MTA Breast cancer (early) - Intrabeam IORT [ID618]. Committee papers. Available at: https://www.nice.org.uk/guidance/ta501/documents/committee-papers (accessed 17/03/2022). 2013.
179. Hsu T, Ennis M, Hood N, et al. Quality of life in long-term breast cancer survivors. J Clin Oncol 2013;31:3540-8.
180. Sullivan J, Snider J, van Eijndhoven E, et al. The Well-Being of Long-Term Cancer Survivors. Am J Manag Care 2018;24:188-195.
181. Kaur MN, Yan J, Klassen AF, et al. A Systematic Literature Review of Health Utility Values in Breast Cancer. Med Decis Making 2022:272989x211065471.
182. Grann VR, Patel PR, Jacobson JS, et al. Comparative effectiveness of screening and prevention strategies among BRCA1/2-affected mutation carriers. Breast Cancer Res Treat 2011;125:837-47.
183. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. Value Health 2010;13:509-18.
184. NICE. TA563: Abemaciclib with an aromatase inhibitor for untreated advanced hormonereceptor positive, HER2-negative breast cancer [ID1227]. Committee Papers. Available at: https://www.nice.org.uk/guidance/ta563/documents/committee-papers-2 (accessed 17/03/2022). 2018.
185. Nafees B, Stafford M, Gavriel S, et al. Health state utilities for non small cell lung cancer. Health Qual Life Outcomes 2008;6:84.
186. UK Government. Drugs and pharmaceutical electronic market information tool (eMIT). Available at: https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit (accessed 17/03/2022), 2021.
187. A.W.B. H, M. M, E. H, et al. 5793 - Real world treatment sequencing patterns in secondary breast cancer (SBC): Pathway visualisation using national datasets. ESMO 2019.
188. British National Formulary. Abemaciclib. Available at: https://bnf.nice.org.uk/medicinal-forms/abemaciclib.html (accessed 17/03/2022).
189. British National Formulary. Palbociclib. Available at: https://bnf.nice.org.uk/medicinal-forms/palbociclib.html (accessed 17/03/2022).
190. British National Formulary. Ribociclib. Available at: https://bnf.nice.org.uk/medicinal-forms/ribociclib.html (accessed 17/03/2022).
191. British National Formulary. Atezolizumab. Available at: https://bnf.nice.org.uk/medicinal-forms/atezolizumab.html (accessed 17/03/2022).
192. NHS England. Carboplatin, 2020.
193. NHS England. Cyclophosphamide-Docetaxel-Doxorubicin. Available at: https://www.uhs.nhs.uk/Media/UHS-website-2019/Docs/Chemotherapy-SOPs1/Breastcancer/BreastCyclophosphamideDocetaxelDoxorubicinTACVer11.pdf (accessed 13/04/2022), 2014.
194. Robertson JFR, Bondarenko IM, Trishkina E, et al. Fulvestrant 500 mg versus anastrozole 1 mg for hormone receptor-positive advanced breast cancer (FALCON): an international, randomised, double-blind, phase 3 trial. The Lancet 2016;388:2997-3005.

195. NHS England. Paclitaxel. Avaliable at: https://www.uhs.nhs.uk/Media/UHS-website-2019/Docs/Chemotherapy-SOPs1/Breastcancer/Paclitaxel-21-day.pdf (accessed 13/04/2022), 2020.
196. Thames Valley Cancer Alliance. Docetaxel. Available at: https://thamesvalleycanceralliance.nhs.uk/wp-content/uploads/2021/06/Docetaxel-5.2.pdf (accessed 13/04/2022, 2021.
197. Goetz MP, Toi M, Campone M, et al. MONARCH 3: Abemaciclib As Initial Therapy for Advanced Breast Cancer. Journal of Clinical Oncology 2017;35:3638-3646.
198. NHS England. Everolimus and Exemestane. Available at: https://www.uhs.nhs.uk/Media/SUHTExtranet/Services/Chemotherapy-SOPs/Breastcancer/Everolimus-Exemestane.pdf (accessed 13/04/2022), 2018.
199. Belkacemi Y, Hanna NE, Besnard C, et al. Local and Regional Breast Cancer Recurrences: Salvage Therapy Options in the New Era of Molecular Subtypes. Front Oncol 2018;8:112.
200. NICE. CG81: Advanced breast cancer: diagnosis and treatment. Available from: https://www.nice.org.uk/guidance/cg81 (accessed 17/03/2022). 2017.
201. NHS England. 2019/20 Reference Costs. Available at: https://www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/#ncc1819 (accessed 17/03/2022), 2021.
202. PSSRU. Unit Costs of Health and Social Care 2021. Available at: https://kar.kent.ac.uk/92342/19/Unit%20Costs%20Report%202021%20-%20Final%20version%20for%20publication.pdf (accessed 17/03/2022). 2021.
203. Macmillan Cancer Support. The cost of Macmillan's services fact sheet. 2021.

BRISTOL TAG

EVIDENCE FOR DECISION MAKERS

National Institute for Health and Care Excellence

Health technology evaluation

Olaparib for adjuvant treatment of high-risk HER2-negative, BRCA-positive early breast cancer after chemotherapy [ID3893]

Company Response to Clarification Questions

June 2022

File name	Version	Contains confidential information	Date
ID3893 Olaparib Clarification Question Responses_ACIC REDACTED	1	Yes	01/06/2022

Section A: Clarification on effectiveness data

Data/Results

A1. **Priority Question**: When will the data for the primary analysis data cut be available?

Data for the primary analysis data cut (data cut-off [DCO] 2) have recently become available; an overview of data from DCO2 has been provided in Appendix 1 for the Evidence Assessment Group's (EAG's) reference.

A2. **Priority Question:** It is stated that the analysis presented in the NEJM paper was "at a prespecified event-driven interim analysis". However, the methods suggest that the number of events for the primary analysis were 330 events of invasive disease or death in the intention-to-treat (ITT) population with an interim analysis at 165 events. However, the data reported in both the company submission and NEJM article are at 284 events. Why was the analysis conducted at this point rather than the earlier pre-specified timepoint?

The primary analysis of invasive disease-free survival (iDFS) was planned to be performed when 330 iDFS events had occurred in all randomised patients, whilst the interim analysis of iDFS was protocolled to occur when half of the events required for the primary iDFS analysis (165 events) had been observed from the first 50% of patients randomised (i.e., from the first 900 patients, the "mature cohort"). The iDFS interim analysis was to be performed on all patients, whilst additionally providing a cohort of 900 patients with a similar level of maturity to that planned for the primary iDFS analysis (see Clinical Study Report [CSR] Section 9.8.4 for further information).[1]

At the time of the interim analysis, the number of events in the mature cohort (first 50% of patients recruited) was 169 and the corresponding number of events amongst the intent-to-treat (ITT) population was 284. Upon review of the interim analysis, the independent data monitoring committee (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.

A3. **Priority Question:** Please provide quality of life (QoL) data stratified by recurrence type - metastatic cancer; disease free and non-metastatic recurrence.

Table 1 presents the European Organisation for Research and Treatment of Cancer, quality of life questionnaire (EORTC QLQ)-C30 mapping summary by recurrence state. Please note that this analysis has extremely low numbers, with [redacted] and [redacted] records available after disease recurrence for olaparib and placebo, respectively. This was expected as the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue and EORTC QLQ-C30 were completed at baseline, and then every 6 months for a period of 2 years. Given the high iDFS rates and the fact that compliance with questionnaires was [redacted] in both arms at 24 months, there was a very small volume of patients in the recurrent settings who completed these questionnaires ([redacted]; see page 190 of the Clinical Study Report [CSR]).[1] These data are currently the most appropriate that AstraZeneca have available to answer this question, although AstraZeneca are aware that the small sample size limits the extent to which it is informative.

As outlined in Document B, Section 3.4.1, in the absence of EQ-5D-3L or -5L data, health state utility (HSU) values for the OlympiA trial were estimated by mapping from the EORTC QLQ-C30 data using published algorithms. These data were considered the most robust and applicable source of HSU data for the iDFS state in the economic model given they are based on health-related quality of life (HRQoL) data collected in patients with high-risk, breast cancer susceptibility gene mutated (*BRCA*m) early breast cancer (eBC). As data were only routinely collected every 6 months up to recurrence or for a maximum of 2 years in OlympiA, the HSUs for adverse events (AEs), metastatic and non-metastatic BC had to be sourced from external data sources, including past National Institute for Health and Care Excellence (NICE) evaluations and empirical literature.

Table 1: EORTC QLQ-C30 mapping summary by recurrence state

	Treatment	N	Mean	SD	Median	Min.	Max.
Baseline	Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-baseline, recurrence-free	Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-baseline, post-recurrence	Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer, quality of life questionnaire-C30; max: maximum; min: minimum; SD: standard deviation.

A4. Why are hazard rates reported as the primary results when the proportional hazards assumption has been shown not to hold? We note that individual curves are included in the economic model for this reason, but primary results are still based on hazard ratios.

Hazard ratios have been presented as the primary results in the clinical sections of the submission in line with standard practice. Additionally, this is consistent with the OlympiA Statistical Analysis Plan (SAP).

A5. Please could you provide additional data on the number of patients at risk at each 6-month time point in the survival analyses for invasive disease-free survival (iDFS) and distant disease-free survival (dDFS) and the reasons for dropouts/censoring between time points.

The number of patients at risk at each time point, including the 6-monthly time points, is reported alongside the Kaplan-Meier curves for iDFS and distant disease-free survival (dDFS); please refer to Appendix 1 (Figure 7 and Figure 8) for the numbers at risk based on DCO2.

AstraZeneca have limited information regarding the reasons for dropouts/censoring between 6-month timepoints, and do not have summaries of this information. However, an overall summary of censoring for DCO2 are presented in Table 2.

Table 2. Analysis of iDFS, DCO2 (FAS)

	Olaparib (N=921)	Placebo (N=915)
Olaparib vs placebo		
Number of events	134 (14.5%)	207 (22.6%)
Hazard ratio (95% CI; p-value [log-rank])[a]	0.63 (0.50–0.78; [redacted]	
Median clinical follow-up time, years (minimum, maximum)	[redacted]	[redacted]
Censored[b]	[redacted]	[redacted]
Special cases censored at 0.5d (note 'counted in first subcategory that applies')[c]	[redacted]	[redacted]
Event prior to randomisation	[redacted]	[redacted]
Inadvertent randomisation	[redacted]	[redacted]
Patient withdrew consent, not treated, not followed-up	[redacted]	[redacted]
Clinical follow-up ended	[redacted]	[redacted]
Completed study follow-up at protocol-defined end of study[d]	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]
Patient withdrew consent	[redacted]	[redacted]
Patient being followed up for survival only	[redacted]	[redacted]
Patient withdrew but being followed up for survival	[redacted]	[redacted]
Completed 10-year visit and being followed up for survival[e]	[redacted]	[redacted]
Other	[redacted]	[redacted]
Clinical follow-up ongoing	[redacted]	[redacted]

Footnotes: DCO2: 12 July 2021. [a]Exploratory, not inferential. [b]Patients who have not had a recorded iDFS event at the time of the analysis were censored at the date of their last disease evaluation. Disease evaluation includes mammogram and/or breast MRI (MRI preferred for patients younger than 50 years), other radiological/imaging examination or clinical examination (e.g. physical exam). [c]These randomised patients are counted in the FAS. However these patients are treated as being censored for the iDFS event just after randomisation. Censoring these patients at day 0.5 does not affect the log-rank test. The reason for censoring at day 0.5 is to avoid ties with other patients censored on day 1. [d]Completed study at the protocol defined end of study, 10 years after the last patient has been randomised. [e]Patients will have clinical assessment visits for approximately 10 years following their randomisation if an iDFS endpoint due to distant breast cancer relapse has not been met.
Abbreviations: CI: confidence intervals; DCO: data cut-off; FAS: full analysis set; MRI: magnetic resonance imaging.
Source: AstraZeneca Data on File (Interim analysis of OS in OlympiA [DCO2]);[2] Tutt et al. 2022.[3]

A6. Please clarify whether a sensitivity analysis was undertaken to show that the results for objective outcomes were not biased by missing data. If not, why this was not conducted?

A sensitivity analysis of iDFS using interval censoring was performed to assess possible evaluation-time bias that may be introduced if assessments are not performed at the protocol-scheduled time points (see CSR Section 9.8.1.6 for full description of approach).[1] The results of these sensitivity analyses were consistent with the primary analysis of iDFS (see Table 32 and Table 35 of the CSR).[1]

A7. At the 27 Mar 2020 data cut-off (DCO), section B.2.6.2.2 for overall survival (OS) states there was “a 31.7% reduction in risk of death observed for patients treated with olaparib in comparison with placebo (hazard ratio: 0.68; 99% confidence interval [CI]: 0.44, 1.05; p=0.0236; Table 14, Figure 11).” At the second interim analysis for OS on 12 July 2021 DCO, “statistical significance was reached in this key secondary endpoint (hazard ratio: 0.68; 98.5% CI 0.47-0.97; p=0.009)”. Please clarify why a 98.5% CI was used for this second interim analysis for OS, and why this differs to the 99.5% CI or 95% CI used for other results in the submission.

As per the pre-specified OlympiA SAP, the confidence intervals for alpha-controlled endpoints (iDFS, dDFS and overall survival [OS]) were presented according to the significance level applied. For the hazard ratio for OS at DCO1, 99% confidence intervals are shown because a p value of <0.01 was required to indicate statistical significance.[4] Similarly, at DCO2, 98.5% confidence intervals are shown for the hazard ratio of OS because a p value of <0.015 was required.

A8. Please could you provide patient characteristics of those who completed and those who did not complete the QoL questionnaires at each time point.

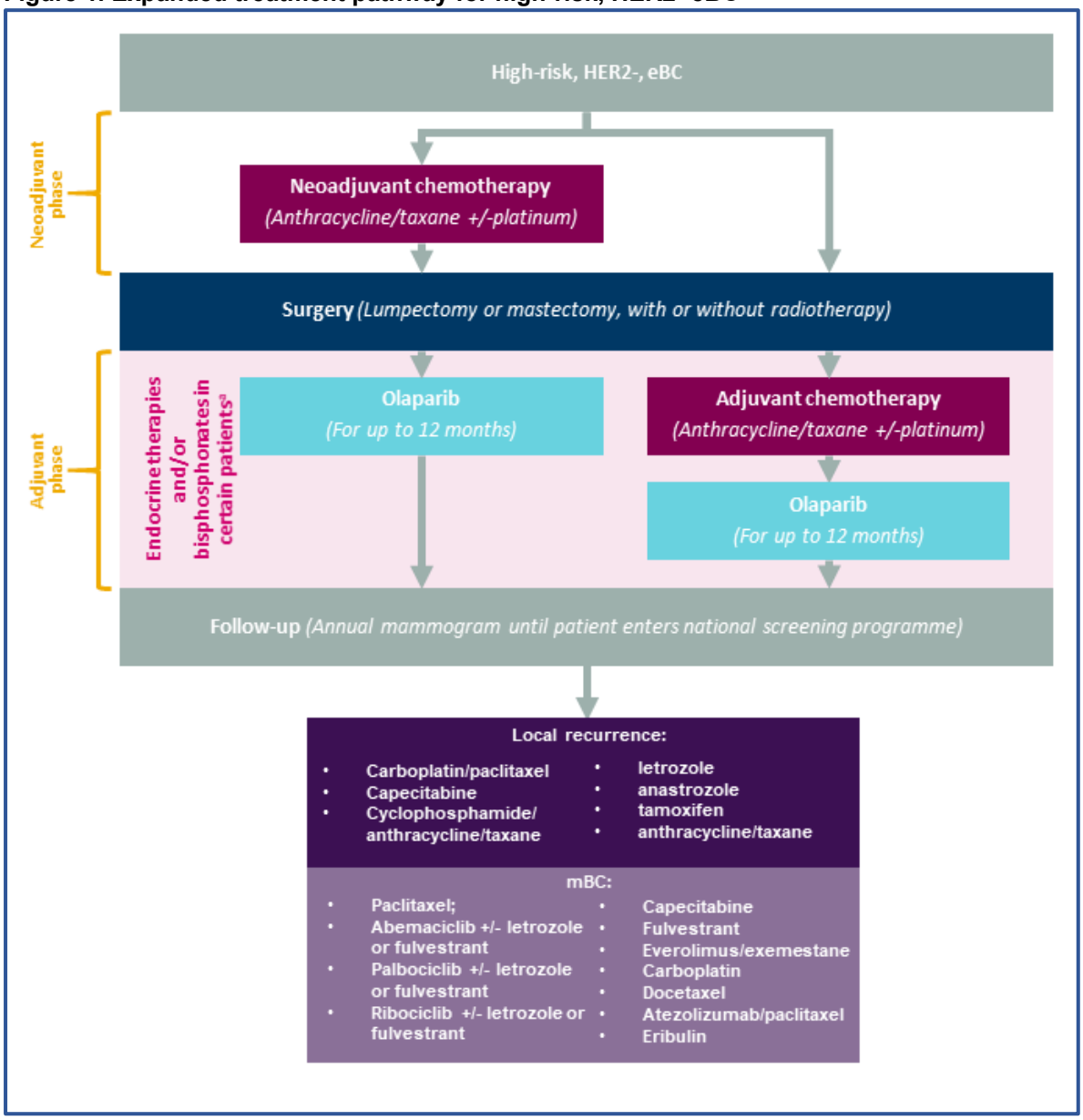
There is difficulty in dividing participants from OlympiA into those who completed (‘responders’) and did not complete (‘non-responders’) the HRQoL questionnaires, as multiple rounds of questionnaires were undertaken in the trial. AstraZeneca have not analysed this data by patient characteristics for responders and non-responders for each questionnaire round individually. However, AstraZeneca have provided updated patient-reported outcome (PRO) data from DCO2 in Appendix 1.

Treatment pathway

A9. **Priority Question**: The economic model considers treatments post olaparib but the treatment pathway stops at olaparib. Please expand the treatment pathway to match what is modelled.

Please see Figure 1 for an expanded treatment pathway. The metastatic pathway is too complex to comprehensively define the treatment sequence; therefore, as described in Document B, Section 3.10, clinical inputs including subsequent treatment splits were compared and aligned with data from UK empirical literature and informed and/or validated by external UK clinical expert opinion through two rounds of interviews. This ensured that all input parameters and clinical outcomes were properly validated to present robust base case assumptions.[5, 6]

Figure 1. Expanded treatment pathway for high-risk, HER2- eBC



Footnotes: [a]Endocrine therapies recommended for HR+ patients; bisphosphonates recommended for post-menopausal women. Carboplatin/paclitaxel, NG101; capecitabine, TA62; letrozole, NG101; anastrozole, CG164; tamoxifen, CG164; anthracycline/taxane, NG101; abemaciclib +/- letrozole or fulvestrant, TA725; palbociclib +/- letrozole or fulvestrant, TA619; ribociclib +/- letrozole or fulvestrant, TA687; fulvestrant, TA503; everolimus/exemestane, TA421, GID-TA10028; docetaxel, CG81; atezolizumab/paclitaxel, TA639; eribulin, TA423.
Abbreviations: eBC: early breast cancer; ER: oestrogen receptor; HER2: human epidermal growth factor receptor 2; mBC: metastatic breast cancer; PR: progesterone receptor; TNBC, triple-negative breast cancer.
Source: NG101;[7] Robson et al., 2019;[8] TA62;[9] CG164;[10] TA725;[11] TA619;[12] TA687;[13] CG81;[14] TA639;[15] TA423;[16] TA503; NHS England (Cyclophosphamide-Docetaxel-Doxorubicin);[17] NHS England (Paclitaxel);[18] NHS England (Carboplatin);[19] Robertson et al., 2016;[20] NHS England (Everolimus and Exemestane);[21] AstraZeneca Data on File (UK clinical expert Interviews, December 2021 and March 2022).[5, 6]

Outcome definition

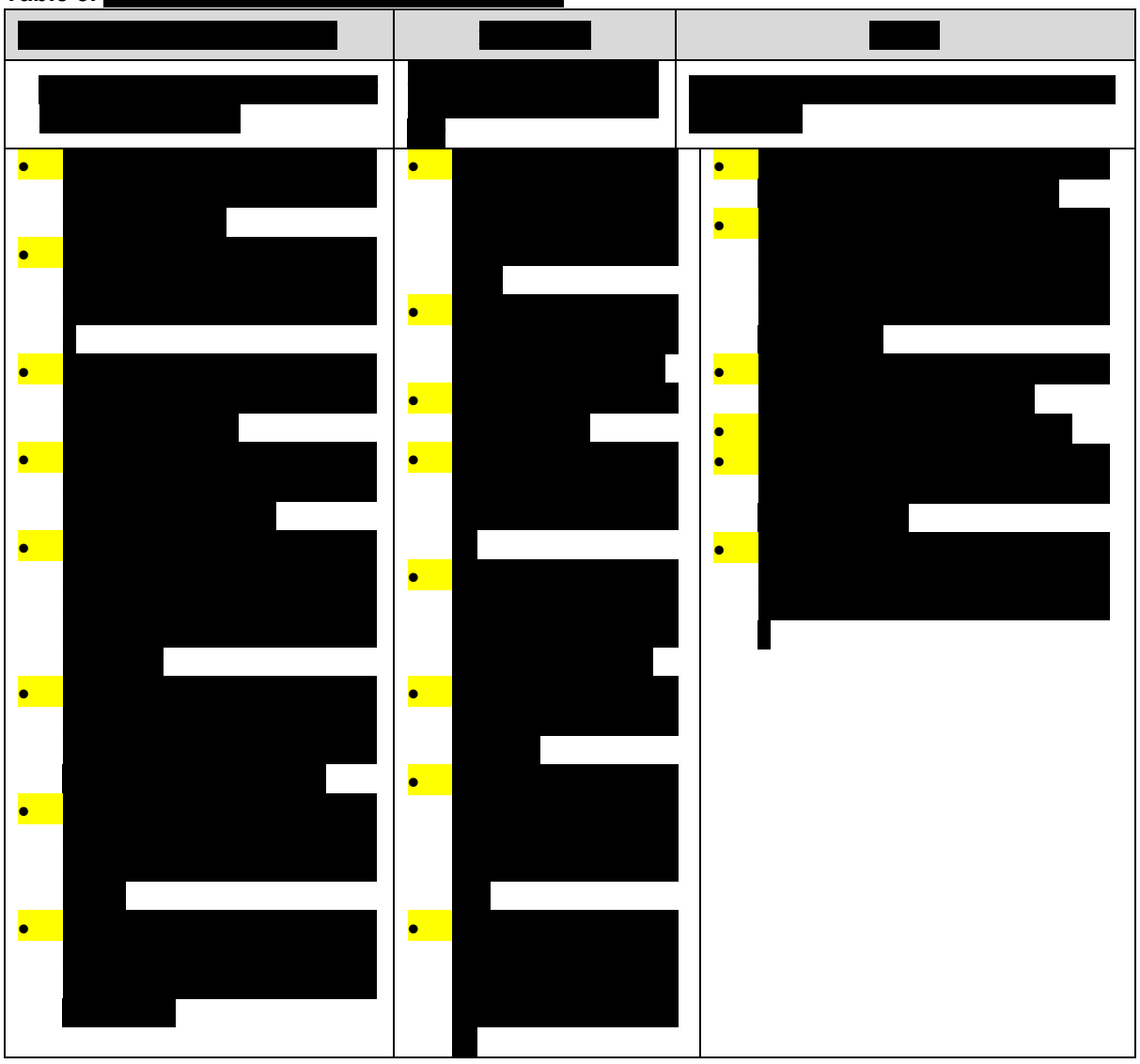
A10. How were the clinicians chosen for the interview studies to determine how to classify patients as having high risk breast cancer?

The clinicians chosen for the interviews were practicing UK oncologists, who are considered experts in eBC and are currently treating such patients in clinical practice. A significant

proportion of the clinicians involved had also used olaparib before, in either a clinical trial setting, or in clinical practice for ovarian cancer patients (one clinician from the December 2021 round of interviews, and four from the March 2022 round of interviews). The consultation process with UK clinical oncologists was robust, consisting of two rounds of interviews to gain their expert opinion; the first round of interviews gained preliminary feedback, while the second round was used to validate and corroborate these initial findings. This structured method was used to align with the recommended approach in the updated NICE process and methods guide.[22, 23] Additionally, AstraZeneca have carried out two further follow-up interviews with clinicians who had previously participated in the March 2022 round of interviews, specifically in response to these clarification questions (used in response to questions B3, B10, and as part of appendix 2).

[redacted]
3[redacted].

Table 3. [redacted]



[redacted]	[redacted]	[redacted]
• [redacted] • [redacted]		

Study Population

A11. In Document B, why is there a subgroup in Table 10 for 'no germline breast cancer susceptibility gene mutation (gBRCAm)' when gBRCAm was an inclusion criteria? This subgroup is also reported in table 22 in the clinical study report (CSR). Why is this subgroup not mentioned in the NEJM report or in the results?

AstraZeneca have provided updated subgroup data from the more recent DCO2 in Appendix 1; at DCO2, there are three non-germline *BRCA*m (g*BRCA*m) patients in each study arm i.e., six in total.[24] As the number of non-g*BRCA*m patients is consistent across arms, it is therefore not likely to overly bias results.

This subgroup of patients are listed as protocol deviations in the OlympiA CSR and in the supplementary appendix to the NEJM report (S18).[1, 4] In the OlympiA SAP, only *BRCA*1, *BRCA*2 and *BRCA*1/2 were prespecified according to the following criteria: "If subgroup levels for *BRCA*1 and *BRCA*2 have at least five events in both treatment arms, and there are less than five events in either one of the *BRCA*1/2 treatment arms then the patients associated with subgroup *BRCA*1/2 will still be included in the analysis as the level provides valuable information, however the hazard ratio will not be generated." The subgroup analysis of no g*BRCA*m patients was not outlined in the SAP, and would not be considered feasible given the small number of patients available.

AstraZeneca do not intend for olaparib to be used in patients without a BRCA mutation, and these patients will not be included in the regulatory label. Therefore, results for this subgroup are not considered relevant to the decision problem.

Section B: Clarification on cost-effectiveness data

Latest OlympiA data-cut

B1. **Priority Question**: Any update on when we can expect the latest data-cut from the OlympiA trial?

Patient-level data from the second interim OS analysis of the OlympiA trial (DCO2, 12th July 2021) is now available. Please refer to Appendix 1, which presents the updated clinical data, and Appendix 2, which outlines how the economic model has been updated and how the base case assumptions and results have changed.

B2. **Priority Question**: Will the latest data cut provide sufficient data to model recurrence for hormone receptor positive (HR+)/ human epidermal growth factor receptor 2 negative (HER2-) subgroup using subgroup-specific outcomes? If so, then please provide this.

Although DCO2 provides some additional iDFS data for the HR+/HER2-sub-group, the level of additional data is not considered sufficient to overcome the challenges associated with using data from this subgroup to model iDFS that were outlined in the original submission dossier (Document B, Section 3.3.1). As a result, it remains infeasible to reliably estimate the survival of patients with HR+/HER2- disease in OlympiA using conventional subgroup analysis (i.e., fitting models to a subset of the study) due to the number of iDFS events observed in this subgroup (n=25 for olaparib and n=34 for placebo in DCO2 vs. n=19 for olaparib and n=25 for placebo in DCO1).[2] The relatively small number of events observed for this population greatly prohibits the scope of statistical analysis for iDFS and post-recurrence survival for input to the economic model.

Furthermore, consistent with the analyses conducted using data from DCO1, there remains no statistical evidence of a differential treatment effect by HR subgroup, with the benefit of olaparib being observed irrespective of HR status (please see Appendix 1, Figure 10). The baseline survival rates (i.e., in the placebo arm) for iDFS in the HR+/HER2- and TNBC subgroups of OlympiA also continue to be similar across the duration of study follow-up (see Table 4), with only a ~1.4% difference in observed iDFS and no difference in observed OS at 4 years.[2] For this reason, the primary ITT analysis is again used as a proxy to model the baseline efficacy of placebo in the HR+/HER2- population. However, we have explored the scenario analysis requested in Question B11, which uses the baseline (placebo) curves for the HR+/HER2- subgroup but applies the ITT time-varying hazard ratios to model the survival in the olaparib arm; please refer to our response to this question for further details on the analysis and results.

Table 4: Comparison of landmark iDFS and OS for HR+/HER2- and TNBC patients in the placebo arm of OlympiA, DCO2

Time point, years	iDFS in patients randomised to placebo		OS in patients randomised to placebo	
	TNBC N=758	HER2-/HR+ N=157	TNBC N=758	HER2-/HR+ N=157
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]
4	75.2%	76.6%	86.3%	86.3%

Footnotes: DCO2: 12 July 2021.
Abbreviations: DCO: data cut-off; HR: hormone receptor; HER2: human epidermal growth factor receptor 2; iDFS: invasive disease-free survival; OS: overall survival; TNBC: triple negative breast cancer.
Source: AstraZeneca Data on File (Interim analysis of OS in OlympiA [DCO2]).[2]

B3. **Priority Question**: Will the latest data-cut allow the assumptions that transition probability 4 (TP4) and TP5 do not depend on treatment arm or subgroup to be tested and relaxed if appropriate? If so, please do so.

At DCO2, 81 patients in the ITT population had experienced a non-metastatic recurrence: 33 patients from the olaparib arm and 48 patients from the placebo arm. Of the 81 patients with non-metastatic recurrence, [redacted] had experienced a distant metastatic recurrence and [redacted] had died without recurrence during follow-up.[2] Similar to the DCO1 data, there remain too few

events to separately estimate TP4 and TP5 by treatment arm or subgroup for the economic analysis, as is shown in Table 5 below.

Table 5: Number of patients experiencing a metastatic recurrence in OlympiA, DCO1 vs DCO2 (FAS)

	DCO1: [redacted]		DCO2: N=81	
	Olaparib	**Placebo**	**Olaparib**	**Placebo**
Total number of patients entering the non-mBC state	[redacted]	[redacted]	33	48
Non-mBC –> mBC	[redacted]		[redacted]	
Non-mBC –> death	[redacted]		[redacted]	

Footnotes: DCO2: 12 July 2021.
Abbreviations: DCO: data cut-off; FAS: full analysis set; mBC: metastatic breast cancer.

The pooling of data across treatment arms and sub-groups is still considered appropriate because:

1. The post-recurrence survival (i.e., time from non-metastatic recurrence to death) of patients with non-metastatic recurrence did [redacted] in survival across arms (Figure 2).[2] Therefore, to maximise the sample for analysis, TP4 and TP5 were estimated from a pooled dataset containing data from both arms. The resulting transition probabilities were applied to both arms of the model. This potentially leads to a conservative estimate of the post-recurrence survival of patients with locoregional recurrence in the olaparib arm of the model given the [redacted] (Figure 2).
2. Although there is no direct empirical evidence to inform whether the risk of developing metastatic recurrence from locoregional disease (TP4) differs by HR status, it is reasonable to assume no differences between the triple negative and HR+/HER2- subgroups considering that all patients have (1) high-risk disease, (2) are *BRCA*m and (3) receive very similar primary chemotherapy regimens (please refer to Document B, Table 42). This was further validated by two UK clinical oncologists who were interviewed as part of developing this response document, who commented that they would not expect HR status to impact patients' risk of progression/mortality after they have developed locoregional disease. They also noted that mortality from locoregional disease is either non-cancer related or associated with severe comorbidities and thus likely not influenced by HR status.[25]

Figure 2: Post-recurrence survival of patients who had locoregional or contralateral invasive breast cancer in OlympiA, DCO2

Footnotes: DCO2: 12 July 2021.
Abbreviations: DCO: data cut-off.
Source: AstraZeneca Data on File (Interim analysis of OS in OlympiA [DCO2]).[2]

Model structure

B4. **Priority Question**: TP4. Which (i.e., early or late) metastatic state do patients from non-metastatic recurrence transition to? If it depends on time, is it time in model or time since entering the non-metastatic recurrence state? In the model tab "TP Matrix1", cell F1471 (for example), it appears that time in model (i.e., current cycle) is used, rather than time in state, but the justification for this is unclear.

Patients that enter the non-metastatic breast cancer (mBC) health state remain in this state until the onset of distant mBC (TP4) or death (TP5). As described in Section 3.2.2 in Document B, patients that develop a distant metastatic recurrence in the first 2 years of the model's time horizon will enter the 'early onset' mBC state and those that have recurrence after 2 years enter the 'late onset' state, in the same manner as those who transition straight from iDFS to metastatic disease. Patients transitioning from the non-mBC health state to either one of two metastatic health states therefore depends on time spent in the model, not the time since entering the non-mBC state itself.

The justification for this is that the clinical definition of 'early' vs. 'late' onset mBC is based on the number of years patients remain disease-free after completing local treatment in the early disease setting. For example, if a patient experiences a metastatic recurrence 2 months after developing locoregional disease but completed surgery or adjuvant chemotherapy in the eBC setting 16 months prior, they are still considered to have particularly aggressive and treatment-insensitive disease and are thus classed as having 'early onset' mBC. This definition was validated with UK medical oncologists[5, 6] and is aligned with (UK) empirical literature.[5, 6, 26-28]

B5. **Priority Question**: "TP Matrix1" cell O12 is implementing the method described in Appendix N.1 but both are incorrect. It multiplies the instantaneous hazard of recurrence (from “Efficacy calcs” column L) by the probability of that recurrence being non-metastatic (named variable e_cond.prob_nmBC). Columns W-Y then uses this hazard, along with other possible hazards from iDFS, in a competing risks formula to calculate transition probabilities from iDFS to n-mBC, mBC and Death, respectively. Please correct so that the probability of recurrence is multiplied by e_cond.prob_nmBC instead. This should be done by changing the competing risks formula to use the hazard of recurrence and death to calculate TP3 and an intermediary TP1_or_TP2. TP1 and TP2 would then be calculated as TP1_or_TP2* e_cond.prob_nmBC and TP1_or_TP2*(1- e_cond.prob_nmBC), respectively.

We have reviewed the proposed method and can confirm that it generates the same transition probabilities for TP1–3 as the method which is currently used in the economic model. We have provided an Excel file comparing the two methods and demonstrating their identical outcomes, which has been submitted as part of this response.

B6. **Priority Question**: "TP Matrix1" and "TP Matrix2" the names in column T (TP6: Late onset mBC - Death) and U (TP7: Early onset mBC - Death) are mixed up. The calculations are also referring to swapped columns of "Efficacy Calcs” so TP6 is used as TP7 and TP7 as TP6. It is not clear if this is a labelling issue as the tunnel states in the Model “TP Matrix1” implemented from cells D1467 (early mBC) and D2195 (late mBC) seem to swap them back. Please correct labels and (if needed) calculations.

This is simply a labelling issue – the economic model submitted as part of this response has been updated accordingly.

Model clinical parameters

B7. **Priority Question**: It is argued that different treatment options are available for late onset mBC by subgroup and so efficacy of subsequent treatments is modelled separately by subgroup. Why not take the same approach for early onset mBC rather than rely on the immature data from OlympiA?

The decision to use the data from the OlympiA trial to model the transition probabilities for 'early onset' metastatic breast cancer (TP6), but use external data to model the transition probabilities for ‘late onset’ metastatic breast cancer (TP7) was based on two key factors:

1. Firstly, at the primary iDFS analysis of OlympiA (DCO1), there were already a sizable number of events to robustly estimate TP6: [redacted] deaths out of the [redacted] patients who had a distant metastatic recurrence in the olaparib arm, and [redacted] deaths out of [redacted] patients with distant metastases in the placebo arm. The maturity of this data has only further strengthened with the availability of the DCO2 data:[2] [redacted] deaths out of [redacted] mBC patients in the olaparib arm and [redacted] deaths out of [redacted] mBC patients in the placebo arm, with a median time to death of [redacted] and [redacted] months respectively (please refer to Section 2.3 , Appendix 2 for further information).
2. Secondly, there were no other appropriate external data sources to model the mortality risk of patients with 'early onset' mBC, especially for those with high-risk, *BRCA*m disease. This was an important consideration when developing the

economic analysis as patients with early recurrence tend to have more aggressive disease and thus different survival outcomes than patients who have 'late onset' mBC, something which was informed by both empirical literature[26-28] and UK clinical expert advice.[6] The external studies (OlympiAD, Collins et al., 2021 and IMpassion 130) identified to model the transition probabilities for 'late onset' mBC to death (TP7) are more reflective of patients who experience metastatic recurrence at a later stage after being disease-free following initial eBC treatment.

For example, in both the OlympiAD trial and the RWE study on CDK4/6 inhibitor treatment, the mean time from diagnosis to randomisation (OlympiAD) or start of treatment (CDK4/6 inhibitor RWE study) was greater than 2 years, indicating that patients in these studies were likely to have developed metastatic disease in a 'late onset' setting (the range was between 4.5 to 5.0 years).[8, 29, 30] Furthermore, the baseline ECOG performance status of these patients (60–80% with normal activity) suggests worse overall health status versus the baseline status in OlympiA (>85% with normal activity). This is consistent with clinical expectations of worsening health status following a metastatic diagnosis.

The OlympiA data therefore presents the most appropriate and only available dataset to inform the survival outcomes for patients with g*BRCA*m, high-risk, HER2- disease who had an 'early' metastatic recurrence.

Finally, although it is acknowledged that the treatment options for patients with either triple negative or HR+/HER2- disease received in the 'early onset' or 'late onset' metastatic states are similar, clinical experts highlighted that patients who experience an 'early' distant recurrence may constitute a group with particularly treatment-insensitive disease.[5] As such, these patients may also be less responsive to subsequent treatments that they receive in the metastatic setting. It is therefore reasonable to assume that even though patients in the OlympiA trial received a slightly different case mix of treatments in the metastatic setting vs. what is being modelled using the external studies for TP7, it is unlikely this will have had a significant impact on the survival outcomes for these patients.

B8. **Priority Question**: Provide evidence that TP4 and TP5 in the model do not depend on treatment arm or subgroup. Please test and relax these assumptions with the latest data-cut if appropriate.

Please refer to our response to Question B3.

B9. **Priority Question**: TP3. The company assumes excess mortality (SMR) in the gBRCAm population due to causes other than cancer-related estimated as 1.46 from the Mai study. This estimate is highly uncertain with a confidence interval of between 0.5 and 2.82. We agree that the study population entering the model may have excess mortality due to comorbidity associated with cancer and cancer treatments; but not necessarily due their breast cancer susceptibility gene (BRCA) mutation. Is this excess mortality captured in TP3? Please revise the source of SMR for TP3 or provide additional justification (and data source) for your assumption.

As part of developing the economic analysis for this appraisal, a targeted literature review (TLR) was performed to identify any appropriate sources of data to inform the level of excess mortality associated with breast cancer, especially for those patients with *BRCA*m and high-risk disease, either from having a *BRCA* mutation or as a result of other cancer-related comorbidities. However, almost all identified studies reported excess mortality directly

associated with breast cancer, including recurrences, secondary tumours or death, but not with other non-breast cancer related causes.[31-36] Other studies either estimated excess mortality associated with breast cancer to compare new population-based screening options,[31, 36] were conducted in non-relevant patient populations,[32, 34, 37] or simply showed that there is no excess mortality associated with patients who remain disease-free over time.[38]

Out of the eleven studies identified in the TLR,[31-41] only two studies reported the excess mortality risk of other causes of death after breast cancer treatment:

1. A 2001 Dutch population-based study by Louwman et al. comparing the pattern of causes of death in deceased breast cancer patients with the general female population using standard mortality rates (SMRs) showed that the total SMR associated with any cause of death was 1.3, 1.0 and 0.6 in the 10–14, 15–19 and >20 years of follow-up after patients' initial diagnosis respectively.[39]
2. Similar results were reported in a Swiss-based study by Levi et al. (2002), who analysed mortality from breast cancer, other selected causes of death and all causes in a population-based series of 1,095 women diagnosed with breast cancer in the Swiss Vaud Cancer Registry between 1974 and 1984.[40] Their findings show that the SMR associated with all other non-cancer related causes (e.g., cardiovascular, digestive and respiratory disease or other external causes) in breast cancer patients is 2.0 in any of the different follow-up periods after diagnosis (10–14 years, 15–19 years and 10–19 years).[40] However, it should be noted that this study is highly outdated and does not analyse a population remotely comparable to the OlympiA population of interest. The reported SMR is therefore not a reliable and accurate reference when validating the SMR used in the OlympiA economic analysis and is likely highly conservative given the improvements in BC treatments and management of cancer-related comorbidities today.

In addition to the paper by Mai et al. (2009),[41] only one other study was identified that reported on the excess mortality associated with having a *BRCA*m.[41] Ofverholm et al. (2019) investigated the SMRs for women with a *BRCA*m, in a population-based cohort of women in Western Sweden.[35] However, their findings only report the SMR for overall mortality based on *all* causes of death, which mainly includes deaths from either breast or ovarian cancer. This study was therefore not considered relevant to inform an SMR for the excess risk of non-cancer mortality associated with a *BRCA*m. To our knowledge, the study by Mai et al. (2009) is the only available source that reports such an estimate.[41]

Considering that the SMR (1.46) reported by Mai et al. (2009) is substantially higher than the rates reported by Louwman et al. (2001) and already captures the excess mortality risks from other illnesses that may lead to shortened life expectancy in individuals with a *BRCA*m, it was not deemed necessary to further increase this rate to account for patients' excess mortality due to comorbidities associated with cancer treatments, which would be an overly conservative assumption. Although we acknowledge there are limitations with using this estimate, it is considered the best available source of data that captures all non-cancer related mortality risks and is specific to patients with a *BRCA*m. There is also precedent for using this SMR estimate from previous NICE appraisals in other disease areas to capture the elevated mortality risk in patients with a *BRCA*m.[42]

B10. **Priority Question**: TP5 and TP6, section B.3.3.5.2. Different subgroups receive different subsequent therapies when modelling costs of non-metastatic and metastatic recurrence. Please justify your assumption for the same probabilities of death (i.e., why assume TP5 and TP6 are the same for triple-negative breast cancer (TNBC) and HR+/HER2- subgroups)

As outlined in our response to Question B8, feedback from UK clinical experts has indicated that it is reasonable to assume that the risk of death of patients with locoregional disease (TP5) does not differ by subgroup given that mortality from this health state is either non-cancer related or associated with severe comorbidities and thus likely not influenced by HR status.[25] It should also be noted that the modelled survival for this transition is not a key driver in the economic analysis; if slightly different probabilities of death from locoregional disease would be assumed for the TNBC vs. HR+/HER- subgroups the impact on the results is negligible (Document B, Section 3.3.4).

For TP6, as the OlympiA trial specifically includes patients who are g*BRCA*m and at a high-risk of recurrence, both eligibility criteria which are associated with particularly aggressive disease, survival across both TNBC and HR+/HER2- subgroups is expected to be short and therefore any differences between the two groups would likely be minimal. Furthermore, patients who experience an “early” distant recurrence generally constitute a group with relatively treatment-insensitive breast cancer, and as such, may also be less responsive to subsequent treatment for metastatic disease. It is therefore reasonable to assume that even though patients in the OlympiA trial received a slightly different case mix of treatments in the metastatic setting based on their HR status, this will likely not have had a significant impact on their survival outcomes. This was validated by two UK clinical oncologists who were interviewed as part of developing this response document, who commented that HR status does not generally have an impact on patients' risk of progression or mortality after they have transitioned from the disease-free health state and that HR status mainly influences the risk of recurrence in the early disease setting. It is therefore a sensible assumption to adopt the same transition probabilities for 'early onset' mBC to death (TP6) across the TNBC and HR+/HER2- analyses in the economic model.

However, to address any concerns around the uncertainty associated with this TP parameter, we have provided a scenario analysis in which TP6 is modelled separately for the TNBC population using the TNBC-specific subgroup data. A similar scenario analysis for the HR+/HER2- subgroup could not be conducted given the low number of death events from the metastatic state in this subgroup. However, considering the almost identical treatment benefit observed in each subgroup, the impact is expected to be similar. Aligned with the analyses provided in the original submission dossier (Section 3.3.5.1 in Document B), the same survival probabilities are assumed across arms given that the median survival after distant recurrence in the OlympiA trial is lower in the olaparib than the placebo arm, which is not reflective of what is expected in clinical practice.

In Table 6 below, the scenario analyses demonstrate that using the subgroup-specific vs. the ITT data to model TP6 for the TNBC analysis has a small, positive impact on the base-case incremental cost-effectiveness ratios (ICERs).

Table 6: Scenario analysis using subgroup-specific data to model TP6

Scenario	ICER (£/QALY) (TNBC)
Base case (with identical survival probabilities assumed across arms)	£35,855
Scenario analysis: TP6 modelled using subgroup-specific data	£34,869

Footnotes: Discounted outcomes.
Abbreviations: HER2: human epidermal growth factor receptor 2; HR: hormone receptor; ICER: incremental cost-effectiveness ratio; QALY: quality adjusted life year; TNBC: triple negative breast cancer; TP: transition probability.

Subgroups

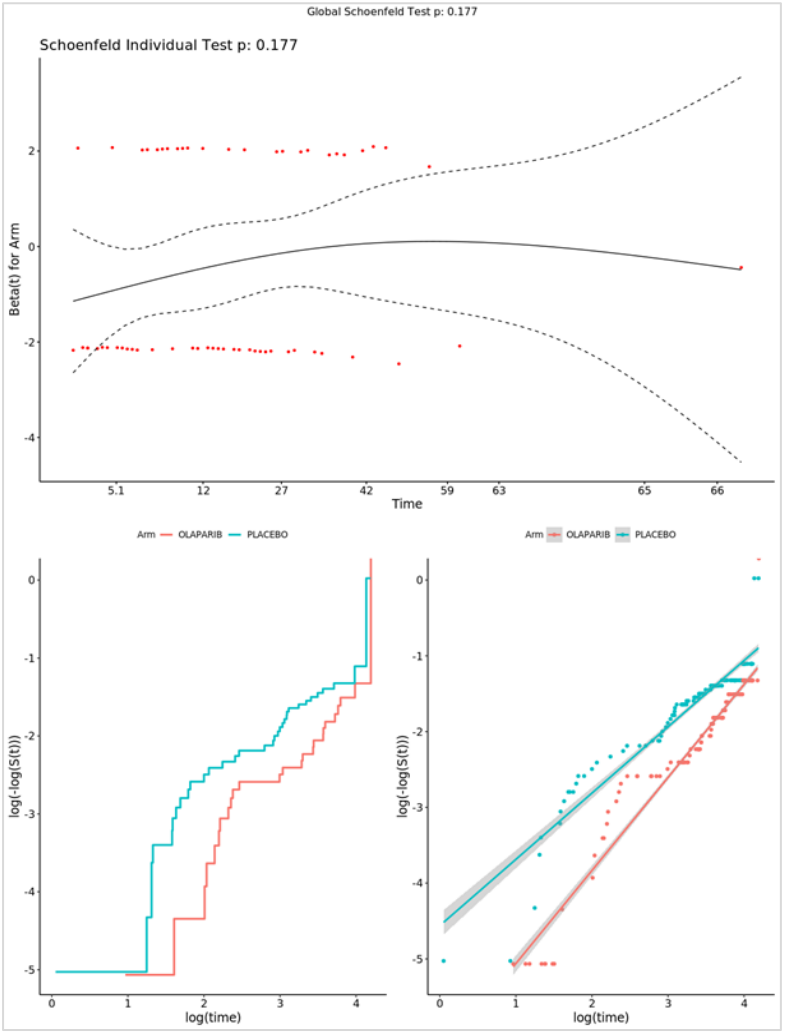
B11. **Priority Question**: Estimates for the HR+/HER2- subgroup economic model are informed by the full OlympiA ITT population, based on lack of data for this subgroup and no evidence of difference in efficacy for the hazard ratio. However, baseline recurrence rates are expected to be different between the subgroups (Fig. 5, Doc B). Whilst it seems reasonable to assume that the hazard ratio is similar for the subgroups, the model uses the fitted curves from each arm which are not expected to be the same across subgroups. Can you provide an analysis where the baseline curves depend on subgroup, but the same hazard ratio is applied for both subgroups (could be a time-varying hazard ratio)?

We have provided a scenario to implement the suggestion above, in which the OlympiA ITT time-varying hazard ratios are applied to the subgroup-specific baseline (placebo) curves. Please note that the statistical analysis for iDFS for the HR+/HER2- population should be interpreted with caution given the continuing low number of iDFS events observed in this subgroup. The sections below briefly outline the derivation of the clinical parameters for TP1 and TP2 for the HR+/HER2- subgroup (identical to the original submission), followed by an overview of the OlympiA ITT time-varying hazard ratios, the updated base case results and some additional scenario analyses. The derivation of the clinical parameters for TP1-2 for the TNBC subgroup using the updated DCO2 data can be found in Section 2.2.1 in Appendix 2.

Parametric survival analysis for iDFS (TP1 and TP2) for the HR+/HER2- subgroup using the subgroup-specific data

The assessment of PH for iDFS using the HR+/HER2- subgroup using the DCO2 data is shown in the Schoenfeld and log-cumulative hazard plots presented in Figure 3. Both figures provide evidence of non-PH in the form of a non-horizontal log-hazard ratio and non-parallel lines between arms, respectively. These results indicate that with the DCO2 data, the PH assumption likely does not hold for the iDFS endpoint in this subgroup.

Figure 3: Schoenfeld residual and log-cumulative hazards versus log-time plots of iDFS for the placebo and Olaparib arms of OlympiA (HR+/HER2- using the subgroup-specific data)



Abbreviations: HER2: human epidermal growth factor receptor 2; HR: hormone receptor; iDFS: invasive disease-free survival.

Following DSU guidance, a series of independent parametric survival models was therefore fitted to patient-level data from each arm of OlympiA. The statistical goodness of fit was reported in terms of the Akaike Information Criteria (AIC) and Bayesian Information Criteria (BIC) scores, where a lower score indicates improved fit (Table 7). For the HR+/HER2- subgroup, the AIC scores favoured the lognormal and generalised gamma in the placebo arm, whereas the exponential model scored lowest based on both the AIC and BIC in the olaparib arm.

Table 7: AIC and BIC values for the parametric survival models fitted to the time from randomisation to distant metastatic or non-distant metastatic recurrence (HR+/HER2- subgroup-specific data, DCO2)

Model	Olaparib		Placebo	
	AIC	BIC	AIC	BIC
Exponential	323.25 (1)	326.37 (1)	411.85 (3)	414.90 (1)
Lognormal	323.89 (2)	330.14 (2)	410.86 (1)	416.97 (2)
Gompertz	324.04 (3)	330.29 (3)	412.48 (4)	418.59 (3)
Weibull	324.09 (4)	330.34 (4)	413.33 (6)	419.44 (5)

Model	Olaparib		Placebo	
	AIC	BIC	AIC	BIC
Gamma	324.09 (5)	330.34 (5)	413.45 (7)	419.56 (6)
Log-logistic	324.28 (6)	330.53 (6)	412.79 (5)	418.91 (4)
Generalised Gamma	325.89 (7)	335.27 (7)	411.74 (2)	420.91 (7)

Footnotes: Footnotes: DCO2: 12 July 2021. (X) indicates the rank of each model based on the goodness-of-fit statistics.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; DCO: data cut-off; HER2: human epidermal growth factor receptor 2; HR: hormone receptor.

To inform the choice of parametric function to model the baseline curves for the HR+/HER2- subgroup for our response to this question, the long-term iDFS estimates from the three best-fitting parametric models[1] were compared to the empirical evidence and validation presented in Section 2.2.2 , Appendix 2. It is clear from Table 8 that most of the parametric models produce long-term survival estimates that are less consistent with the available external data and insights from UK clinicians vs. the approach used in the original submission dossier of using the ITT data as a proxy, further confirming the appropriateness of this approach. However, considering the goodness-of-fit statistics and consistency with the empirical data (see Table 26, Appendix 2), the generalised gamma produces the most plausible long-term iDFS rates on standard of care and was thus chosen to model the baseline curves for the HR+/HER2- subgroup as part of the scenario analysis presented in this response.

Table 8: Long-term extrapolations of iDFS for the comparator (placebo) OlympiA arm using fully fitted parametric models (independent, HR+/HER2- subgroup-specific data, DCO2)

	Time (years)	1	2	3	4	5	10	20
	Kaplan-Meier placebo	[redacted]	[redacted]	[redacted]	*76.6%*	[redacted]	[redacted]	[redacted]
Parametric models fitted to the OlympiA HR+/HER2- data	Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gen. gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: DCO2: 12 July 2021; lifetime risk of recurrence assumed
Abbreviations: DCO: data cut-off; HER2: human epidermal growth factor receptor 2; HR: hormone receptor; iDFS: invasive disease-free survival.

Parametric survival analysis for iDFS (TP1 and TP2) for the TNBC subgroup

Please refer to Section 2.2 , Appendix 2, for an overview of the updated selection process of the most appropriate parametric survival model for the TNBC subgroup using the DCO2 data. To summarise, the lognormal model, which has the second-best statistical fit according to the AIC/BIC values, shows good consistency with the observed Kaplan-Meier data, and produces the most plausible long-term iDFS rates on standard of care was chosen in the base-case analysis for the TNBC population.

Presentation of the scenario analysis

The OlympiA ITT time-varying hazard ratios for the 3.5 median follow-up based on DCO2 data are presented in Table 9. To explore the scenario analysis suggested in this question, the hazard ratios have been applied to the modelled instant hazards of the placebo arm for

[1] Please note the exponential model has not been presented as assuming a constant hazard over time is not a realistic assumption to make for patients with high-risk HR+/HER2- disease.

each respective subgroup in the economic model, i.e., [redacted] for Year 1, [redacted] in Year 2 and [redacted] from Year 3 onwards.

Table 9: OlympiA ITT time-varying hazard ratios, DCO2

Time (years)	Olaparib Kaplan-Meier data	Placebo Kaplan-Meier data	Hazard ratio
0	1	1	–
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]

Footnote: DCO2, 12st July 2021; median follow-up 3.5 years
Abbreviations: DCO: data cut-off.

The updated base case results using this approach are presented in Table 10 and Table 11. In this scenario analysis, adjuvant olaparib treatment generates [redacted] incremental QALYs and [redacted] incremental costs over a lifetime time horizon compared with placebo ("watch & wait") for the TNBC subgroup, and [redacted] incremental QALYs and [redacted] incremental costs in the HR+/HER2- subgroup, resulting in an ICER of £33,528 and £29,671 respectively. When comparing these results to the updated base case ICERs using the DCO2 data as presented in Section 2.6 in Appendix 2 (£35,855 and £41,879 respectively), they suggest that the current base case analyses might be conservative given the consistent benefit of olaparib shown over time.

Table 10: Base case results – scenario analysis question B11 (TNBC, olaparib PAS price)

Treatment	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY gained)
Placebo ("watch & wait)	[redacted]	[redacted]	[redacted]				
Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£33,528

Footnotes: discounted outcomes; TNBC subgroup-specific data.
Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life year gained; PAS: patient access scheme; TNBC: triple negative breast cancer; QALY: quality-adjusted life year.

Table 11: Base case results – scenario analysis question B11 (HR+/HER2-, olaparib PAS price)

Treatment	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY gained)
Placebo ("watch & wait)	[redacted]	[redacted]	[redacted]				
Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£29,671

Footnotes: discounted outcomes; HR+/HER2- subgroup-specific data.
Abbreviations: HER2: human epidermal growth factor receptor 2; HR: hormone receptor; ICER: incremental cost-effectiveness ratio; LYG: life year gained; PAS: patient access scheme; QALY: quality-adjusted life year.

Finally, we acknowledge that in this approach we are unable to model the long-term treatment effect as effectively as the independent models used in our base case analysis. Therefore, to explore the impact of a constant hazard ratio (i.e., no assumed further benefit of olaparib treatment) beyond the observed trial follow-up we have conducted additional exploratory analyses below whereby we set the hazard ratio to 1.0 at 7 and 10 years, respectively.

Table 12: Additional scenario analyses (olaparib PAS price)

Scenario	ICER (£/QALY) (TNBC)	ICER (£/QALY) (HR+/HER2-)
Base case	£33,528	£29,671
Scenario 1: hazard ratio set to 1.0 at 7 years	£33,528	£37,000
Scenario 2: hazard ratio set to 1.0 at 10 years	£33,528	£34,139

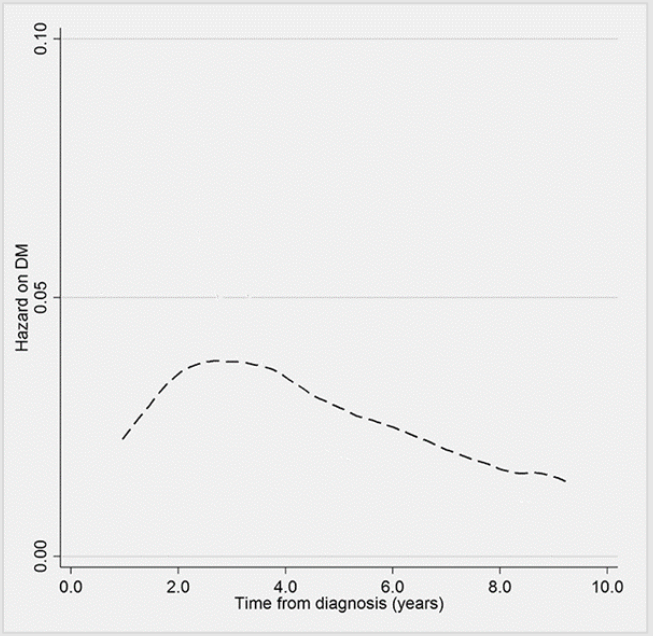
Footnotes: Discounted outcomes; no impact of the scenarios on the TNBC subgroup analyses as zero risk of recurrence is assumed after 5 years for both arms
Abbreviations: HER2: human epidermal growth factor receptor 2; HR: hormone receptor; ICER: incremental cost-effectiveness ratio; PAS: patient access scheme; TNBC: triple negative breast cancer; QALY: quality-adjusted life year.

B12. **Priority Question**: For the HR+/HER2- subgroup the fitted curves are extrapolated into the long-term, but Fig.5 shows that recurrence rates become constant in the long-term. Could you provide an analysis where the recurrence rates become constant from an appropriate point in the curve?

Although we acknowledge this interpretation of Figure 5 in Document B by the EAG, we would like to point out that the analysis on which this figure is based was conducted in a non-biomarker selected, broader HR+ population and does not specifically include patients with only HER2- and high-risk, g*BRCA*m disease.[43] As such, we should not expect the outcomes in an OlympiA patient cohort in UK clinical practice to follow this precise trend. The data presented in this figure simply illustrate the important differences in risk profile between the TNBC and HR+/HER2- subgroups that needed to be considered and accounted for in the economic analysis. However, they are not considered as relevant data for validating the long-term risk of recurrence in the two key subgroups of the OlympiA population.

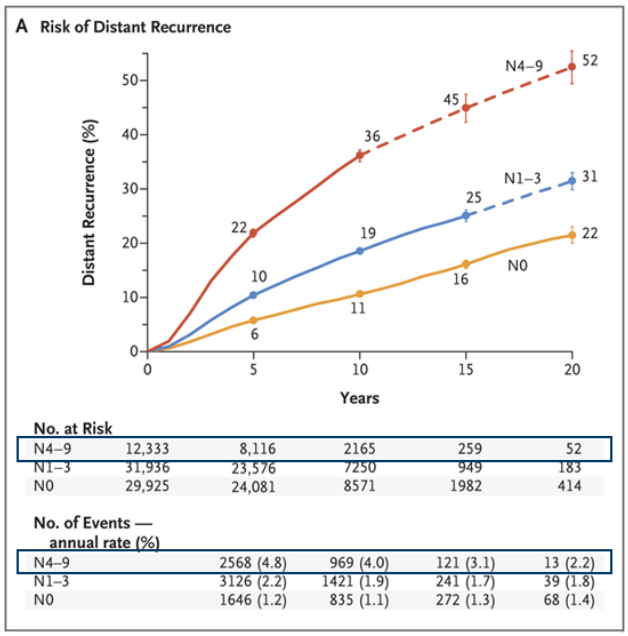
For example, when considering other studies which report on the long-term recurrence rate in eBC such as the 2018 Dutch population-based study by Van Maaren et al.[44] or the meta-analysis on absolute risk of subsequent distant recurrence after endocrine therapy (ET) in HR+ BC patients by Pan et al. (2018),[45] it is clear that the although the hazards on recurrences for patients with HR+/HER2- disease drop over time, they do not become completely constant in the long-term (Figure 4 and Figure 5). We would therefore not expect a scenario as requested in this question to be applicable for patients with high-risk, g*BRCA*m, HR+/HER2- disease.

Figure 4: Hazards on recurrences in 10 years after diagnosis for patients with 'luminal B' disease[2] from a study by Van Maaren et al. (2018)



Abbreviations: DM: distant metastases.
Source: Van Maaren et al 2018.[44]

Figure 5: Association between pathological nodal status and the risk of distant recurrence or death from HR+ eBC during the 20-year study period from a study by Pan et al. (2018)



Footnotes: HR+ patients with pathological nodal status N4–9 are generally considered to have 'high-risk' disease, which is aligned with the inclusion criteria for HR+ patients in OlympiA (see Document B, Table 7). As is shown in Figure 4, patients with high-risk disease have a decreasing, not constant, risk over time.
Abbreviations: HR: hormone receptor, N: number
Source: Pan et al 2018[45]

[2] In the study by Van Maaren et al. (2018), 'luminal A' BC is defined as grade 1/2 (tumour) HR+/HER2- disease, whereas 'luminal B' BC is defined as either HR+/HER2+ or grade 3 (tumour) HR+/HER2- disease. Considering that OlympiA covers HR+/HER2- patients with a high-risk of recurrence, the data on 'luminal B' disease provides a more suitable proxy for these patients than the data on 'luminal A' disease as grade 3 tumours tend to grow more rapidly and spread faster than tumors with a lower grade, i.e., indicating a potential higher risk of disease recurrence.

Costs

B13. **Priority Question**: BRCA testing. The company have stated that testing will be expanded to cover all eligible patients for olaparib and so have not included costs of BRCA testing in their base-case. Whilst many high-risk patients are tested, it is not currently the case that all eligible patients would be tested. Can the company please incorporate the cost of testing for gBRCAm in the olaparib arm in the base-case scenario (can exclude testing costs in a sensitivity analysis)?

Although we acknowledge that in current UK clinical practice not *all* high-risk HER2- patients are tested for *BRCA*, it is expected that *BRCA* testing will be routinely used in the NHS in the eBC pathway by 2023. As presented in Document B, Section 3.5.5.2, it is the UK government's ambitions to "… *create the most advanced healthcare system in the world*", which will incorporate the latest genomics advances in routine healthcare to improve outcomes.[46] Examples of this related to *BRCA* testing include the [redacted], as well as a recent change in the NTD's criteria for germline *BRCA* testing, which now includes all newly diagnosed breast cancer patients under the age of 40 instead of the previous cut-off of 30 years.

Furthermore, AstraZeneca has recently [redacted], which is currently [redacted] with an [redacted]. It should also be noted that the widening of *BRCA* testing in breast cancer is not solely linked to the upcoming OlympiA indication but is driven by an increasingly wider recognition that identifying a *BRCA*-gene in patients can be of high clinical and prognostic value. For example, early results from the *BRCA* Direct trial, which examines the feasibility and acceptability of a new digital pathway for *BRCA* testing in breast cancer, show that an increasing number of breast cancer patients are being tested in the UK each year;[47] a number which is expected to continue to rise in the future. It is thus unreasonable to assume a base case scenario which includes *BRCA* testing costs, considering that (1) the relevance of this scenario will likely not apply anymore in the near future and (2) the widening of *BRCA* testing is independent of the treatment decision for olaparib use in breast cancer. The inclusion of *BRCA* testing is therefore explored in scenario analyses only.

B14. **Priority Question**: What treatments were received post-recurrence in the non-mBC and in the early-onset mBC states in OlympiA? Are these included in the disease management costs of the model?

In the economic model, patients who experience recurrence in the non-mBC state are assumed to enter one of the mBC states ('early' or 'late' recurrence) and accrue the costs of treatment from this state, i.e., treatment in the non-metastatic recurrence state is limited to a single line of therapy on the assumption that second line (2L)+ treatment would only be required upon further progression or recurrence of disease. An overview of the subsequent treatment options patients receive in the mBC setting is presented in Document B, Table 42.

Patients who experience a recurrence in the 'early onset' mBC state progress to further lines of therapy (2L+), in which they receive a variety of treatment options depending on their HR status, presented in the final seven rows of Table 42 (Document B). The treatments patients receive post-recurrence (2L+) in the 'early onset' mBC state are therefore the same as those

received by patients who progress in the 'late onset' mBC. This assumption was validated by UK clinical experts, who commented that even though treatment options in 2L+ are dependent on prior treatments received (and how well they were tolerated), they are not heavily influenced by the timing of a patient's initial metastatic recurrence.[5] This is also driven by the fact that both TNBC and HR+/HER2- patients receive almost identical treatments in the 'early' vs. 'late' onset mBC health states.

Finally, disease management costs are applied separately from drug acquisition costs in the economic model, i.e., assumptions are made about the frequency of hospital/GP/nursing visits, scans and complete blood counts in each health state regardless of the type of treatment patients receive. This is considered to be a reasonable and pragmatic assumption which is consistent with the approach adopted in past HER2-negative eBC appraisals[48-50] and was validated with UK clinical experts who did not expect to see meaningful differences in the management costs between treatment regimens.[6]

B15. **Priority Question**: Section B.3.5.1. Company have modelled subsequent therapy costs as a one-off cost for non-metastatic and metastatic BC, but this will over-estimate costs for those who die before completing therapy, and because more patients reach these states under watch-and-wait this could overestimate the costs for the comparator. The tunnel states used to model time-varying metastasis/death rates could have been used to model changes in treatment status or line of therapy. Please implement this in a revised model.

Although we acknowledge the EAG's request to consider a different modelling approach for the subsequent therapy costs, it should be noted that:

- Subsequent drug acquisition costs account for only [redacted] of the absolute cost increment between arms in the economic model. It was therefore judged that the use of more complex modelling approaches for capturing subsequent drug costs would have a minimal impact on results and serve to only complicate the analysis, and introduce further assumptions, as outlined below.
- There are insufficient data to model health states for the individual treatment lines or pre- vs. post-progression in metastatic disease, preventing the accurate modelling of drug costs using a time-in-state method. As a result, it is not feasible to accurately track when patients are on first vs. later lines of treatment, and more importantly, off treatment. With the EAG's proposed method, the economic model would have to attempt to account for periods off treatment and the switch between treatment lines in the monthly costs, further complicating the analysis.
- This method is also ill-suited to the modelling of therapies with a fixed number of cycles (e.g., chemotherapy regimens), as it would require the complex modelling and tracking of individual treatment durations.

Instead, although the approach to model a one-off weighted cost average may require the need for some simplifying assumptions, such an approach was preferred considering that the costs of subsequent treatment are generally limited. Furthermore, for most subsequent therapy options, especially those which are expensive and significant drivers of the total one-off subsequent treatment cost, the duration of treatment is informed by mean estimates taken from trials investigating the relevant population of interest. For example, for the CDK4/6 inhibitors (abemaciclib, palbociclib and ribociclib) which are used as a 1L therapy option for HR+ patients with metastatic disease, the median number of cycles and median time to first subsequent therapy from the MONARCH-3 trial and RWE study by Collins et al.

(2021) respectively were used to inform the treatment duration inputs in the model.[30, 51] The approach suggested by the EAG to use the health state occupancy in each cycle to calculate the per cycle subsequent treatment cost is only more accurate if patients are expected to receive each treatment right up until death. However, this is likely not the case for most drug therapies, especially those with longer treatment durations and more severe adverse events, and it is certainly not the case for therapies that are administered for a fixed number of cycles, such as chemotherapy regimens.

The approach of using mean treatment duration estimates (where available) to calculate a one-off cost should adequately account for discontinuation due to factors such as progression, adverse events or mortality where appropriate. For therapies given for a fixed number of cycles (e.g., chemotherapy regimens), where information is not available on the mean number of cycles administered, the maximum number of cycles specified in the relevant treatment protocols are used instead as a proxy. However, given that these therapies are administered over a relatively short period of time it is expected that the vast majority of patients will complete the full course of treatment, and thus any overestimation of cost from using the maximum duration estimates is likely to be minimal.

Finally, as mentioned above, considering that subsequent drug acquisition costs are not a big cost driver in the model, the impact of altering any of the assumptions or the costing approach is likely to be negligible. For example, in the table below a scenario is run in which the subsequent therapy costs in the placebo arm are 5% lower than the current base case analysis, adjusting for any potential overestimation. In this scenario, the impact on the base case ICERs across both subgroups is only ~0.5-2%, highlighting that regardless of modelling approach, this is not a significant driver in the model. For this reason, a simplified approach to the modelling of subsequent costs was preferred.

Table 13: Scenario analysis with adjusted subsequent therapy costs in the placebo arm

Scenario	ICER (£/QALY) (TNBC)	ICER (£/QALY) (HR+/HER2-)
Base case	£35,855	£41,879
Scenario analysis: 5% lower subsequent therapy costs in the placebo arm	£36,005	£42,816

Footnotes: Discounted outcomes.
Abbreviations: HER2: human epidermal growth factor receptor 2; HR: hormone receptor; ICER: incremental cost-effectiveness ratio; QALY: quality adjusted life year; TNBC: triple negative breast cancer.

B16. Why model disutilities due to adverse events from external sources instead of using the difference in QoL estimated from regression analysis in OlympiA (Table 36 Doc B)?

In the regression analysis on the mapped HSUs from OlympiA (Document B, Table 36), [redacted] in HSU was found between the arms of OlympiA (olaparib vs placebo = [redacted], *p*=[redacted]), thereby [redacted] the use of the same HSU for iDFS across the olaparib and placebo arms in the economic model. This is consistent with the primary analysis of EORTC QLQ-C30 in the OlympiA trial, which showed no detriment in QoL across arms. Based on these data alone, no additional disutility should be expected from any AEs in the olaparib vs the placebo arm. However, to recognise that HRQoL measures may not be collected at the time of AEs, the economic analysis includes additional one-off QALY adjustments for AEs, which is considered to be a conservative approach in the [redacted] between the arms.

We therefore believe the inclusion of disutilities due to AEs in the model has been appropriately accounted for.

B17. In sensitivity analysis, assume a scenario where the utilities in the health states of iDFS and non-metastatic BC recurrence are lower for the olaparib arm, to reflect the increased side effect profile of the drug.

As described above, [redacted] in HSU was found between the arms of OlympiA (olaparib vs placebo = [redacted], *p*=[redacted]). It is therefore unreasonable to assume that patients would experience a lower utility in the iDFS and non-mBC health states, especially after completing treatment and remaining disease-free long-term. Any additional disutility from adjuvant olaparib therapy vs. placebo is already accounted for in the model and is linked to AEs that were ≥Grade 3 and in ≥2% of patients, of which only 2 were identified in the olaparib arm: anaemia and neutropenia. In addition to the non-statistically significant results from the mapped HSU regression analysis, these AEs are not expected to have a lasting detrimental impact on patients' QoL that warrants a lower utility value for the olaparib arm in the iDFS and non-metastatic BC health states.

Utilities

B18. **Priority Question**: Adverse events (AEs). Why are disutilities and costs not included for AEs other than anaemia and neutropenia. Can you incorporate these?

As stated in Document B, Section 3.4.5, the economic analysis only includes a one-off QALY adjustment and costs for AEs that were:

- ≥Grade 3: AEs were included if they were classified as CTCAE Grade 3 or above. The costs of Grade 1 and 2 events are assumed to be negligible and therefore omitted from the analysis.
- ≥2% of patients: to ensure that key events were captured while ensuring the list of included events was manageable.

This approach is more conservative than previous NICE appraisals in HER2+ eBC, including TA632,[50] TA612[52] and TA569,[49] in which it was assumed that any disutility associated with AEs would have already been captured in the HRQoL data collected in the respective trials to avoid double counting. The included AEs based on the selection criteria above are highlighted in blue in Table 14. Given the low incidence of the observed grade ≥3 AEs, incorporating disutilities for any additional AEs to the ones already included in the model (anaemia and neutropenia) will not materially alter the conclusions of the analysis.

Table 14: AEs CTCAE ≥Grade 3 by system organ class and preferred term, DCO2 (SAS)

Adverse events	Olaparib (N=911)	Watch & wait (N=904)	Total
Anaemia	8.70%	0.30%	4.51%
Nausea	0.80%	0.00%	0.40%
Vomiting	0.70%	0.00%	0.35%
Fatigue	1.80%	0.70%	1.25%
Diarrhoea	0.30%	0.30%	0.30%
Neutropenia	4.90%	0.80%	2.86%
Leukaemia	[redacted]	[redacted]	[redacted]
White blood cell decreased	3.00%	0.30%	1.65%

Abbreviations: CTCAE: Common Terminology Criteria for Adverse Events; DCO: data cut-off.
Sources: AstraZeneca Data on File (Interim analysis of OS in OlympiA [DCO2]);[2] Tutt et al. 2022.[3]

B19. **Priority Question**: Previous studies have shown an elevated risk of leukaemia with olaparib (Morice et al Lancet Haematol. 2020. doi:10.1016/S2352-3026(20)30360-4). Why is this not included in the model?

Based on the DCO2 data after a median follow-up of 3.5 years, there is no evidence of any excess risk of leukaemia for patients treated with olaparib in the OlympiA trial. Specifically, as shown in Table 14, the number of leukaemia events is significantly small and consistent across arms ([redacted]) and is therefore not expected to have a significant impact on patients' HRQoL.

B20. **Priority Question**: Patients who have had chemotherapy are at increased risk of leukaemia. Is this included in the model?

As described in our response to Question B9, it was not deemed necessary to increase the SMR in the economic model to account for patients' excess mortality due to comorbidities associated with cancer treatments, such as leukaemia, considering that it already captures the excess mortality risks from other illnesses and is aligned with empirical evidence on SMR in the eBC space. Furthermore, we are not aware of any evidence of excess mortality relating to chemotherapy use in patients with a positive *BRCA*m, who are relatively young and have high-risk disease. Finally, as mentioned in our response to Question B19, the incidence of leukaemia based on the DCO2 OlympiA data is consistent across both arms ([redacted]) and any adjustments to the model would therefore not alter the conclusions of this economic analysis.

B21. **Priority Question**: Can you provide a scenario where utilities are lower in the non-metastatic recurrence group compared with iDFS?

Following approaches accepted in past NICE evaluations (TA632, TA569), the utility value for the non-mBC state in the base case analysis was assumed equal to the HSUV for iDFS. Although it is acknowledged this might be a slightly optimistic assumption, imputing a HSUV for non-mBC equal or slightly lower than the disease-free state in the economic analysis has a small positive impact on results, as is demonstrated in Table 15. Please note that in the absence of any direct empirical evidence on the utility patients experience in a non-mBC/locoregional disease health state, a mid-point between the disease-free (0.869) and mBC (0.685) HSUVs was selected as a reasonable estimate (0.777).

Table 15: Scenario analysis with a lower HSUV for the non-mBC than the DF health state

Scenario	ICER (£/QALY) (TNBC)	ICER (£/QALY) (HR+/HER2-)
Base case: HSUs of 0.869 for both the disease-free and non-mBC health states	£35,855	£41,879
Scenario analysis: HSU of 0.869 for the disease-free health state, HSU of 0.777 for the non-mBC health state	£35,599	£41,592

Footnotes: Discounted outcomes.
Abbreviations: HER2: human epidermal growth factor receptor 2; HR: hormone receptor; HSU: health state utility values; ICER: incremental cost-effectiveness ratio; QALY: quality adjusted life year; TNBC: triple negative breast cancer.

B22. Can you confirm that olaparib would be prescribed on a monthly basis?

This is correct, olaparib is prescribed on a monthly basis, i.e., patients collect a monthly supply of olaparib tablets at the local hospital pharmacy each month and take the tablets at home. For this reason, the administration cost for olaparib treatment is the cost to account for the pharmacist's time during the prescription and preparation of olaparib treatment, which is £8.80 per month. It should however be noted that this is a conservative estimate considering that patients who have stable disease often collect their supply of treatment every quarter instead of on a monthly basis.

This administration cost is also aligned with previous NICE appraisals in the eBC setting, including TA632, TA569 and TA424. In the economic model submitted as part of the original submission documents this had not been correctly implemented for olaparib treatment. In the model submitted as part of this response this has been updated and corrected. A complete overview of the new base case and scenario results (also including the DCO2 data) is presented in Appendix 2.

Literature searches for economic studies

B23. The structure of your search for economic evaluations (Appendix, Table 12, pg. 53, MEDLINE search strategy screen shot below) could be causing you to miss studies or study data.

12	((economic or pharmacoeconomic) adj1 (evaluation or assessment or analys?s or stud*)).mp.	19804	21779
13	("CEA" or "CMA" or "CBA" or "CUA" or "CCA").mp.	64385	67436
14	exp Decision Trees/	11339	11817
15	decision tree.mp.	8003	9624
16	economic model.mp. or exp Models, Economic/	16441	17194
17	(markov or deterministic).mp.	42399	46218
18	((transition adj1 probabilit*) or (health adj1 stat*) or (sensitivity adj1 analys*) or (health adj1 outcome)).mp.	221629	239705
19	((patient level or patient-level or discrete event or discrete-event) adj1 simulat*).mp.	864	966
20	exp Patient Preference/	8963	10047
21	(Patient* adj2 preferen*).mp.	21693	23761
22	discrete choice*.mp.	2267	2681
23	(incremental-cost or incremental cost).mp.	12098	13463
24	("ICER" or "QALY" or "DALY" or "WTP" or "TTO").mp.	15397	17328
25	13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24	378817	408250
26	12 and 25	7631	8389

At Line 26, you combined Line 12 and Line 25, which would return economic evaluation studies that contain model terms or outcome data. You might miss economic evaluations which do not report their structure or outcomes in the title or abstract or use a different one to those you list. Please amend Lines 25 and 26 to reflect this, followed by de-duplication. Suggested alternative search terms are:

- Line 25 "12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24"
- Line 26 "11 or 25"
- Line 27 "5 and 26"

Please screen the additional studies, alerting us to any new evaluations or data retrieved, and provide corrected 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses' (PRISMA) tables.

The literature searches for the economic studies were re-run using the changes suggested by the EAG. The search strategy and results are summarised in Appendix 3. Searches were

re-run from database inception and the results were deduplicated against results from the original searches run in November 2020, and the update search run in January 2022.

This resulted in 1440 additional Medline and EBMR records to screen, and no additional relevant economic evaluations were identified

Section C: Textual clarification and additional points

Missing Information

C1. The appendices start at Appendix C. Why is there no appendix A or B? Is there some information missing?

In line with the NICE User Guide for company evidence submission template (PMG24), the appendices start at Appendix C,[53] with Document A (i.e. Appendix A) as the submission summary and Document B (i.e. Appendix B) as the main submission. No information is missing.

C2. The marketing authorisation for olaparib is expected in July 2022. Is there any update on this?

AstraZeneca are expected to receive the Committee for Medicinal Products for Human Use (CHMP) opinion in June 2022 and a final European Commission decision between July and August. The Medicines and Healthcare products Regulatory Agency (MHRA) decision is expected to follow shortly thereafter, as AstraZeneca are following the Reliance Route for European marketing authorisation.

Presenting additional information

C3. In B.3.2.2 Table B.24 presenting evidence on timepoint for early vs late recurrence, please further clarify the proportions of each population that are HR-/HER2- and HR+/HER2-.

Table 16 presents an overview of the proportion of patients who have TNBC vs HR+/HER2- disease in each study population. Please note that for some of the studies only top-level data on HR or HER2 status was available, but not specifically for triple-negative or HR+/HER2- disease.

Table 16: Proportion of patients with TNBC and HR+/HER2- disease in each study as reported in Document B, Table 23

Study	Population	Post-recurrence survival for early vs. late	Proportion patients TNBC vs. HR+/HER2-
McKenzie et al. (2020)[28]	Young women aged <40 years (n=3,021) with initially localized invasive breast cancer diagnosed between 2000–2008	2-year post-recurrence survival: • <24 months: 25% • 24–60 months: 43% • >60 months: 49%	**<24 months (n=268):** TNBC: 37.3% (n=100) HR+/HER2-: 28.7% (n=77) **24–60 months (n=360):** TNBC: 15.3% (n=55) HR+/HER2-: 46.9% (n=169) **>60 months (n=158):** TNBC: 9.5% (n=15) HR+/HER2-: 57.6% (n=91) Post-recurrence survival by subgroup is not available.
Lobbezoo et al. (2015)[27]	Consecutive patients diagnosed with mBC in 2007–2009 from 8	Median survival: • ≤2 years: 9.1 months	Only top-level data on HR or HER2 status is available, but not combined:

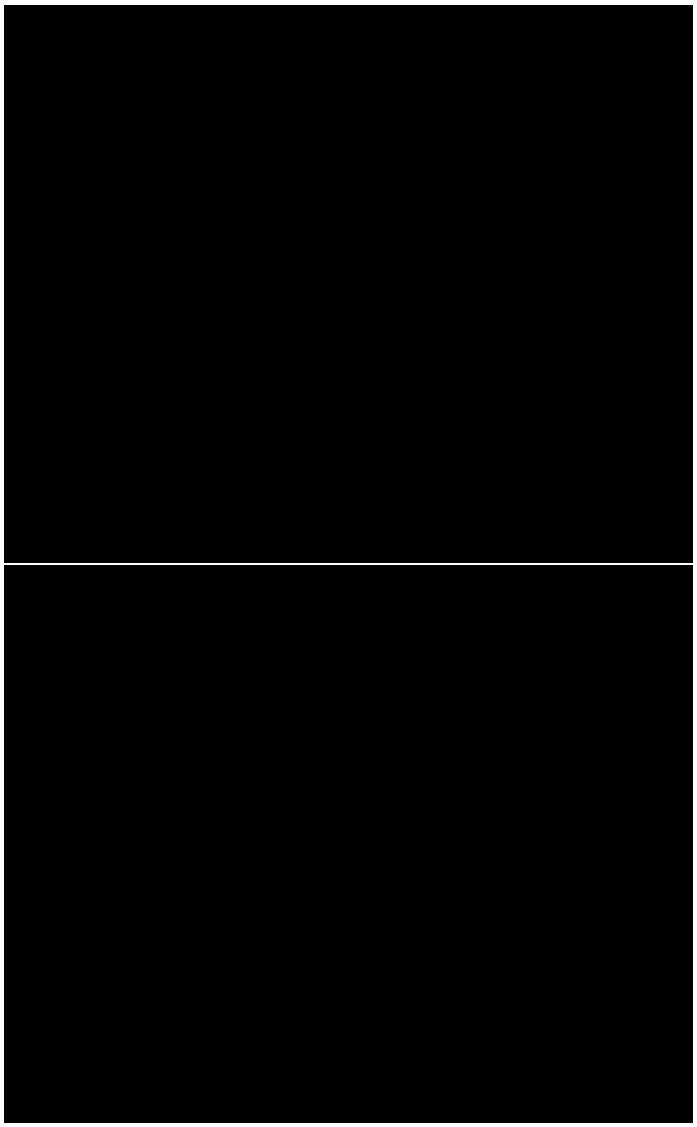
	Southeast Dutch hospitals	• >2 years: 27.9 months	**Recurrence ≤2 years (n=176):** HR+: 55% (n=96), HR-: 45% (n=78) HER2+: 21% (n=37), HER2-: 79% (n=137) **Recurrence >2 years (n=485):** HR+: 83% (n=394), HR-: 17% (n=78) HER2+: 18% (n=85), HER2-: 82% (n=387)
Dawood et al. (2010)[26]	Female patients diagnosed between 1992–2007 with either de novo stage IV or relapsed breast cancer at the Department of Breast Medical Oncology of The University of Texas M. D. Anderson Cancer Centre	Median OS: • <6 months: 17.4 months • 6–24 months: 17.3 months • 2–5 years: 30.4 months • >5 years: 47.4 months	Only top-level data on HR or HER2 status for women with relapsed disease (n=2881) is available, but not combined and not by each time period: HR+: 62.5% (n=1,570), HR-: 37.5% (n=940) HER2+: 23.8% (n=433), HER2-: 76.2% (n=1,389)

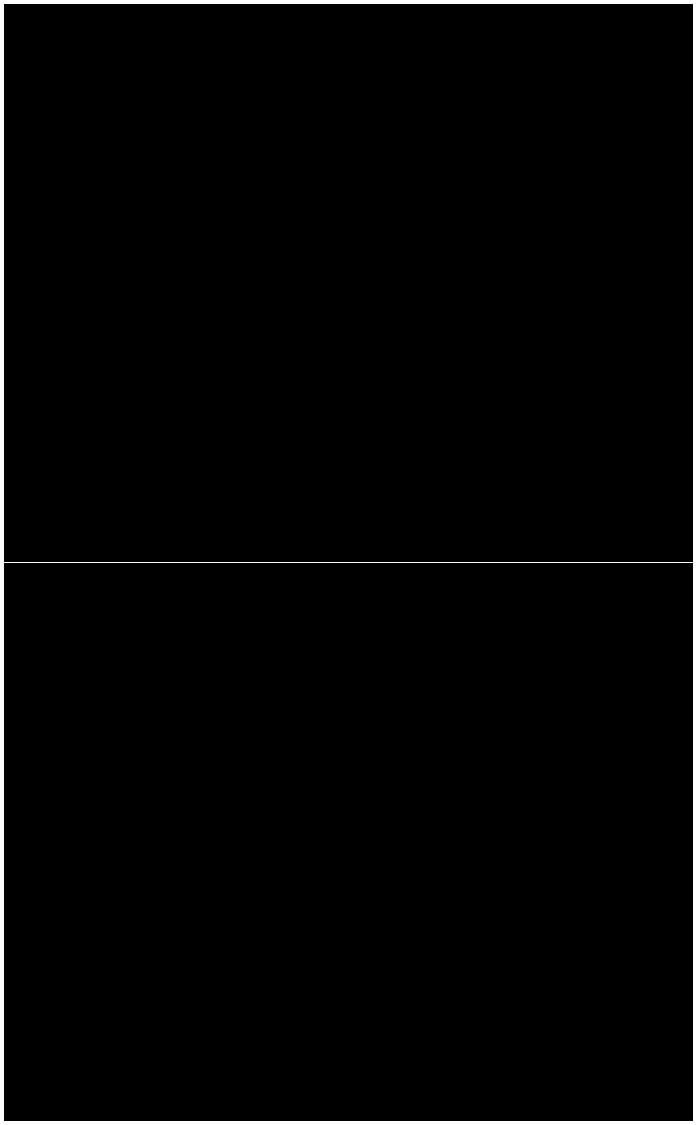
Abbreviations: HER2: human epidermal growth factor receptor 2; HR: hormone receptor; mBC: metastatic breast cancer; TNBC: triple negative breast cancer; OS: overall survival

C4. In Section B.3.3.3. please change Figure B17 to show actual extrapolations of each curve in the TNBC subgroup (the zero risk of recurrence lines after 5 years can be left to illustrate what is used in the model). This will allow us to see what is being used in the 10 year zero-recurrence scenario analysis. Please include zero risk of recurrence lines after 3 and 10 years as well so all information is presented.

Please find below the fit of the parametric survival models to the KM data for iDFS in the TNBC subgroup for four different scenarios: (1) 5-year zero risk of recurrence, (2) 3-year zero risk of recurrence, (3) 10-year zero risk of recurrence and (4) lifetime risk of recurrence. We have provided separate figures as combining all four scenarios in one graph makes it impossible to distinguish between the different models and scenarios.

Figure 6: Fit of the parametric survival models to the TNBC subgroup Kaplan-Meier data for iDFS in OlympiA (from top to bottom: 5-year zero risk of recurrence, 3-year zero risk of recurrence, 10-year zero risk of recurrence, 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

Differences between documents

C5. Document B and the CSR reports a hazard ratio of 5.70 for the subgroup 'type of chemotherapy (anthracycline and taxane regimen), whilst the trial report a hazard ratio of 5.80. Please confirm the correct result.

AstraZeneca have provided more recent DCO2 data in Appendix 1, which includes an updated hazard ratio for this subgroup.

AstraZeneca can clarify that neither the Document B, CSR or NEJM article hazard ratio is 5.70 or 5.80 for this subgroup. The value in the CSR for the anthracycline + taxane subgroup is 0.57 (see Figure 5, page 174)[1] and the value in the NEJM article for this subgroup analysis is 0.58 (see Supplementary Appendix Table S10, page 60).[4] AstraZeneca can confirm that the CSR value of 0.57 is correct. Additionally, there is no meaningful difference between the chemotherapy-based subgroups and the benefit is consistent across groups.

C6. The number of patients in the BRCA subgroups differs between the NEJM report (Table 1), Document B (Table 10) and the CSR (Table 22). Document B and the CSR are in agreement. Which figures are correct?

OlympiA is a collaborative group study being coordinated worldwide by the Breast International Group (BIG) in partnership with Frontier Science (FS), NRG Oncology (NCI supported National Clinical Trials Network Group) and AstraZeneca. The NEJM publication was submitted by the joint academic partnership in order to support academic exchange, whilst the CSR was generated by AstraZeneca in order to support regulatory activities and thus had a different focus.

In OlympiA, patients were enrolled into the trial based on their g*BRCA* status determined via local test results, where available. If local test results were not available, then this was determined via a prospective central test. Any patient that was enrolled based on a local testing result was required to undergo retrospective central testing using the Myriad g*BRCA* test.

In the CSR generated by AstraZeneca, the iDFS subgroup analysis by *BRCA* status (DCO1) was based on the results of the central Myriad test only (Table 24 of CSR) in order to support regulatory activities, particularly those required for the companion diagnostic.[1] Contrastingly, the NEJM analysis was performed using a combination of local and Myriad testing results.[4] The differences in the numbers of patients by *BRCA* status across the CSR and NEJM report is therefore due to the inclusion of local testing results in the NEJM subgroup analysis.

Overall interpretation by *BRCA* status is the same regardless of approach undertaken. The results of subgroup analyses according to Myriad *BRCA* status (reported in the AstraZeneca CSR and regulatory labels), and combined local/myriad *BRCA* status (reported in the NEJM) showed consistent treatment effects with the analysis of iDFS in the full analysis set (FAS) population, with a treatment benefit of olaparib vs placebo evidenced across all of the *BRCA* subgroups, regardless of approach undertaken.

C7. The number of patients in the BRCA subgroups presented in Table 1 of the NEJM trial report differs to the number of patients in the BRCA groups included in the subgroup analysis (Figure 2 in NEJM trial report) for iDFS. Why is this?

Please refer to the response to Question C6.

C8. The result for iDFS for the BRCA2 subgroup differs between the NEJM trial report (Figure 2) and Document B (Figure 14)/the CSR (Figure 5). Please clarify why this is and what the correct result is.

Please refer to the response to Question C6.

C9. In the CSR, in table 19, it says there were 3 protocol deviations in each arm due to ‘no documented germline mutation in BRCA1 or BRCA2’. This does not match what is reported in Document B table 10 for ‘no gBRCAm’ – why is this?

The summary of protocol deviations for “no documented germline mutation in BRCA1 or BRCA2” includes one patient in the Olaparib arm who was tested by Myriad under a different AstraZeneca study code. This patient was confirmed to have an eligible gBRCA mutation but their Myriad BRCA status could not be transferred into the OlympiA trial data set. Because of this, the patient was classified as a protocol deviation.

References

1.AstraZeneca Data on File. OlympiA Clinical Study Report. 2021.
2.AstraZeneca Data on File. Interim analysis of Overall Survival in OlympiA (DCO2). 2022.
3.Tutt A, Garber J, Gelber R, et al. VP1-2022: Pre-specified event driven analysis of Overall Survival (OS) in the OlympiA phase III trial of adjuvant olaparib (OL) in germline BRCA1/2 mutation (gBRCAm) associated breast cancer. Annals of Oncology. 2022.
4.Tutt ANJ, Garber JE, Kaufman B, et al. Adjuvant Olaparib for Patients with BRCA1- or BRCA2-Mutated Breast Cancer. *N Engl J Med*. Jun 24 2021;384(25):2394-2405. doi:10.1056/NEJMoa2105215
5.AstraZeneca Data on File. Early breast cancer clinical interviews March 2022 (Data on File Number: GB-35540). 2022.
6.AstraZeneca Data on File. Early breast cancer clinical interviews December 2021 (Data on File Number: GB-35535). 2022.
7.NICE. NICE Guideline [NG101]: Early and locally advanced breast cancer: diagnosis and management. 2018. Available at: https://www.nice.org.uk/guidance/ng101 (accessed 06/01/2022).
8.Robson ME, Tung N, Conte P, et al. OlympiAD final overall survival and tolerability results: Olaparib versus chemotherapy treatment of physician's choice in patients with a germline BRCA mutation and HER2-negative metastatic breast cancer. *Ann Oncol*. Apr 1 2019;30(4):558-566. doi:10.1093/annonc/mdz012
9.NICE. TA62: Guidance on the use of capecitabine for the treatment of locally advanced or metastatic breast cancer. 2003. Available at: https://www.nice.org.uk/guidance/ta62 (accessed 27/05/2022).
10.NICE. Familial breast cancer: classification, care and managing breast cancer and related risks in people with a family history of breast cancer (Clinical guideline [CG164]). 2013. Available at: https://www.nice.org.uk/guidance/cg164 (accessed 06/01/2022).
11.NICE. TA725: Abemaciclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy. 2021. Available at: https://www.nice.org.uk/guidance/ta725 (accessed 16/03/2022).
12.NICE. TA619: Palbociclib with fulvestrant for treating hormone receptor-positive, HER2-negative, advanced breast cancer. 2020. Available at: https://www.nice.org.uk/guidance/ta619 (accessed 16/03/2022).
13.NICE. TA687: Ribociclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy. 2021. Available at: https://www.nice.org.uk/guidance/ta687 (accessed 16/03/2022).
14.NICE. CG81: Advanced breast cancer: diagnosis and treatment. 2017. Available at: https://www.nice.org.uk/guidance/cg81 (accessed 17/03/2022).
15.NICE. TA639: Atezolizumab with nab-paclitaxel for untreated PD-L1-positive, locally advanced or metastatic, triple-negative breast cancer. 2020. Available at: https://www.nice.org.uk/guidance/ta639 (accessed 09/02/2022).
16.NICE. TA432: Everolimus for the second-line treatment of metastatic renal cell carcinoma (review of TA219). Committee Papers. 2016. Available at: https://www.nice.org.uk/guidance/ta432/documents/committee-papers-5 (accessed 17/03/2022).
17.NHS England. Cyclophosphamide-Docetaxel-Doxorubicin. Available at: https://www.uhs.nhs.uk/Media/UHS-website-2019/Docs/Chemotherapy-SOPs1/Breastcancer/BreastCyclophosphamideDocetaxelDoxorubicinTACVer11.pdf (accessed 13/04/2022).
18.NHS England. Paclitaxel. Avaliable at: https://www.uhs.nhs.uk/Media/UHS-website-2019/Docs/Chemotherapy-SOPs1/Breastcancer/Paclitaxel-21-day.pdf (accessed 13/04/2022).
19.NHS England. Carboplatin.

20.Robertson JFR, Bondarenko IM, Trishkina E, et al. Fulvestrant 500 mg versus anastrozole 1 mg for hormone receptor-positive advanced breast cancer (FALCON): an international, randomised, double-blind, phase 3 trial. *The Lancet*. 2016;388(10063):2997-3005. doi:10.1016/S0140-6736(16)32389-3
21.NHS England. Everolimus and Exemestane. Available at: https://www.uhs.nhs.uk/Media/SUHTExtranet/Services/Chemotherapy-SOPs/Breastcancer/Everolimus-Exemestane.pdf (accessed 13/04/2022).
22.NICE. NICE health technology evaluations: the manual. 2022. Available at: https://www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technology-evaluation (accessed 12/04/2022).
23.NICE. NICE health technology evaluation topic selection: the manual. 2022. Available at: https://www.nice.org.uk/process/pmg37/chapter/about-this-guide (accessed 12/04/2022).
24.AstraZeneca Data on File. OlympiA Population Analysis (DCO2). 2022.
25.Kimmick GG, Li X, Fleming ST, et al. Risk of cancer death by comorbidity severity and use of adjuvant chemotherapy among women with locoregional breast cancer. *J Geriatr Oncol*. May 2018;9(3):214-220. doi:10.1016/j.jgo.2017.11.004
26.Dawood S, Broglio K, Ensor J, Hortobagyi GN, Giordano SH. Survival differences among women with de novo stage IV and relapsed breast cancer. *Ann Oncol*. Nov 2010;21(11):2169-2174. doi:10.1093/annonc/mdq220
27.Lobbezoo DJ, van Kampen RJ, Voogd AC, et al. Prognosis of metastatic breast cancer: are there differences between patients with de novo and recurrent metastatic breast cancer? *Br J Cancer*. Apr 28 2015;112(9):1445-51. doi:10.1038/bjc.2015.127
28.McKenzie HS, Maishman T, Simmonds P, Durcan L, Eccles D, Copson E. Survival and disease characteristics of de novo versus recurrent metastatic breast cancer in a cohort of young patients. *Br J Cancer*. May 2020;122(11):1618-1629. doi:10.1038/s41416-020-0784-z
29.Robson M, Ruddy KJ, Im SA, et al. Patient-reported outcomes in patients with a germline BRCA mutation and HER2-negative metastatic breast cancer receiving olaparib versus chemotherapy in the OlympiAD trial. *Eur J Cancer*. Oct 2019;120:20-30. doi:10.1016/j.ejca.2019.06.023
30.Collins JM, Nordstrom BL, McLaurin KK, et al. A Real-World Evidence Study of CDK4/6 Inhibitor Treatment Patterns and Outcomes in Metastatic Breast Cancer by Germline BRCA Mutation Status. *Oncol Ther*. Dec 2021;9(2):575-589. doi:10.1007/s40487-021-00162-4
31.Lenner P, Jonsson H. Excess mortality from breast cancer in relation to mammography screening in northern Sweden. *J Med Screen*. 1997;4(1):6-9. doi:10.1177/096914139700400104
32.Hanis TM, Yaacob NM, Hairon SM, et al. Modelling excess mortality among breast cancer patients in the North East Region of Peninsular Malaysia, 2007-2011: a population-based study. *BMC Public Health*. Dec 30 2019;19(1):1754. doi:10.1186/s12889-019-8113-2
33.Janssen-Heijnen ML, van Steenbergen LN, Voogd AC, et al. Small but significant excess mortality compared with the general population for long-term survivors of breast cancer in the Netherlands. *Ann Oncol*. Jan 2014;25(1):64-8. doi:10.1093/annonc/mdt424
34.Haghighat S, Akbari ME, Ghaffari S, Yavari P. Standardized breast cancer mortality rate compared to the general female population of Iran. *Asian Pac J Cancer Prev*. 2012;13(11):5525-8. doi:10.7314/apjcp.2012.13.11.5525
35.Öfverholm A, Einbeigi Z, Wigermo A, Holmberg E, Karsson P. Increased Overall Mortality Even after Risk Reducing Surgery for BRCA-Positive Women in Western Sweden. *Genes (Basel)*. Dec 16 2019;10(12)doi:10.3390/genes10121046
36.Warner E, Zhu S, Plewes DB, et al. Breast Cancer Mortality among Women with a BRCA1 or BRCA2 Mutation in a Magnetic Resonance Imaging Plus Mammography Screening Program. *Cancers (Basel)*. Nov 23 2020;12(11)doi:10.3390/cancers12113479
37.Ahlgrén-Rimpiläinen AJ, Arffman M, Suvisaari J, et al. Excess mortality from breast cancer in female breast cancer patients with severe mental illness. *Psychiatry Res*. Apr 2020;286:112801. doi:10.1016/j.psychres.2020.112801
38.Clèries R, Buxó M, Vilardell M, et al. No Excess Mortality up to 10 Years in Early Stages of Breast Cancer in Women Adherent to Oral Endocrine Therapy: A Probabilistic Graphical

Modeling Approach. *Int J Environ Res Public Health*. Mar 18 2022;19(6)doi:10.3390/ijerph19063605
39.Louwman WJ, Klokman WJ, Coebergh JW. Excess mortality from breast cancer 20 years after diagnosis when life expectancy is normal. *Br J Cancer*. Mar 2 2001;84(5):700-3. doi:10.1054/bjoc.2000.1616
40.Levi F, Randimbison L, Te VC, La Vecchia C. Long-term mortality of women with a diagnosis of breast cancer. *Oncology*. 2002;63(3):266-9. doi:10.1159/000065475
41.Mai PL, Chatterjee N, Hartge P, et al. Potential excess mortality in BRCA1/2 mutation carriers beyond breast, ovarian, prostate, and pancreatic cancers, and melanoma. *PLoS One*. 2009;4(3):e4812. doi:10.1371/journal.pone.0004812
42.NICE. TA598: Olaparib for maintenance treatment of BRCA mutation-positive advanced ovarian, fallopian tube or peritoneal cancer after response to first-line platinum-based chemotherapy. 2019. Available at: https://www.nice.org.uk/guidance/ta598 (accessed 31/05/2022).
43.Sopik V, Sun P, Narod SA. Predictors of time to death after distant recurrence in breast cancer patients. *Breast Cancer Res Treat*. Jan 2019;173(2):465-474. doi:10.1007/s10549-018-5002-9
44.van Maaren MC, de Munck L, Strobbe LJA, et al. Ten-year recurrence rates for breast cancer subtypes in the Netherlands: A large population-based study. *Int J Cancer*. Jan 15 2019;144(2):263-272. doi:10.1002/ijc.31914
45.Pan H, Gray R, Braybrooke J, et al. 20-Year Risks of Breast-Cancer Recurrence after Stopping Endocrine Therapy at 5 Years. *N Engl J Med*. Nov 9 2017;377(19):1836-1846. doi:10.1056/NEJMoa1701830
46.UK Government. Genome UK: The Future of Healthcare. 2020. Available at: https://www.gov.uk/government/publications/genome-uk-the-future-of-healthcare (accessed 31/05/2022). .
47.BRCA-Direct. Available at: https://www.brca-direct.org/ (accessed 31/05/2022).
48.NICE. TA424: Pertuzumab for the neoadjuvant treatment of HER2-positive breast cancer [ID767]. Committee Papers. 2016. Available at: https://www.nice.org.uk/guidance/ta424/documents/committee-papers-2 (accessed 31/05/2022).
49.NICE. TA569: Pertuzumab for adjuvant treatment of HER2-positive early breast cancer [ID1192]. Committee Papers. 2018. Available at: https://www.nice.org.uk/guidance/ta569/evidence/appraisal-consultation-1-committee-papers-pdf-6720470173 (accessed 31/05/2022).
50.NICE. TA632: Trastuzumab emtansine for adjuvant treatment of HER2-positive early breast cancer [ID1516]. Committee Papers. 2020. Available at: https://www.nice.org.uk/guidance/ta632/evidence/committee-papers-pdf-8771187997 (accessed 31/05/2022).
51.Goetz MP, Toi M, Campone M, et al. MONARCH 3: Abemaciclib As Initial Therapy for Advanced Breast Cancer. *J Clin Oncol*. Nov 10 2017;35(32):3638-3646. doi:10.1200/jco.2017.75.6155
52.NICE. TA612: Neratinib for extended adjuvant treatment of hormone receptor-positive, HER2-positive early stage breast cancer after adjuvant trastuzumab [ID981]. Committee Papers. 2019. Available at: https://www.nice.org.uk/guidance/ta612/evidence/appraisal-consultation-committee-papers-pdf-6967189694 (accessed 31/05/2022).
53.NICE. PMG24: Single technology appraisal and highly specialised technologies evaluation: User guide for company evidence submission template. 2015. Available at: https://www.nice.org.uk/process/pmg24/chapter/appendices (accessed 27/05/2022).
54.Tutt A, Garber JE, Kaufman B, et al. OlympiA: A phase III, multicenter, randomized, placebo-controlled trial of adjuvant olaparib after (neo) adjuvant chemotherapy in patients with germline BRCA1/2 mutations and high-risk HER2-negative early breast cancer. American Society of Clinical Oncology; 2021.
55.AstraZeneca Data on File. Early breast cancer clinical interviews May 2022 (Data on File Number: GB-35535). 2022.

56.Colleoni M, Sun Z, Price KN, et al. Annual Hazard Rates of Recurrence for Breast Cancer During 24 Years of Follow-Up: Results From the International Breast Cancer Study Group Trials I to V. *J Clin Oncol*. Mar 20 2016;34(9):927-35. doi:10.1200/jco.2015.62.3504
57.Salvo EM, Ramirez AO, Cueto J, et al. Risk of recurrence among patients with HR-positive, HER2-negative, early breast cancer receiving adjuvant endocrine therapy: A systematic review and meta-analysis. *Breast*. Jun 2021;57:5-17. doi:10.1016/j.breast.2021.02.009
58.Early Breast Cancer Trialists' Collaborative G. Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. *The Lancet*. 2011;378(9793):771-784. doi:10.1016/S0140-6736(11)60993-8

Appendix 1. OlympiA trial, second interim analysis for OS (DCO2: 12 July 2021)

1.1 Introduction

The company submission for olaparib as monotherapy for the adjuvant treatment of adult patients with germline *BRCA* mutation (g*BRCA*m), human epidermal growth factor receptor 2-negative (HER2-), high-risk early breast cancer (eBC) who have previously been treated with neoadjuvant or adjuvant chemotherapy was based on data from the early primary analysis of OlympiA (data cut-off 1 [DCO1]: 27 March 2020). Data from the secondary interim analysis for IDFS (DCO2: 12 July 2021) have since become available; this appendix provides an overview of the key efficacy and safety results from the OlympiA study at this analysis.

1.2 Efficacy

1.2.1 Summary of key endpoints from OlympiA

Key efficacy endpoints data are presented in Table 1, including a side-by-side comparison of the DCO2 data alongside the DCO1 data included in the initial submission dossier.

Observations at DCO2 are largely consistent with those from DCO1, and these updated data provide more mature evidence in support of the clinical benefit that olaparib affords patients with g*BRCA*m, HER2-, high-risk eBC. In particular, data from DCO2 demonstrate that **treatment with olaparib provides a statistically significant and clinically meaningful improvement in OS compared with placebo.** The reduction in invasive and distant disease-free recurrence (iDFS and dDFS, respectively) are also consistently observed at both analyses. These results are **remarkable for an interim readout of OS in an adjuvant eBC setting**, and **clearly demonstrate the sustained survival benefit of olaparib** in this setting.

Table 17: Summary of OlympiA primary and key secondary endpoints, DCO1 and DCO2 (FAS)

	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)
Estimate of hazard ratio (95% CI)[a, b, c]	0.58 [redacted]		0.63 (0.50–0.78)	
Estimate of hazard ratio (99.5% CI)[a, b]	0.58 [redacted]		NA	
Log-rank test: p-value[d]	0.0000073		[redacted]	
Percentage (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]
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)
Estimate of hazard ratio (95% CI) [a, b, c]	0.57 [redacted]		0.61 (0.48–0.77)	

	DCO1 (27 March 2020)		DCO2 (12 July 2021)	
	Olaparib (N=921)	Placebo (N=915)	Olaparib (N=921)	Placebo (N=915)
Estimate of hazard ratio (99.5% CI) [a, b]	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)
Estimate of hazard ratio (95% CI) [a, b, c]	0.68 ([redacted])		0.68 [redacted]	
Estimate of hazard ratio (98.5% CI) [a, b, e]	NA		0.68 (0.47–0.97)	
Estimate of hazard ratio (99% CI) [a, b]	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]

	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]

Footnotes: DCO1: 27 March 2020; DCO2: 12 July 2021. [a]Estimate of the treatment hazard ratio based on the stratified Cox's Proportional Hazards Model, <1 indicates a lower risk with olaparib compared with placebo arm. Stratification factors are the same as those used in the stratified log-rank test. [b]The CI for the hazard ratio was estimated using the profile likelihood approach. [c]Exploratory, not inferential; [d]p-value from a stratified log-rank test. Stratification is by chemotherapy type (2 levels: adjuvant vs neoadjuvant), hormone receptor status (2 levels: ER and/or PR-positive/HER2-negative vs TNBC) and prior platinum therapy (2 levels: yes vs no). Stratification factors were based upon the categories used in the randomisation system and were chosen by the pooling strategy. [e]Inferential, according to alpha spending rules for the interim analysis of overall survival.

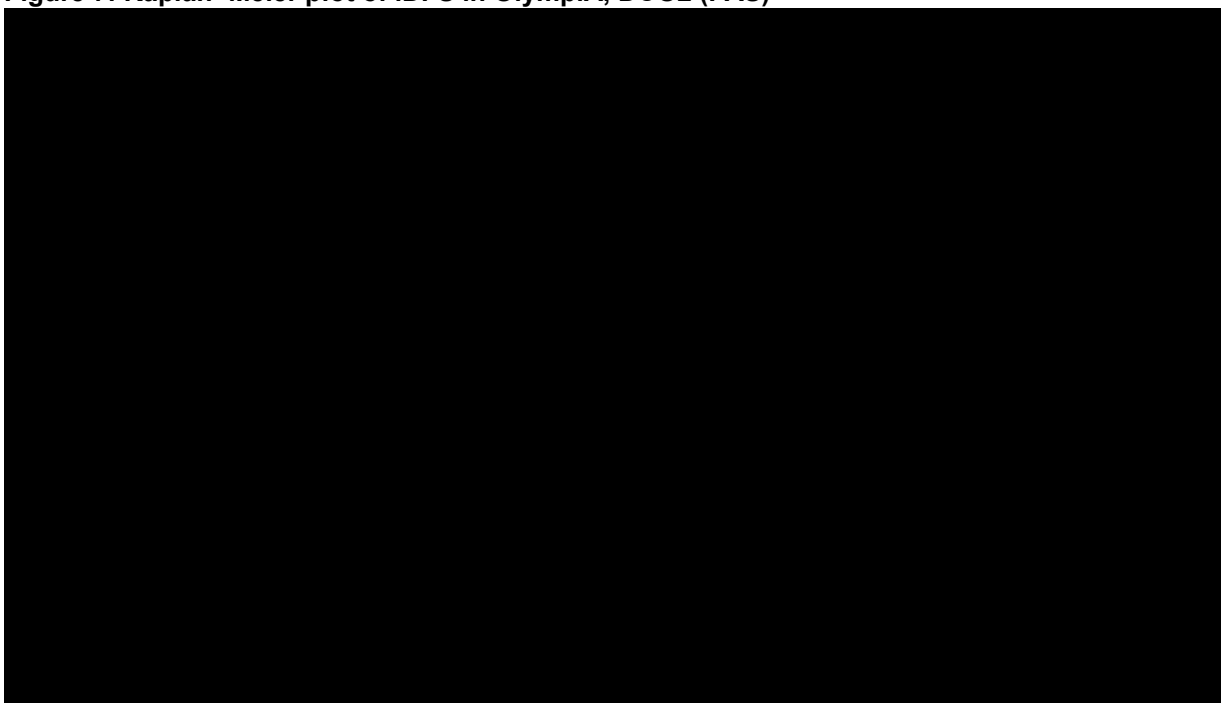
Abbreviations: CI: confidence interval; DCO: data cut-off; dDFS: distant disease-free survival; FAS: full analysis set; iDFS: invasive disease-free survival; NA: not applicable; OS: overall survival.

Source: AstraZeneca Data on File (OlympiA CSR);[1] Tutt et al. 2021a;[54] Tutt et al. 2021b;[4] AstraZeneca Data on File (Interim analysis of OS in OlympiA [DCO2]);[2] Tutt et al. 2022.[3]

1.2.2 Primary endpoint: Invasive disease-free survival (iDFS)

At DCO2, iDFS data were 18.6% mature (341 events/1,836 patients). Consistent with results from DCO1 for iDFS, at DCO2, a statistically significant and clinically meaningful investigator-assessed iDFS benefit was observed in patients treated with olaparib compared with those treated with placebo (37% reduction in risk of invasive disease recurrence or death; hazard ratio: 0.63, 95% confidence interval [CI]: 0.50–0.78; p[redacted]). Updated Kaplan-Meier curves for DCO2 continue to demonstrate sustained separation between treatment arms; moreover, Kaplan-Meier estimates indicate that the statistically significant iDFS hazard ratio translates into a clinically meaningful increase in the percentage of patients who remained invasive disease free in the olaparib arm at all timepoints compared with placebo (Table 17 and Figure 7).

Figure 7: Kaplan−Meier plot of iDFS in OlympiA, DCO2 (FAS)



Footnotes: DCO2: 12 July 2021.
Abbreviations: CI: confidence interval; DCO: data cut-off; FAS: full analysis set; iDFS: invasive disease-free survival.
Source: AstraZeneca Data on File (Interim analysis of OS in OlympiA [DCO2]).[2]

1.2.3 Secondary endpoints

Distant disease-free survival (dDFS)

At DCO2, dDFS data were 15.2% mature (279 events/1,836 patients). Similarly to that seen for iDFS at DCO1, the updated dDFS data are consistent with the observed iDFS benefit; at DCO2, olaparib treatment demonstrates a statistically and clinically meaningful benefit in dDFS compared with placebo (Table 17 and Figure 8). Furthermore, aligned to iDFS, an early and sustained separation in Kaplan-Meier curves continues to be observed for dDFS, and based on Kaplan-Meier estimates, a greater proportion of patients treated with olaparib remained free of distant disease over 4 years, compared with placebo.

Overall, 107 patients (11.6%) in the olaparib arm and 172 patients (18.8%) in the placebo arm had experienced a dDFS event, with a 39.3% reduction in risk of distance recurrence

observed for patients treated with olaparib vs placebo (hazard ratio: 0.61; 95% CI: 0.48, 0.77; p[redacted]).

Figure 8: Kaplan−Meier plot of dDFS in OlympiA, DCO2 (FAS)

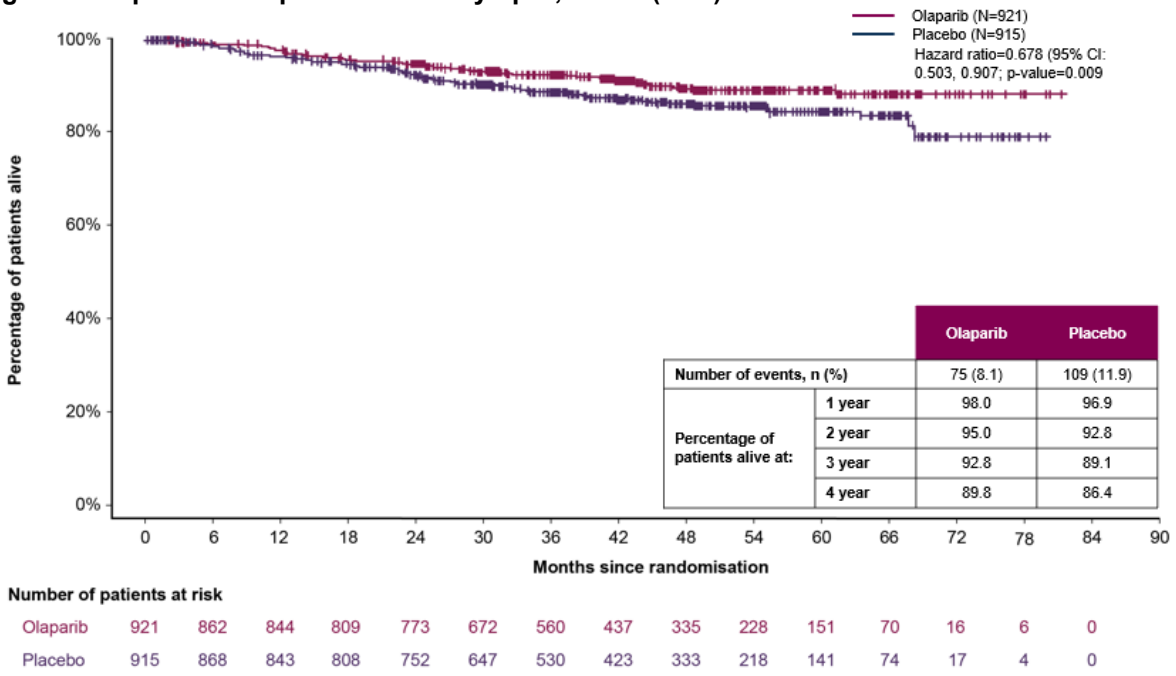
Footnotes: DCO2: 12 July 2021.
Abbreviations: CI: confidence interval; DCO: data cut-off; FAS: full analysis set; dDFS: distant disease-free survival.
Source: AstraZeneca Data on File (Interim analysis of OS in OlympiA [DCO2]).[2]

Overall survival (OS)

At DCO2, OS data were 10.0% mature (184 events/1,836 patients). Consistent with the positive trend in OS for olaparib observed at DCO1, at DCO2, **treatment with olaparib resulted in a statistically significant and clinically meaningful improvement in OS compared with placebo**, with fewer deaths reported in the olaparib group than the placebo group (32% reduction in risk of death; hazard ratio: 0.68; 95% CI, 0.47–0.97; p=0.009). Updated Kaplan−Meier curves for DCO2 continue to demonstrate sustained separation between treatment arms; moreover, Kaplan-Meier estimates indicate that the statistically significant OS hazard ratio translates into a clinically meaningful increase in the percentage of patients who remain alive in the olaparib arm at all timepoints compared with placebo (Table 17 and Figure 9).

These observed results are **remarkable for an interim readout of OS in an adjuvant eBC setting**, and **clearly demonstrate the sustained survival benefit of olaparib** in this setting.

Figure 9: Kaplan−Meier plot of OS in OlympiA, DCO2 (FAS)



Footnotes: DCO2: 12 July 2021.
Abbreviations: CI: confidence interval; DCO: data cut-off; FAS: full analysis set; OS: overall survival.
Source: AstraZeneca Data on File (Interim analysis of OS in OlympiA [DCO2]).[2]

Incidence of new primary breast or ovarian cancer

A summary of all new cancers that occurred post-randomisation at DCO2 is provided in Table 18, including a side-by-side comparison to the DCO1 data included in the initial submission dossier.

Observations at DCO2 are largely consistent with those from DCO1, and these updated data provide more mature evidence in support of the clinical benefit that olaparib affords patients with [redacted] incidences of new breast and ovarian cancer. At DCO2, the incidences of primary contralateral breast cancers (invasive and non-invasive), new primary ovarian cancer, new primary fallopian tube cancer and new primary peritoneal cancer, without considering competing risks, were [redacted], but [redacted] in the olaparib arm ([redacted], 0.1%, 0.1%, and [redacted], respectively) compared with the placebo arm ([redacted], 0.7%, 0.4%, and [redacted], respectively).

Table 18. A summary of all cancers that occurred post randomisation in OlympiA, DCO1 and DCO2 (FAS)

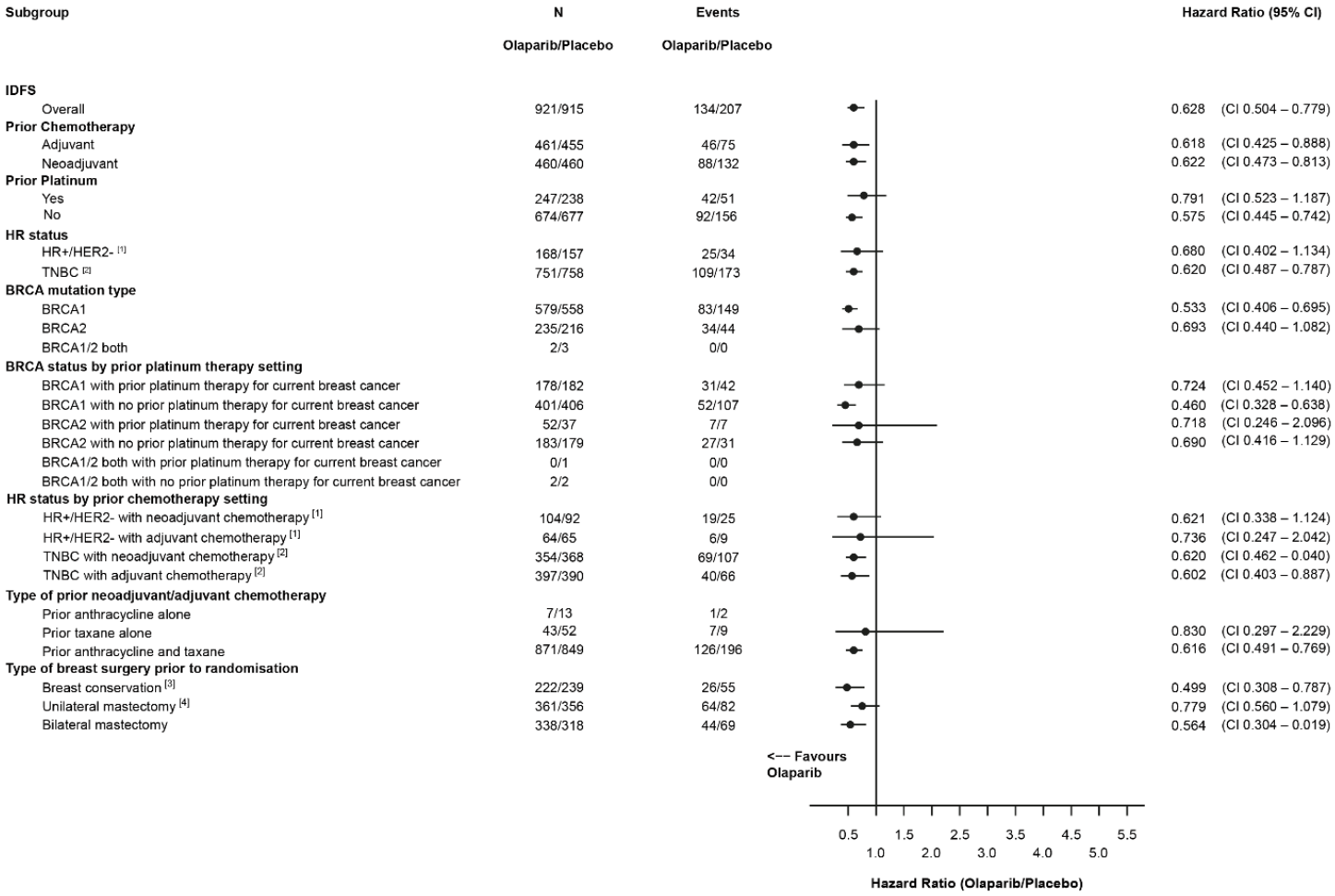
	DCO1 (27 March 2020)a		DCO2 (12 July 2021)b	
Number (%) of patients with	**Olaparib (N=921)**	**Placebo (N=915)**	**Olaparib (N=921)**	**Placebo (N=915)**
Contralateral invasive breast cancer	[redacted]	[redacted]	[redacted]	[redacted]
Contralateral non-invasive breast cancer	[redacted]	[redacted]	[redacted]	[redacted]
New primary ovarian cancer[c]	[redacted]	[redacted]	[redacted]	[redacted]
Ovarian cancer	[redacted]	[redacted]	1 (0.1)	6 (0.7)
Fallopian tube cancer	[redacted]	[redacted]	1 (0.1)	4 (0.4)
Peritoneal cancer	[redacted]	[redacted]	0	0
New primary invasive non-breast non-ovarian malignancies	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: DCO1: 27 March 2020; DCO2: 12 July 2021. Summary of cancers without considering competing risks. [a]This includes all new cancers. [b]This includes all cancers, both new and recurrent for contralateral breast cancer, and new primary for ovarian, fallopian & peritoneal cancers. [c]Includes new primary ovarian, fallopian, and peritoneal cancers, without considering competing risks. [d]One patient was captured in the database with ovarian cancer recurrence.
Abbreviations: DCO: data cut-off; FAS: full-analysis set.
Source: AstraZeneca Data on File (OlympiA CSR);[1] AstraZeneca Data on File (Interim analysis of OS in OlympiA [DCO2]).[2]

1.2.4 Subgroup analysis

Subgroup analyses of iDFS data were undertaken to assess consistency of treatment effect across a range of key clinical, prognostic and demographic characteristics, including prior chemotherapy status, prior platinum therapy use, HR-status, and *BRCA* mutation type (Figure 10). Consistent with subgroup analyses of iDFS data from DCO1, at DCO2, iDFS benefit observed in the intention-to-treat (ITT) population was generally consistent across stratification and pre-specified subgroups.

Figure 10: Forest plot of iDFS according to stratification factors, DCO2 (FAS)



Footnotes: DCO2: 12 July 2021. [1] HR+ is defined as ER-positive and/or PR-positive. [2] Two patients are excluded from the summary of the TNBC subset because they do not have confirmed negative HER2 status. [3] Breast conservation was defined as partial mastectomy/breast quadrantectomy/breast segmentectomy/breast lumpectomy and breast re-excision of margins. [4] Unilateral mastectomy was defined as modified radical mastectomy, radical mastectomy (Halsted), or simple mastectomy.
Abbreviations: CI: confidence interval; DCO: data cut-off; ER: oestrogen receptors; FAS: full analysis set; HER2: human epidermal growth factor receptor 2; HR: hormone receptor; iDFS: invasive disease-free survival; PR: progesterone receptor; TNBC: triple-negative breast cancer.
Source: AstraZeneca (OlympiA Efficacy Analysis DCO2).

1.3 **HRQoL**

1.3.1 EORTC QLQ-C30

At the DCO2, mean (SD) baseline EORTC QLQ-C30 global health status/QoL functioning scores remained comparable between the treatment arms for patients who had received prior neoadjuvant treatment and prior adjuvant treatment. Compliance rates matched those observed at DCO1. The EORTC QLQ-C30 global health status/QoL functioning scores remained stable for both the olaparib and placebo arms at 6 and 12 months; small improvements from baseline were observed in global health status/QoL, role functioning and social functioning in both arms at 18 and 24 months, with no clinically meaningful differences between treatment arms observed (Figure 11 and Figure 12).

Figure 11: Mean change from baseline of EORTC QLQ-C30 Global Health QoL Score in patients who had received prior neoadjuvant chemotherapy in OlympiA, DCO2 (PRO analysis set)

Footnotes: DCO2: 12 July 2021. GHQ score ranges from 0 to 100 with higher score indicating better QoL. Adjusted least-square mean responses and 95% CI are obtained from MMRM analysis of the GHQ score. The model includes treatment, time and treatment by time interaction, corresponding baseline score and the baseline score by time interaction.
Abbreviations: CI: confidence interval; DCO: data cut-off; GHQ: Global Health Quality; MMRM: mixed model for repeated measures; PRO: patient reported outcome.
Source: AstraZeneca Data on File (Interim analysis of OS in OlympiA [DCO2]).[2]

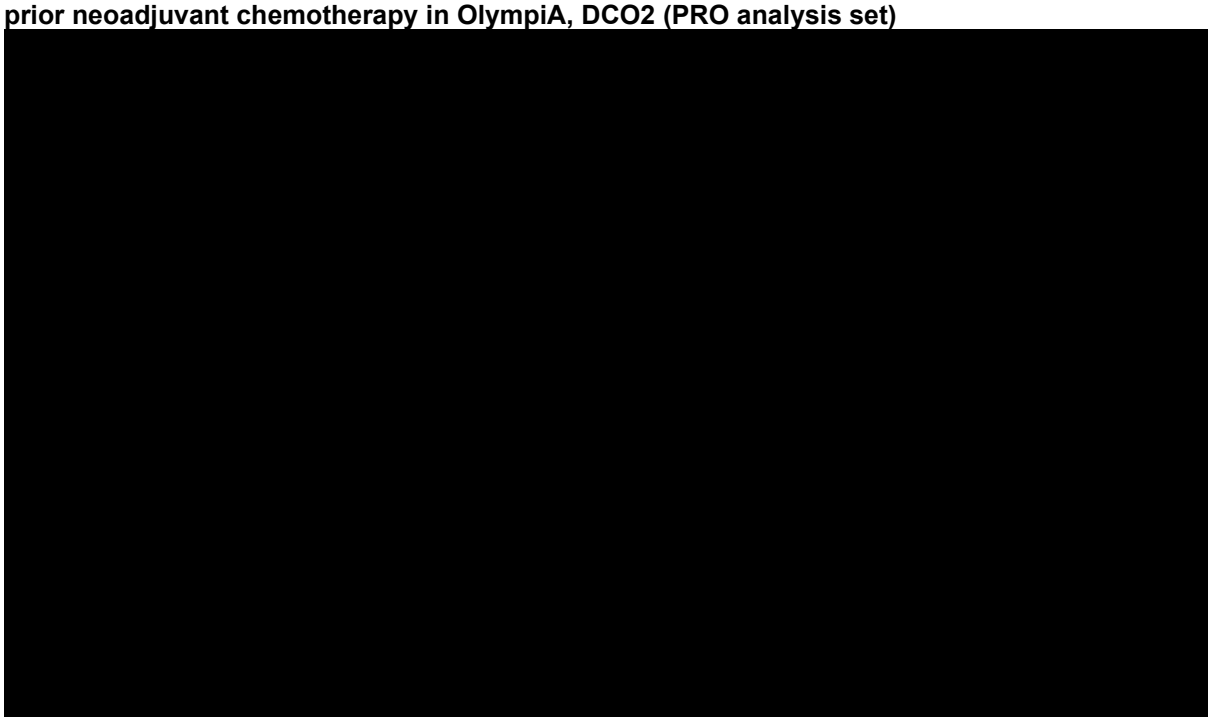
Figure 12: Mean change from baseline of EORTC QLQ-C30 Global Health QoL Score in patients who had received prior adjuvant chemotherapy in OlympiA, DCO2 (PRO analysis set)

Footnotes: DCO2: 12 July 2021. GHQ score ranges from 0 to 100 with higher score indicating better QoL. Adjusted least-square mean responses and 95% CI are obtained from MMRM analysis of the GHQ score. The model includes treatment, time and treatment by time interaction, corresponding baseline score and the baseline score by time interaction.
Abbreviations: CI: confidence interval; DCO: data cut-off; GHQ: Global Health Quality; MMRM: mixed model for repeated measures; PRO: patient reported outcome.
Source: AstraZeneca Data on File (Interim analysis of OS in OlympiA [DCO2]).[2]

1.3.2 FACIT-Fatigue

Consistent with the early primary analysis, FACIT-Fatigue scores from DCO2 indicate that olaparib has [redacted] on patient HRQoL, with [redacted] HRQoL scores observed between placebo and treatment groups. Compliance rates matched those observed at DCO1. Mean baseline FACIT-Fatigue scores were comparable between treatment arms for patients who had received prior neoadjuvant treatment and prior adjuvant treatment (Figure 13 and Figure 14).

Figure 13: Mean change from baseline of FACIT-Fatigue scores in patients who had received prior neoadjuvant chemotherapy in OlympiA, DCO2 (PRO analysis set)



Footnotes: DCO2: 12 July 2021. FACIT-Fatigue score ranges from 0 to 52 with higher score indicating less fatigue. Adjusted least-square mean changes and 95% CI are obtained from mixed model for repeated measures analysis of the change from baseline. The model includes treatment, time and treatment by time interaction, corresponding baseline score and the baseline score by time interaction.
Abbreviations: CI: confidence interval; DCO: data cut-off; FACIT: functional assessment of chronic illness therapy; PRO: patient reported outcome.
Source: AstraZeneca Data on File (Interim analysis of OS in OlympiA [DCO2]).[2]

Figure 14: Mean change from baseline of FACIT-Fatigue scores in patients who had received prior adjuvant chemotherapy in OlympiA, DCO2 (PRO analysis set)

Footnotes: DCO2: 12 July 2021. FACIT-Fatigue score ranges from 0 to 52 with higher score indicating less fatigue. Adjusted least-square mean changes and 95% CI are obtained from mixed model for repeated measures analysis of the change from baseline. The model includes treatment, time and treatment by time interaction, corresponding baseline score and the baseline score by time interaction.
Abbreviations: CI: confidence interval; DCO: data cut-off; FACIT: functional assessment of chronic illness therapy; PRO: patient reported outcome.
Source: AstraZeneca Data on File (Interim analysis of OS in OlympiA [DCO2]).[2]

1.4 **Safety analyses**

At DCO2, data from OlympiA continued to show olaparib to have a favourable safety and tolerability profile, consistent with DCO1 data previously presented for the safety analysis set (SAS) in the submission. Most adverse events (AEs) observed were non-serious, mild or moderate in severity and did not result in treatment discontinuation. The incidence of AEs leading to death and serious adverse events (SAEs) were similar between the treatment arms.

A summary of AEs reported at DCO1 and DCO2 of the OlympiA trial can be found in Table 19.

Table 19: Summary of AEs in OlympiA, DCO1 and DCO2 (SAS)

	DCO1 (27 March 2020)		DCO2 (12 July 2021)	
AEs	**Olaparib (N=911)**	**Placebo (N=904)**	**Olaparib (N=911)**	**Placebo (N=904)**
All grade AEs, n (%)	835 (91.7)	753 (83.3)	836 (91.8)	758 (83.8)
Grade ≥3 AEs, n (%)	221 (24.3)	102 (11.3)	223 (24.5)	102 (11.3)
SAEs, n (%)	79 (8.7)	76 (8.4)	79 (8.7)	78 (8.6)
Deaths, n (%)	1 (0.1)	2 (0.2)	1 (0.1)	2 (0.2)
Dose interruptions due to AEs, n (%)	[redacted]	[redacted]	286 (31.4)	99 (11.0)
Dose reductions due to AEs, n (%)	[redacted]	[redacted]	213 (23.4)	33 (3.7)
Discontinuations due to AEs, n (%)	90 (9.9)	38 (4.2)	98 (10.8)	42 (4.6)

Footnotes: DCO1: 27 March 2020; DCO2: 12 July 2021. Patients with multiple events in the same category were counted only once in that category. Patients with events in more than one category were counted once in each of those categories. CTCAE Version 4.03. MedDRA Version 22.1.
Abbreviations: CTCAE: Common Terminology Criteria for Adverse Events; AEs: adverse events; DCO: data cut-off; MedDRA: Medical Dictionary for Regulatory Activities Terminology; SAEs: serious adverse events; SAS: safety analysis set.
Source: AstraZeneca Data on File (OlympiA CSR);[1] Tutt et al. 2021a;[54] Tutt et al. 2021b;[4] AstraZeneca Data on File (Interim analysis of OS in OlympiA [DCO2]);[2] Tutt et al. 2022.[3]

Appendix 2. Updated cost-effectiveness modelling

2.1 Modelling of subgroup outcomes

As discussed in the Appendix 1 (Section 1.1), with the availability of patient-level data from the second interim OS analysis of the OlympiA trial (DCO2, 12th July 2021), the following subsections outline how the economic model has been updated to incorporate the new data and how the base case assumptions and results have changed.

Although DCO2 provides some additional iDFS data for the HR+/HER2- sub-group, the level of additional data is not considered sufficient to overcome the challenges associated with using data from this subgroup to model iDFS that were outlined in Document B, Section 3.3.1. As a result, it remains infeasible to reliably estimate the survival of patients with HR+/HER2- disease in OlympiA using conventional subgroup analysis (i.e., fitting models to a subset of the study) due to the number of iDFS events observed in this subgroup (n=25 for olaparib and n=34 for placebo in DCO2 vs. n=19 for olaparib and n=25 for placebo in DCO1). The relatively small number of events observed for this population greatly prohibits the scope of statistical analysis for iDFS and post-recurrence survival for input to the model.

Furthermore, consistent with the analyses conducted using data from DCO1, there remains no statistical evidence of a differential treatment effect by HR subgroup, with the benefit of olaparib being observed irrespective of HR status (please see Figure 10, Appendix 1). The baseline survival rates (i.e., in the placebo arm) for iDFS in the HER2-/HR+ and TNBC subgroups of OlympiA continue to be consistent across the duration of study follow-up (see Table 4 below), with only a ~1.4% difference in observed iDFS and no difference in observed OS at 4 years. For this reason, the primary ITT analysis is again used as a proxy to model the baseline efficacy of placebo in the HR+/HER2- population.

Table 20: Comparison of landmark iDFS and OS for HR+/HER2- and TNBC patients in the placebo arm of OlympiA

Time point, years	iDFS in patients randomised to placebo		OS in patients randomised to placebo	
	TNBC N=758	HER2-/HR+ N=157	TNBC N=758	HER2-/HR+ N=157
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]
4	75.2%	76.6%	86.3%	86.3%

Footnotes: DCO2, 12th July 2021
Abbreviations: HER2: human epidermal growth factor receptor 2; HR: hormone receptor; iDFS: invasive disease-free survival; OS: overall survival: TNBC: triple negative breast cancer.

Table 21 provides an overview of which input parameters in the economic model have been updated following DCO2, and which parameters remain identical to the original submission in April 2022. Any changes to the base case assumptions which have been implemented following the EAG's review are also added.

Table 21: Updated input parameters in the economic model following the availability of DCO2 data

Parameter	Submitted economic model April '22	Updated economic model May '22
Efficacy parameters: TP1-TP2	DCO1 data	DCO2 data

Parameter	Submitted economic model April '22	Updated economic model May '22
Efficacy parameters: TP3	External data	No change
Efficacy parameters: TP4-6	DCO1 data	DCO2 data
Efficacy parameters: TP7	External data	No change
Conditional probability of developing a non-mBC vs. a mBC recurrence	DCO1 data	DCO2 data
HSU values	OlympiA mapping analysis and external data	No change
Adverse events	DCO1 data	DCO2 data
Cost inputs	External data	No change

Footnotes: DCO2, 12th July 2021
Abbreviations: DCO: data cut-off; HSU: health state utility; TP: transition probability.

Considering that the key change to the economic model is updating the efficacy parameters to model TP1–2 and TP4–6, the following subsections repeat the description of the parametric survival analysis and the process of selecting the final choice of preferred model for these transition probabilities, now based on DCO2 data, as described in Sections B.3.3.2–B3.3.5 of the original submission dossier.

2.2 Modelling of iDFS

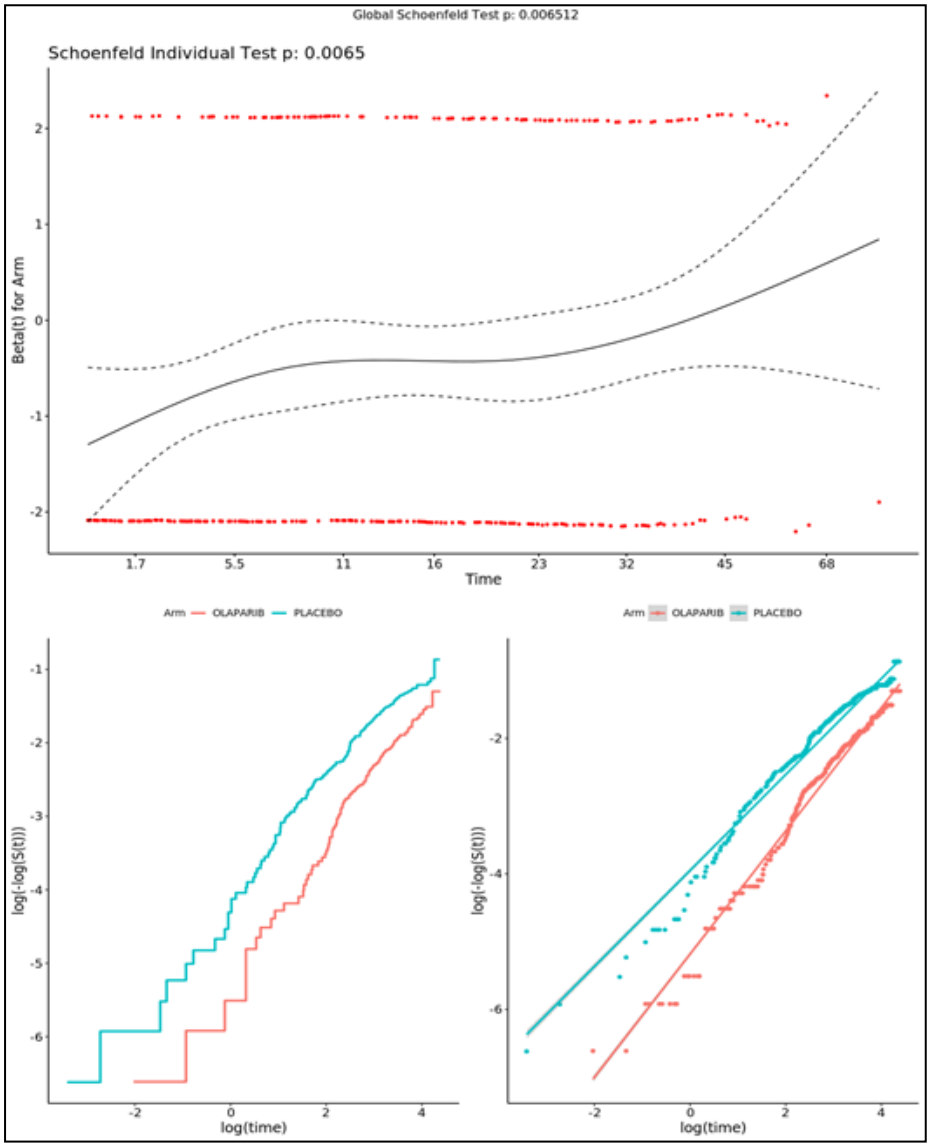
2.2.1 Derivation of the clinical parameters for TP1, TP2 and TP3

Step 1: Parametric survival analysis for iDFS (TP1 and TP2)

At the interim analysis of iDFS (DCO1), an assessment of proportional hazards (PH) was conducted as part of the planned statistical analysis of the OlympiA trial. The PH assumption was assessed by visual inspection of the log-cumulative hazards plot and using the Grambsch–Therneau (G-T) test. Under PH, the log-cumulative hazards plot will show approximately parallel lines by arm, and the G-T test is not statistically significant (p>0.05).

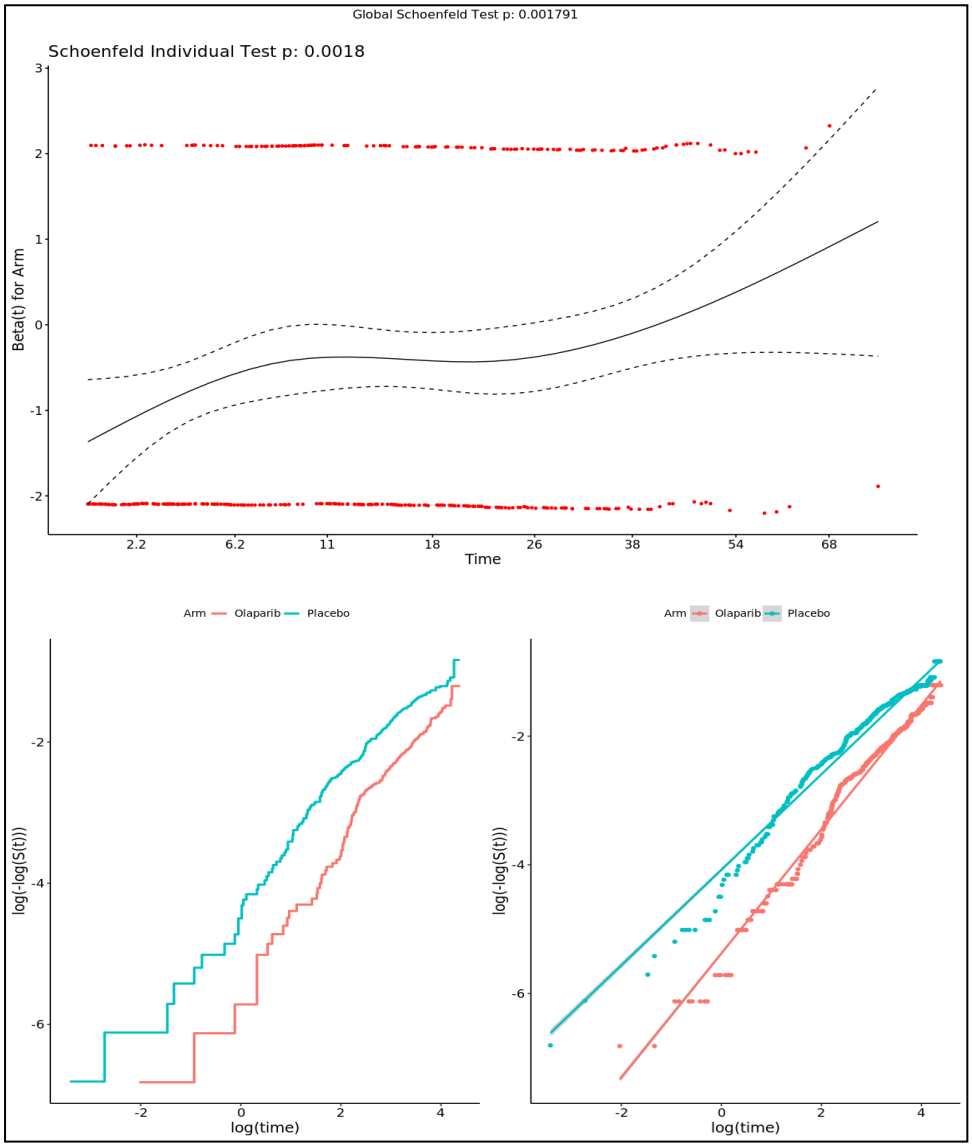
The assessment of PH for iDFS was repeated on the data from DCO2. In the TNBC and ITT (proxy for HR+/HER2-) populations of OlympiA, the unadjusted G-T test results were p=0.0065 and p=0.0018 respectively. The Schoenfeld and log-cumulative hazard plots (Figure 15 for TNBC and Figure 16 for HR+/HER2- using ITT data as a proxy) showed evidence of non-PH in the form of a non-horizontal log-hazard ratio and non-parallel lines between arms, respectively. These results indicate that with the DCO2 data, the PH assumption likely does not hold for the iDFS endpoint.

Figure 15: Schoenfeld residual and log-cumulative hazards versus log-time plots of iDFS for the placebo and olaparib arms of OlympiA (TNBC)



Abbreviations: iDFS: invasive disease-free survival; TNBC: triple negative breast cancer.

Figure 16: Schoenfeld residual and log-cumulative hazards versus log-time plot of iDFS for the placebo and olaparib arms of OlympiA (HR+/HER2-, using ITT data as a proxy)



Abbreviations: HER2: human epidermal growth factor receptor 2; HR: hormone receptor; iDFS: invasive disease-free survival, ITT: intention to treat.

Following Decision Support Unit (DSU) guidance, a series of independent parametric survival models was therefore fitted to patient-level data from each arm of OlympiA. The statistical goodness of fit was reported in terms of the Akaike Information Criteria (AIC) and Bayesian Information Criteria (BIC) scores, where a lower score indicates improved fit (Table 22).

For TNBC, the best fitting distribution based on the AIC statistics was the Gompertz for both the placebo and olaparib arms. For the HR+/HER2- group using the ITT data as a proxy, the AIC scores favoured the lognormal for the olaparib arm, and the Gompertz for the placebo arm. However, as distributions with an AIC/BIC score within 5 are considered to have similar goodness of statistical fit, all the other curves with the exception of the exponential and gamma also showed good data fits for both the TNBC and HR+/HER2- groups. Overall, the Gompertz and lognormal were consistently the best fitting functions according to AIC and BIC score across arms and populations.

Table 22: AIC and BIC values for the parametric survival models fitted to the time from randomisation to distant metastatic or non-distant metastatic recurrence (DCO2 data)

Model	Olaparib		Placebo	
	AIC	BIC	AIC	BIC
TNBC				
Exponential	1428.04 (7)	1428.04 (1)	2098.13 (7)	2102.76 (7)
Weibull	1426.93 (5)	1426.93 (5)	2060.75 (5)	2070.01 (5)
Loglogistic	1425.84 (3)	1425.84 (4)	2056.86 (4)	2066.12 (3)
Lognormal	1424.02 (2)	1424.02 (3)	2050.79 (2)	2060.05 (2)
Gompertz	1423.86 (1)	1423.86 (2)	2047.87 (1)	2057.13 (1)
Generalized gamma	1425.95 (4)	1425.95 (7)	2052.41 (3)	2066.3 (4)
Gamma	1427.26 (6)	1427.26 (6)	2063.23 (6)	2072.5 (6)
ITT as a proxy for HR+/HER2-				
Exponential	1750.43 (5)	1755.26 (1)	2508.00 (7)	2512.82 (7)
Weibull	1750.93 (6)	1760.58 (5)	2472.8 (5)	2482.43 (5)
Loglogistic	1749.86 (3)	1759.51 (4)	2468.38 (4)	2478.02 (4)
Lognormal	1748.18 (1)	1757.83 (2)	2461.37 (2)	2471.01 (2)
Gompertz	1748.88 (2)	1758.53 (3)	2458.98 (1)	2468.62 (1)
Generalized gamma	1749.98 (4)	1764.45 (7)	2463.04 (3)	2477.5 (3)
Gamma	1751.14 (7)	1760.80 (6)	2475.40 (6)	2485.04 (6)

Footnotes: DCO2, 12th July 2021
Notes: (X) indicates the rank of each model based on the goodness-of-fit statistics.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; DCO: data cut-off; HER2: human epidermal growth factor receptor 2; HR: hormone receptor; ITT: intention to treat; TNBC: triple negative breast cancer.

The fit of the models to the Kaplan-Meier plots for iDFS is shown in Figure 17. For the olaparib arm, all models provided a reasonable prediction of the Kaplan-Meier probabilities for iDFS up to the end of study follow-up (~78 months). For the placebo arm, most models yielded a reasonable fit to the Kaplan-Meier for iDFS. Similar to the extrapolations based on DCO1 data, the exponential model gave a notably poor fit to the data and was found to overestimate survival in the first 2-years and underestimate placebo survival at later time points.

Figure 17: Fit of the parametric survival models to the Kaplan-Meier data for iDFS in OlympiA (TNBC, left; ITT used as a proxy for HR+/HER2, right)

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

When reviewing the modelled hazards over time, clinical opinion and empirical literature (as described in Section B.3.3.3.1 in the original submission dossier) suggest an initial upward and then downward trend in the risk of recurrence for patients with high-risk, *BRCA*m, HER2-negative disease, which is well-observed in the best-fitting models (e.g., the lognormal), with the exception of the Gompertz which simply assumes a monotonical decrease in hazard over time. For the olaparib arm, the long-term trend in the hazard rate for olaparib was similar to placebo, with rates that are predicted to be initially increasing and then decreasing (e.g., lognormal) or simply decreasing over time (e.g., Gompertz).

However, when overlaying the plots for the modelled hazards rates for iDFS for the olaparib and placebo arms, in all of the parametric models the two curves eventually cross over time, thereby suggesting that the risk of recurrence of patients in the placebo arm will eventually be lower than the risk of recurrence of patients who instead received olaparib treatment. This unrealistic characterisation of the long-term hazard is likely driven by data uncertainty towards the end of the trial follow-up and is inconsistent with the observed trend of olaparib maintaining a lower rate of occurrence or death versus placebo. Therefore, in order to model a reliable estimate of long-term iDFS in this population, the olaparib hazards were assumed to equal that of placebo at the point of the curves crossing, which implies no further benefit of treatment. We believe this approach remains conservative, particularly given the observed and statistically significant iDFS and OS benefit observed already in the OlympiA trial, and was ultimately validated by UK medical oncologists, who consistently commented that they do not expect that the risk of recurrence for patients on “watch & wait” following active treatment would ever be lower than patients who receive olaparib in the adjuvant setting.

In summary, the Gompertz and lognormal models consistently provide the best fit to the iDFS data in OlympiA and are therefore considered the primary candidate models for the base case in both the TNBC and HR+/HER2- analyses. The log-logistic and generalised gamma models are suitable alternative options with a plausible fit to the data. For the olaparib arm, the exponential provided a reasonable fit to the data but was shown to poorly estimate iDFS for the placebo arm, as well as assuming an unrealistic constant hazard over time. The Weibull and gamma distributions were consistently amongst the worst fitting models based on statistics and visual fit to iDFS, across the arms and populations of OlympiA. An overview of the characteristics of each model fitted to the iDFS in the TNBC and ITT populations of OlympiA is given in Table 23 below.

Table 23: Overview of characteristics of the parametric models fitted to the iDFS data in the TNBC and ITT populations of OlympiA

Characteristic	**TNBC**		**HR+/HER2- (using ITT data as a proxy)**	
	Olaparib	**Placebo**	**Olaparib**	**Placebo**
Proportional hazards	Does not hold			
Trend in hazard rates over time	Hazards converge at approximately 3-years			
Goodness of fit based on AIC, BIC, and visual fit to data (✓ = best fitting, ~ = plausible fit, × = poor fit)				
Exponential	~	×	~	×
Weibull	×	×	×	×
Loglogistic	~	~	~	~
Lognormal	✓ (2nd)	✓ (2nd)	✓ (1st)	✓ (2nd)
Gompertz	✓ (1st)	✓ (1st)	✓ (2nd)	✓ (1st)
Gen. gamma	~	~	~	~
Gamma	×	×	×	×

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; HER2: human epidermal growth factor receptor 2; HR: hormone receptor; iDFS: invasive disease-free survival, ITT: intention to treat; TNBC: triple negative breast cancer.

Step 2: Modelling the long-term risk of recurrence in TNBC and HR+/HER2-

No changes to the economic model have been made following the availability of the DCO2 data with regards to capturing the differences in long-term baseline risk of recurrence in patients with TNBC vs. HR+/HER2- disease. As described in Document B, Section 3.3.3.1, the baseline risk of recurrence for patients with TNBC is assumed to be equal to zero from year 5 of the model's time horizon, reflecting feedback provided by UK clinical experts and data from long-term studies in eBC. For patients with HR+/HER2- disease, the risk of recurrence is assumed to remain throughout the lifetime horizon of the model.

Step 3: Conditional probability of a non-distant recurrence

For both the TNBC and HR+/HER2- analyses, the conditional probability of developing a non-distant recurrence as part of an iDFS event was estimated from the summary of first iDFS event types in the OlympiA ITT population. At DCO2, 134 patients (14.5% of the total cohort) in the olaparib arm and 207 patients (22.6% of the total cohort) in the placebo arm experienced an iDFS event. Of the 134 patients with an iDFS event in the olaparib arm, 33 had experienced a non-distant recurrence comprising 9 regional recurrences, 9 local recurrences and 15 contralateral invasive breast cancer events. The conditional probability of an iDFS event being a non-distant recurrence for olaparib is therefore estimated at 24.6% (33 divided by 134). For the placebo arm, 48 of 207 patients with an iDFS event had experienced a non-distant recurrence, comprising of 18 regional recurrences, 12 local recurrences and 18 contralateral invasive breast cancer events. The associated probability of an iDFS event being a non-distant recurrence for placebo is therefore 23.2% (48 divided by 207).

Similar to the assumption made in the initial submission, given the lack of evidence that olaparib treatment has any impact on the type of event experienced (difference between event probabilities between the olaparib vs placebo arm of <1.5%), the conditional probability of non-distant recurrence was assumed the same across arms. In the updated base case economic analysis, the conditional probability for a non-distant recurrence is thus set at 23.8% (81 divided by 341 patients) for the TNBC and HR+/HER2- subgroups respectively, with the corresponding conditional probability of a distant recurrence at 76.2%. An overview of the conditional probabilities based on DCO1 vs. DCO2 data is given in Table 24 below.

Table 24: Difference in observed conditional probabilities of any iDFS being a non-distant vs a distant recurrence based on OlympiA, DCO1 vs DCO2 data

	OlympiA DCO1 data*	OlympiA DCO2 data*
Probability of any iDFS event being a non-distant recurrence	20.4%	23.8%
Probability of any iDFS event being a distant recurrence, new cancer, or death	79.6%	76.2%

Notes: * all patients, OlympiA ITT population.
Abbreviations: DCO: data cut-off; iDFS: invasive disease-free survival; ITT: intention-to-treat.

Step 4: Modelling of transitions from iDFS to death (TP3)

No changes were made to the modelling of TP3 following the introduction of OlympiA DCO2 data. Using the all-cause mortality curve for the general population with the adjustment for a positive *BRCA*m status has therefore remained the same.

2.2.2 Overall model fit and plausibility of the extrapolation of iDFS

Table 25 and Table 26 summarise the landmark survival probabilities for iDFS for both arms in TNBC and HR+/HER2- patients, as predicted by the economic model. These estimates were obtained using the parametric survival models for iDFS (step 1) with adjustment for the long-term rate of recurrence (step 2), imputing the conditional probability of non-distant recurrence (step 3) and the modelling of death without recurrence (step four).

Similar to the process in the initial submission, in order to select the most appropriate parametric survival model for the base case economic analysis, the predicted survival probabilities for iDFS in TNBC and HR+/HER2- patients are compared with the respective observed iDFS in OlympiA, relevant empirical data and RWE, and validated by UK clinical experts. An update to the targeted literature search in January 2022 was conducted to identify any additional clinical outcome data in patients with *BRCA*m, HER2-, high-risk eBC to further inform the validation process. Only one additional study was found by Pan et al. (2017)[45] which tracked the 20-year risk of breast cancer recurrence in patients with HR+ eBC after stopping with endocrine therapy after 5 years. The study reports outcome data in different subgroups, including one in patients with 4 or more nodes involved, which is generally reflective of having 'high-risk' disease and thus provides a good reference to validate the long-term survival probabilities for iDFS in the OlympiA HR+/HER2- analysis.

TNBC

- When comparing the long-term iDFS rates from the UK Prospective study of Outcomes in Sporadic versus Hereditary breast cancer (POSH) study, which was previously identified as the most relevant and UK-specific data source for this economic analysis on olaparib in the 'OlympiA' indication to date, with the updated estimates from the placebo arm from the four best-fitting parametric models (Table 25), it is clear that all models predict a relatively similar 10-year TNBC iDFS rate to the POSH study (70.6%). Considering that the POSH study does not specifically include patients with high-risk disease, the respective long-term iDFS rates are likely a slight overestimate of what should be expected in OlympiA. As such, it may be concluded that the Gompertz slightly overpredicts long-term iDFS after 5 years, whereas the lognormal and generalised gamma models present more realistic estimates for patients with *BRCA*m, high-risk, eBC.
- UK medical oncologists who reviewed the updated extrapolated data also noted that there was no clear difference between the models in terms of long-term survival estimates; instead, the 5-, 10- and 20-year iDFS estimates across all models seemed reasonable. Generally, they commented that >60% iDFS at 20 years was a realistic expectation for patients with TNBC, especially considering their low risk of recurrence after being disease-free for more than 5 years.
- Therefore, similar to the choice of model based on DCO1 data, the lognormal model, which has the second-best statistical fit according to the AIC/BIC values, shows good consistency with the observed Kaplan-Meier data, and produces the most plausible long-term iDFS rates on standard of care was chosen in the base-case analysis for the TNBC population. The Gompertz, generalised gamma and loglogistic models were considered in scenario analyses to test the impact of alternative survival model choices.

Table 25: Comparison of Kaplan-Meier data, empirical data and long-term extrapolation of iDFS for the comparator (placebo) OlympiA arm using fully fitted parametric models (independent, TNBC)

	Time (years)	1	2	3	4	5	10	20
	Kaplan-Meier placebo	[redacted]	[redacted]	[redacted]	*75.2%*	–	–	–
Parametric models fitted to the OlympiA TNBC data	Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gen. gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Loglogistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Empirical data	POSH study	–	85.0%	–	–	76.5%	70.6%	–

Abbreviations: iDFS: invasive disease-free survival; TNBC: triple negative breast cancer; POSH: Prospective study of Outcomes in Sporadic versus Hereditary breast cancer.

HR+/HER2-

- For the HR+/HER2- analysis using the ITT iDFS data as a proxy, when comparing the long-term estimates from the best fitting models for the placebo arm with the empirical data as presented in Table 26, it is clear that the Gompertz significantly overestimates long-term survival at 10 and 20 years (~68% and ~64%) vs. any of the other models (lognormal, generalised gamma & loglogistic; ~60% and ~45% respectively).
- UK medical oncologists who reviewed the updated extrapolated data also confirmed that the long-term iDFS estimates from the lognormal and generalised gamma models for the SoC arm seemed most reflective of current clinical practice. Furthermore, it was mentioned that as the risk of recurrence of patients with HR+/HER2- and triple negative high-risk disease will eventually cross, HR+/HER2- patients will ultimately experience worse long-term prognosis.[5] This is reflected in the 20-year iDFS estimates from the lognormal (47.1%) and generalised gamma (48.5%) models, which are lower than those estimated by the lognormal model (65.7%) model in the TNBC population analysis.
- Therefore, the lognormal model, which has the best statistical fit for the olaparib arm and the second-best fit for the placebo arm, shows good consistency with the observed Kaplan-Meier data, and produces the most plausible long-term iDFS rates on standard of care was chosen in the base-case analysis for the HR+/HER2- population. The generalised gamma and loglogistic models were considered in scenario analysis to test the impact of alternative survival model choices.

Table 26: Comparison of Kaplan-Meier data, empirical data and long-term extrapolation of iDFS for the comparator (placebo) OlympiA arm using fully fitted parametric models (independent, ITT as a proxy for HR+/HER2-)

	Time (years)	1	2	3	4	5	10	20
	Kaplan-Meier placebo	*88.4%*	*81.4%*	*77.3%*	*75.4%*			
Parametric models fitted to the	Lognormal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

OlympiA TNBC data	Gen. gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Loglogistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Empirical data	EBCTCG (2005)	–	88.5%	–	–	73.3%	59.5%	52.7% (15 yrs)
	Pan et al. (2017)					78.0%	64.0%	48.0%

Abbreviations: EBCTCG: Early Breast Cancer Trialists' Collaborative Group; HR: hormone receptor; HER2: human epidermal growth factor 2; iDFS: invasive disease-free survival; ITT: intention-to-treat.

Final iDFS extrapolations as per the updated base case economic analysis (DCO2 data)

The final iDFS extrapolations as per the model's base case for the TNBC population (lognormal parametric model, assuming a zero risk of recurrence from year 5 of the model's time horizon) and the HR+/HER2- population (lognormal parametric model, assuming a lifetime risk of recurrence) are presented in Figure 18 below.

Figure 18: Base case iDFS extrapolation for the TNBC population (top) and the HR+/HER2- population (bottom)

[redacted]

Footnotes: 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: iDFS: invasive disease-free survival; HER2: human epidermal growth factor receptor; HR: hormone receptor; TNBC: triple negative breast cancer.

2.3 Modelling of non-metastatic recurrence

The transition probabilities for non-metastatic to metastatic breast cancer (TP4) and non-metastatic breast cancer to death (without metastatic diagnosis) (TP5) were modelled using data from the OlympiA trial.

At the interim OS analysis of OlympiA (DCO2), 81 patients had experienced a non-metastatic recurrence: 33 patients from the olaparib arm and 48 patients from the placebo arm. Of the 81 patients with non-metastatic recurrence, [redacted] had experienced a distant metastatic recurrence and [redacted] had died without recurrence during follow-up. Similar to the DCO1 data, there were too few events to separately estimate TP4 and TP5 for the olaparib and placebo arms of the model. Furthermore, the post-recurrence survival (i.e., time from non-metastatic recurrence to death) of patients with non-metastatic recurrence [redacted] for the placebo arm (Figure 19). Therefore, to maximise the sample for analysis, TP4 and TP5 were estimated from a pooled dataset containing data from both arms. The resulting transition probabilities were applied to both arms of the model. This leads to a conservative estimate of the post-recurrence survival of patients with locoregional recurrence in the olaparib arm of the model given the [redacted] in Figure 19.

Figure 19: Post-recurrence survival of patients who had locoregional or contralateral invasive breast cancer in OlympiA

Parametric survival analysis for non-metastatic breast cancer (TP4 and TP5)

A series of parametric survival models were fitted to the cause-specific time to event data for TP4 and TP5. The AIC and BIC statistics for each of the parametric models are shown in Table 27 below. For TP4, the AIC and BIC scores favoured the lognormal (1st for AIC) and exponential (1st for BIC). For TP5, the lognormal was the best fitting model according to both AIC and BIC. However, as distributions with AIC/BIC scores within 5 are considered to have similar goodness of statistical fit, all curves demonstrated reasonably good statistical fits to the data.

Table 27: AIC and BIC values for the parametric survival models fitted to data on the time from non-distant metastatic recurrence to distant metastatic and the time from non-distant metastatic recurrence to death

Model	Pooled data (N=81) (olaparib, n=33; placebo, n=48)	
	AIC	BIC
Time from non-metastatic recurrence to distant metastatic recurrence [TP4]		
Exponential	159.99 (2)	162.38 (1)
Weibull	160.70 (4)	165.48 (4)
Loglogistic	160.33 (3)	165.12 (3)
Lognormal	159.61 (1)	164.40 (2)
Gompertz	161.57 (6)	166.36 (5)
Generalized gamma	161.54 (5)	168.72 (6)
Time from non-metastatic recurrence to death [TP5]		
Exponential	43.25 (2)	45.65 (1)
Weibull	45.10 (6)	49.89 (5)
Loglogistic	45.04 (5)	49.83 (4)
Lognormal	44.58 (4)	49.37 (3)
Gompertz	44.25 (3)	49.04 (2)
Generalized gamma	43.23 (1)	50.41 (6)

Footnotes: (X): rank on lowest AIC/BIC by arm.

Abbreviations: AIC: Akaike Information Criteria; BIC: Bayesian Information Criteria: TP: transitional probability.

The fit of the models to the Kaplan-Meier probabilities for non-metastatic to metastatic recurrence (TP4) and for non-metastatic to death (TP5) are shown in Figure 20. These graphs provide an indication of model fit but should be viewed with caution given that the Kaplan-Meier plots of competing risks, such as TP4 and TP5, are biased by informative censoring.

The choice of preferred model for both TP4 and TP5 is identical to the validation process described in the initial submission. Guided by the goodness of fit statistics, the lognormal model was selected as the preferred model for TP4, and the exponential model for the base case analysis for TP5. The impact of using other models for both transition probabilities on the base case results was considered in sensitivity analysis; it should however again be noted that the choice of the parametric model for extrapolating TP4 and TP5 only has a minor impact on results.

Figure 20: Fit of the parametric survival models to the ITT OlympiA Kaplan-Meier data for non-metastatic to metastatic recurrence (left) and for non-metastatic to death (right) in OlympiA, pooled arms

Abbreviations: ITT: intention-to-treat

2.4 Modelling of metastatic recurrence

2.4.1 Early onset mBC

The transition probabilities for ‘early onset’ metastatic breast cancer to death (TP6) were modelled using data on the time from distant metastatic recurrence to death in the OlympiA trial. These data represent the survival outcomes of patients who had distant recurrence during the approximate 3.5-year median follow-up of OlympiA (DCO2).

At the second interim OS analysis of OlympiA (DCO2), [redacted] patients from the olaparib arm and [redacted] patients from the placebo arm had experienced a distant metastatic recurrence. This included patients whose first IDFS event was a distant recurrence (n=[redacted][3] for olaparib and

[3] 1 patient had experienced a distant recurrence during follow-up but had been censored for their event in the iDFS summary.

n=[redacted] for placebo), and patients that experienced a distant recurrence after first experiencing a locoregional or contralateral invasive breast cancer event (n=[redacted] for olaparib and n=[redacted] for placebo). In total, there were [redacted] deaths after metastatic recurrence in the olaparib arm, and [redacted] deaths after metastatic recurrence in the placebo arm. The median time to death was [redacted] months in the olaparib arm versus [redacted] months in the placebo arm. The Kaplan-Meier plot for post-distant metastatic recurrence survival by arm is shown in Figure 21.

Similar to the plot based on DCO1 data, it is acknowledged that the median survival after distant recurrence in the olaparib arm ([redacted] months) was [redacted] than for placebo ([redacted] months). This difference in post-recurrence survival can be attributed to several factors, including differences in the treatments administered after recurrence and imbalances in the characteristics and prognosis of patients with distant recurrence after olaparib and placebo, which are further described in the original submission dossier in Section B.3.3.5.1.

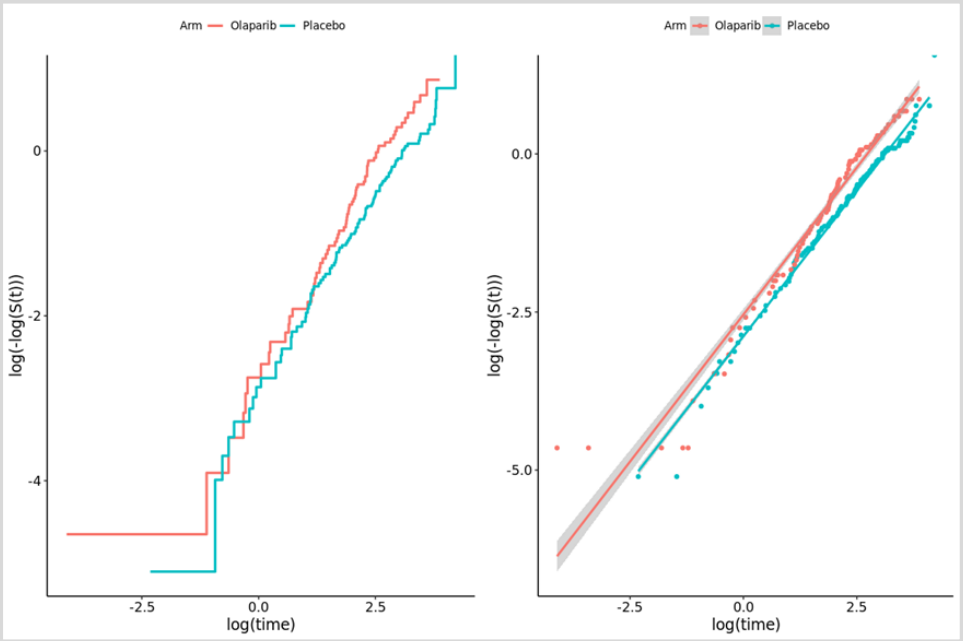
Figure 21: Kaplan-Meier plot of post-distant metastatic recurrence survival by arm in OlympiA

In line with the OlympiA data on the post-distant metastatic recurrence survival, the base case economic analysis applies transition probabilities independently by arm. However, the impact of assuming the same survival after ‘early onset mBC’ across arms is tested in the sensitivity analysis. When implemented, the transition probabilities for the olaparib arm are then modelled using the survival rates estimated from the placebo arm of OlympiA.

Parametric survival analysis for mBC (TP6)

A series of parametric survival models were fitted to the time to event data for TP6. Due to evidence of non-proportional hazards from the overlapping of Kaplan-Meier probabilities across study arms at the beginning of the survival curve for TP6 (Figure 21), the survival models were fitted independently to each arm of the study. This is supported by the log cumulative hazards plot for TP6, which showed lack of proportionality in the survival curves (Figure 22).

Figure 22: Log-cumulative hazards versus log-time plot of post-metastatic recurrence for the placebo and olaparib arms of OlympiA



The AIC and BIC statistics for the fitted models are shown in Table 28. For the olaparib arm, the exponential was the best fitting on both BIC and AIC. For the placebo arm, the Gompertz was best fitting on AIC, and the exponential was best fitting on BIC. The fit of the models to the Kaplan-Meier probabilities for TP6 are shown in Figure 23.

Table 28: AIC and BIC values for the parametric survival models fitted to data on the time from metastatic recurrence to death (placebo arm)

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 23: Fit of parametric survival models to the Kaplan-Meier data for metastatic to death by arm in OlympiA

Abbreviations: ITT: intention-to-treat; KM: Kaplan Meier

Similar to TP4 and TP5, the choice of preferred model for TP6 is identical to the validation process described in the initial submission. The survival estimates for the placebo arm with the exponential model were judged to provide the most plausible prediction when compared to literature estimates of the post-distant recurrence survival of patients with 'early onset mBC' (<24 months since diagnosis; 5.4% at 5-years and ~0% at 10 years).[28] For consistency with the placebo arm, the exponential model was used in the base case for the modelling of TP6 for olaparib. Alternative modelling options are explored in scenario analyses, but as discussed in the original submission document, only have a negligible impact on the results.

2.4.2 Late onset mBC

No changes have been made to the modelling of the transition probabilities for 'late onset' mBC to death (TP7), as data external to the OlympiA trial is used.

2.5 Adverse reactions

As described in Section B.3.4.5 in the initial submission document, a one-off QALY adjustment for adverse events (AEs) was modelled based on each AE respective disutility (loss of utility) multiplied by its assumed duration. The economic analysis only includes AEs that were:

- ≥Grade 3: AEs were included if they were classified as Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or above. The costs of Grade 1 and 2 events are assumed to be negligible and therefore omitted from the analysis.
- ≥2% of patients: to ensure that key events were captured while ensuring the list of included events was manageable.

When updating the economic model with the DCO2 data, two minor errors were identified:

- The number of days that patients experience neutropenia should have been [redacted], not [redacted] as it was imputed in the economic model.
- In the economic model, patients experience a different duration of an AE by treatment arm – this was not accurately reflected in Table 38 in Document B, Section 3.4.5. Table 29 below therefore provides the updated AE data from DCO2 and clarifies which AEs were included in the economic analysis based on the criteria outlined above. The disutility associated with the final included AEs (anaemia and neutropenia) remains the same as per the initial submission (-0.119 and -0.090 respectively).

Table 29: Adverse event frequency and duration (≥Grade 3), OlympiA SAS (DCO2)

Adverse event	Olaparib, N=911		Watch and Wait (proxied by placebo), N=904		Total no. of events %
	No. of events %	Duration (days)	No. of events %	Duration (days)	
Anaemia*	8.70%	[redacted]	0.30%	[redacted]	4.51%
Nausea	0.80%	[redacted]	0.00%	[redacted]	0.40%
Vomiting	0.70%	[redacted]	0.00%	[redacted]	0.35%
Fatigue	1.80%	[redacted]	0.70%	[redacted]	1.25%
Diarrhoea	0.30%	[redacted]	0.30%	[redacted]	0.30%
Neutropenia*	4.90%	[redacted]	0.80%	[redacted]	2.86%
ALT, SGPT increase	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: DCO2 12th July 2021. * Included in the economic analysis.
Abbreviations: ALT: alanine aminotransferase; DCO: data cut-off; SAS: safety analysis set; SGPT: serum glutamic pyruvic transaminase.
Source: AstraZeneca Data on File (Interim analysis of OS in OlympiA [DCO2]).[2]

2.6 Base-case results

2.6.1 TNBC: Updated base-case incremental cost-effectiveness analysis results (DCO2)

Total costs, life years gained (LYG), QALYs, and incremental cost per QALY gained (ICER) in the updated base case for the TNBC analysis (DCO2 data) are presented in

Table 30 below. In the updated base case analysis, adjuvant olaparib treatment generates [redacted] incremental QALYs and [redacted] incremental costs over a lifetime time horizon

compared with placebo (“watch & wait”), resulting in an ICER of £35,855 per QALY gained. It should be noted that these results are based on the current PAS price for olaparib.

Table 30: 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]	£35,855

Note: discounted outcomes
Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life year gained; QALY: quality-adjusted life year

2.6.2 HR+/HER2-: Updated base-case incremental cost-effectiveness analysis results (DCO2)

Base case results for the HR+/HER2- analysis are presented in Table 31 below. In the updated base case analysis using the OlympiA DCO2 data, adjuvant olaparib treatment generates [redacted] incremental QALYs and [redacted] incremental costs over a lifetime time horizon compared with placebo (“watch & wait”), resulting in an ICER of £41,879 per QALY gained. It should be noted that these results are based on the current PAS price for olaparib.

Table 31: 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]	£41,879

Note: discounted outcomes
Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life year gained; QALY: quality-adjusted life year

2.7 Exploring uncertainty

2.7.1 Probabilistic sensitivity analysis

Results from the updated PSA using the OlympiA DCO2 data for the TNBC and HR+/HER2- analyses are presented in Table 32 and Table 33 respectively. The base case probabilistic ICER for the TNBC analysis is £34,685 per QALY gained, and **highly consistent with and slightly lower than the ICER in the deterministic analysis** (£35,855 per QALY gained). **Similar results are shown for the HR+/HER2-**, with a lower base case probabilistic ICER of £40,293 vs. an ICER of £41,879 in the deterministic analysis.

Table 32: Base case results (probabilistic) (TNBC)

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

Note: discounted outcomes; results are based on the current PAS price for olaparib
Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life year gained; QALY: quality-adjusted life year

Table 33: Base case results (probabilistic) (HR+/HER2-)

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

Note: discounted outcomes; results are based on the current PAS price for olaparib
Abbreviations: ICER: incremental cost-effectiveness ratio; LYG: life year gained; QALY: quality-adjusted life year

The cost-effectiveness plane and cost-effectiveness acceptability curve for olaparib versus placebo for the TNBC analysis are presented in Figure 24 and Figure 25, and Figure 26 and Figure 27 for the HR+/HER2- analysis. At a willingness to pay threshold of £30,000, adjuvant olaparib treatment has a [redacted] probability of being cost-effective compared with "watch & wait" in the TNBC analysis, and a [redacted] probability in the HR+/HER2- analysis.

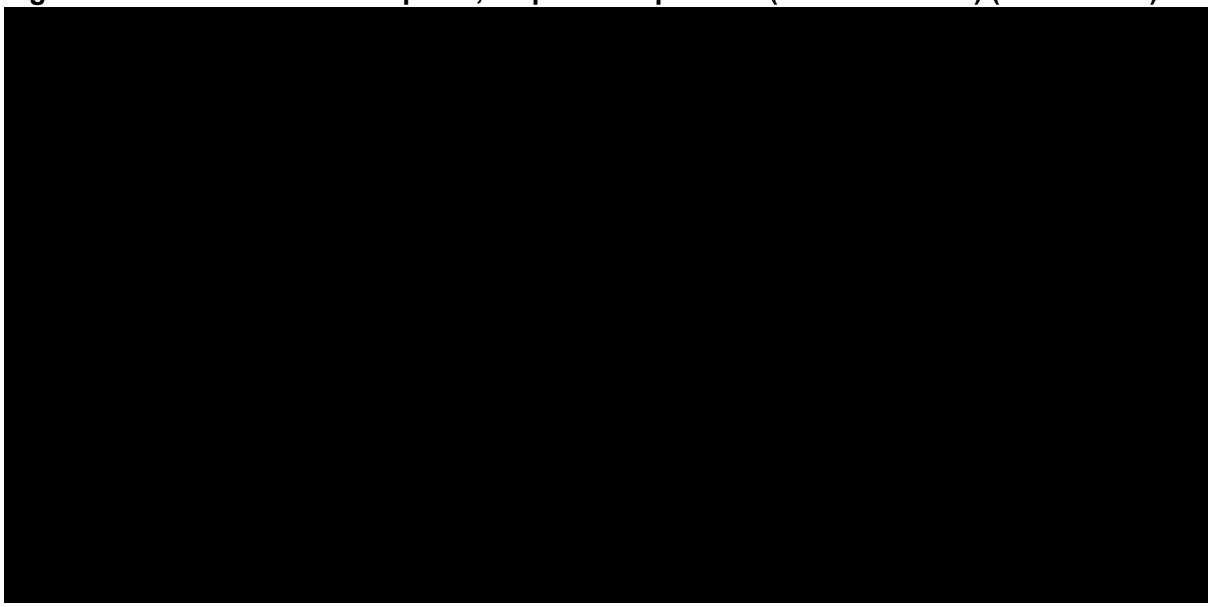
Figure 24: Cost-effectiveness plane, olaparib vs. placebo ("watch & wait") (TNBC)

Abbreviations: QALY: quality adjusted life year; TNBC: triple negative breast cancer

Figure 25: Cost-effectiveness acceptability curve, olaparib vs. placebo ("watch & wait") (TNBC)

Abbreviations: TNBC: triple negative breast cancer

Figure 26: Cost-effectiveness plane, olaparib vs. placebo ("watch & wait") (HR+/HER2-)



Abbreviations: HER2: human epidermal growth factor 2; HR: hormone receptor; QALY: quality adjusted life year

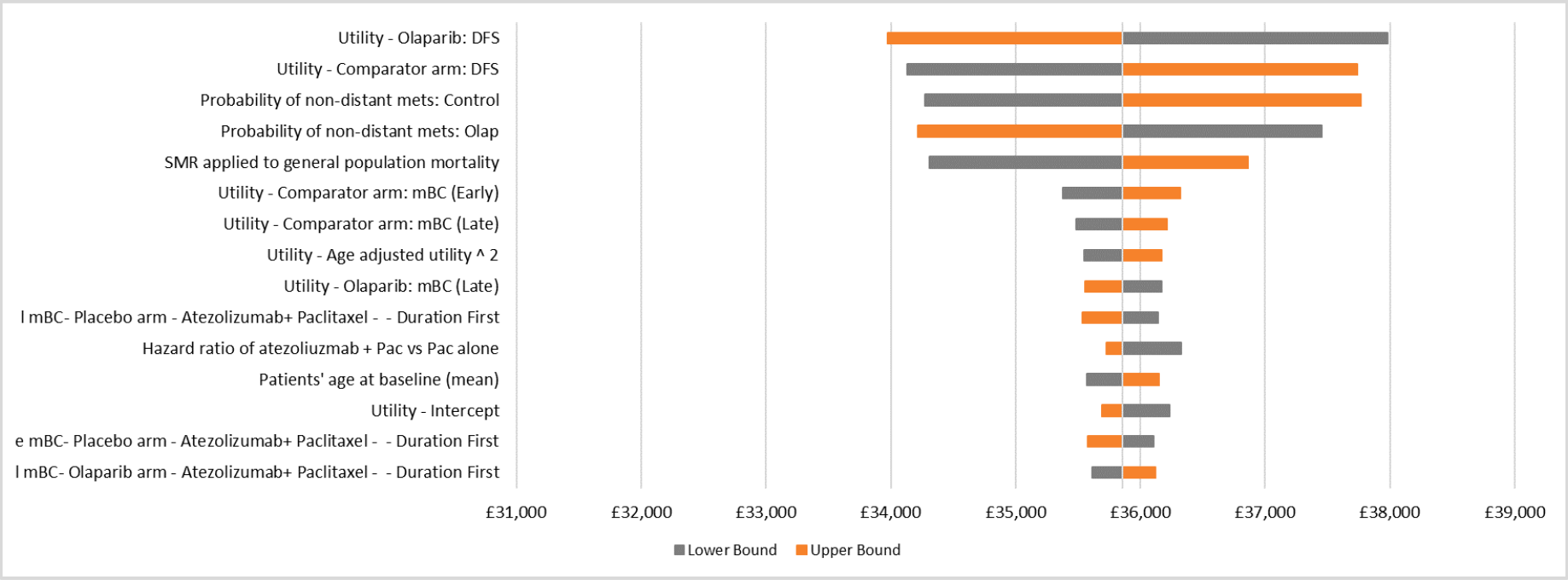
Figure 27: Cost-effectiveness acceptability curve, olaparib vs. placebo ("watch & wait") (HR+/HER2-)

Abbreviations: HER2: human epidermal growth factor 2; HR: hormone receptor

2.7.2 Deterministic sensitivity analysis

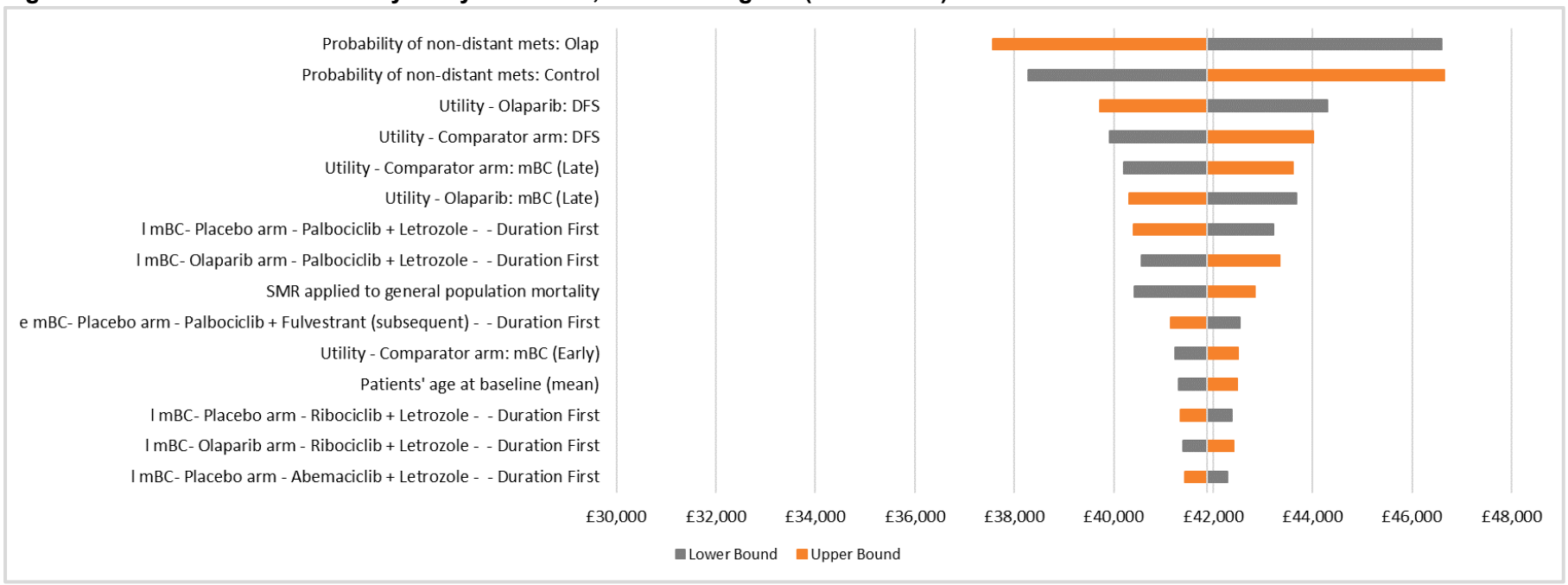
The results of the updated DSA using the OlympiA DCO2 data for the top 15 most influential parameters on the spread of the cost-effectiveness results are shown in Figure 28 for the TNBC analysis and in Figure 29 for the HR+/HER2- analysis. Overall, similar to the DCO1 analyses, the results show the ICER is most sensitive to variation in the utility assigned to iDFS, the probability of developing a distant vs. a locoregional metastasis and the excess mortality risk associated with a *BRCA* mutation. However, for both the TNBC and HR+/HER2- analyses, the highest produced ICER is only a maximum of £2-3k above the respective ICER from the base case analysis, **giving further confidence in the stability of the updated results**.

Figure 28: Deterministic sensitivity analysis results, tornado diagram (TNBC)



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

Figure 29: Deterministic sensitivity analysis results, tornado diagram (HR+/HER2-)



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

2.7.3 Scenario analysis

Table 34 provides a summary of the results of the scenario analyses for both the TNBC and HR+/HER2- populations using the updated DCO2 OlympiA data. For the TNBC analysis, the results of the scenario analysis indicate that the model is most sensitive to the length of the time horizon, the HSUV assigned to the progression free state and the inclusion of *BRCA* testing costs. For the HR+/HER2- analysis, the model is most sensitive to the same parameters as the TNBC analysis, as well as the choice of survival curve for iDFS (TP1/TP2), although this fluctuates in both an upward and downward direction.

The model results were insensitive (<5% change in ICER) to almost all other scenarios and parameters, including the time point for determining early vs. late recurrence, the choice of survival distribution for TP4, TP5, TP6 and TP7, the HSUV assigned to the progressed disease state and using treatment arm-specific probabilities of iDFS being a non-distant recurrence event.

Overall, the results of the scenario analysis suggest that the base case analysis for both the TNBC and HR+/HER2- populations **remains robust to variations** in input parameters.

Table 34: Scenario analysis results (discounted, TNBC & HR+/HER2- analyses)

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
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

Scenario	Base case value	Scenario analysis value	ICER (£/QALY) (TNBC)	ICER (£/QALY) (HR+/HER2-)
		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	PF: 0.869 Non-mBC: 0.869 mBC: 0.685	Scenario 1: PF: 0.802 Non-mBC: 0.802 mBC: 0.685	£39,238	£45,840
		Scenario 2: PF: 0.869 Non-mBC: 0.869 mBC: 0.521	£34,883	£40,723
		Scenario 3: 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

Abbreviations: *BRCA*: breast cancer gene; CDK4/6: cyclin-dependent kinase 4/6; HER2: human epidermal growth factor 2; HR: hormone receptor; ICER: incremental cost-effectiveness ratio; IV: intravenous; mBC: metastatic breast cancer; PF: progression-free; RT: radiotherapy; SC: subcutaneous; QALY: quality adjusted life year; TNBC: triple negative breast cancer; TP: transition probability

Appendix 3. Updated searches for economic evaluations

3.1 Methodology of updated SLR searches

Following clarifications from the EAG suggesting that the original searches run in Medline for EE studies could potentially miss studies/data, the searches were re-run using the changes suggested by the EAG.

Searches were re-run from database inception and the results were deduplicated against results from the original searches run in November 2020, and the update search run in January 2022.

This resulted in 1440 additional Medline and EBMR records to screen.

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions: 1946 to May 13, 2022: searched 17.5.22

#	Searches	Results
1	exp Breast Neoplasms/	326453
2	((breast or mammary) adj5 (tumour$ or tumor$ or cancer$ or neoplasm$ or adenocarcinoma$ or carcinoma$)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	469069
3	1 or 2	469076
4	((early or operab* or locally advanc* or T1 or T2 or T3 or M0 or "stage 0" or stage 1* or stage Ia or stage Ib or stage 2* or stage II* or stage 3* or stage III*) adj4 (breast or mammary or tumour$ or tumor$ or cancer$ or neoplasm$ or adenocarcinoma$ or carcinoma$)).ab,ti,kw.	161053
5	3 and 4	37803
6	(cost minimi?ation analys* or (cost-minimi?ation adj1 analys*)).mp.	841
7	exp Cost-Benefit Analysis/	89649
8	((cost benefit adj1 analys*) or (cost-benefit adj1 analys*)).mp.	92321
9	(cost utility analys* or (cost-utility adj1 analys*)).mp.	3739
10	((cost-effective* adj1 analys*) or "cost adj1 effectiveness adj1 analys*").mp.	15128
11	6 or 7 or 8 or 9 or 10	97632
12	((economic or pharmacoeconomic) adj1 (evaluation or assessment or analys?s or stud*)).mp.	22439
13	("CEA" or "CMA" or "CBA" or "CUA" or "CCA").mp.	68607
14	exp Decision Trees/	11954
15	decision tree.mp.	10232
16	economic model.mp. or exp Models, Economic/	17362
17	(markov or deterministic).mp.	47474
18	((transition adj1 probabilit*) or (health adj1 stat*) or (sensitivity adj1 analys*) or (health adj1 outcome)).mp.	245166
19	((patient level or patient-level or discrete event or discrete-event) adj1 simulat*).mp.	1002

#	Searches	Results
20	exp Patient Preference/	10289
21	(Patient* adj2 preferen*).mp.	24339
22	discrete choice*.mp.	2833
23	(incremental-cost or incremental cost).mp.	13936
24	("ICER" or "QALY" or "DALY" or "WTP" or "TTO").mp.	17954
25	12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24	431347
26	11 or 25	495805
27	5 and 26	1467

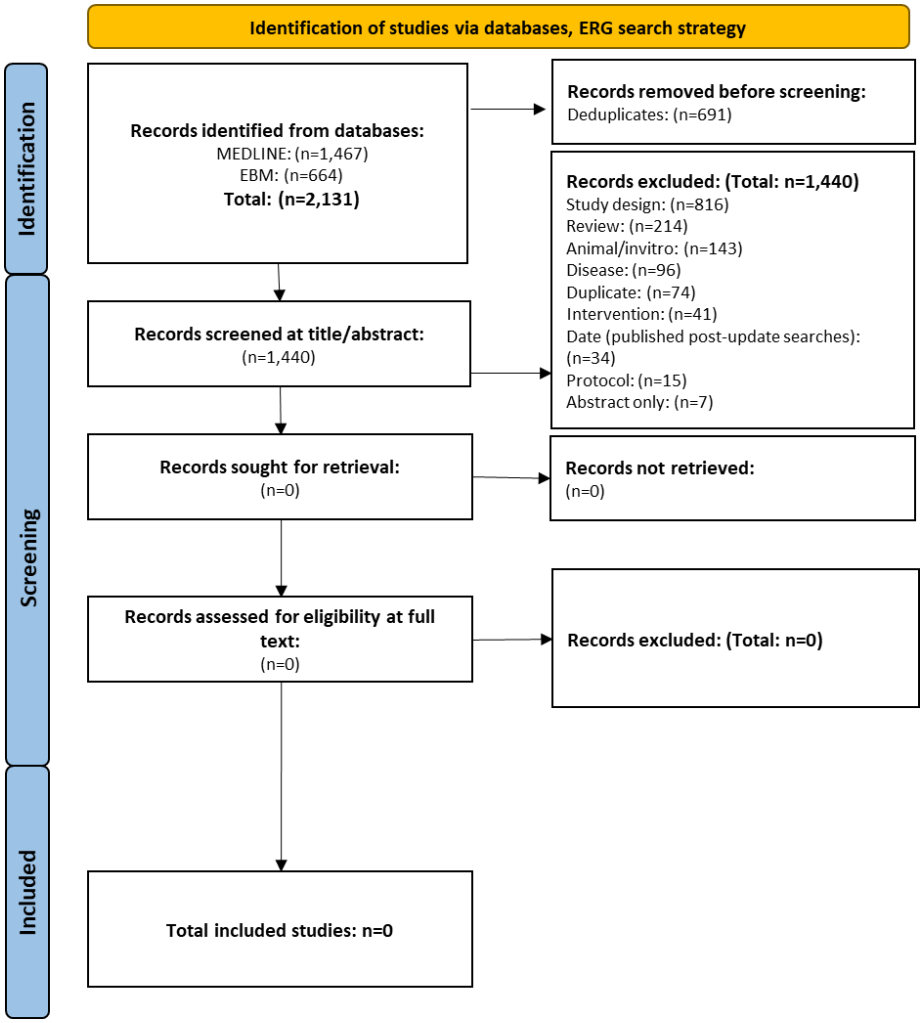
EBM Reviews (Ovid) - Cochrane Methodology Register 3rd Quarter 2012, Database of Abstracts of Reviews of Effects 1st Quarter 2016*, Health Technology Assessment 4th Quarter 2016, NHS Economic Evaluation Database 1st Quarter 2016*, ACP Journal Club 1991 to April 2022, Cochrane Central Register of Controlled Trials April 2022, Cochrane Database of Systematic Reviews 2005 to May 11, 2022, Cochrane Clinical Answers April 2022: searched 17.5.22
***Records last added March 2015**

#	Searches	Results
1	exp Breast Neoplasms/	15539
2	((breast or mammary) adj5 (tumour$ or tumor$ or cancer$ or neoplasm$ or adenocarcinoma$ or carcinoma$)).mp. [mp=ti, ab, hw, tx, kw, ct, ot, fx, sh]	47050
3	1 or 2	47051
4	((early or operab* or locally advanc* or T1 or T2 or T3 or M0 or "stage 0" or stage 1* or stage Ia or stage Ib or stage 2* or stage II* or stage 3* or stage III*) adj4 (breast or mammary or tumour$ or tumor$ or cancer$ or neoplasm$ or adenocarcinoma$ or carcinoma$)).ab,ti,kw.	26251
5	3 and 4	9780
6	(cost minimi?ation analys* or (cost-minimi?ation adj1 analys*)).mp.	872
7	exp Cost-Benefit Analysis/	19938
8	((cost benefit adj1 analys*) or (cost-benefit adj1 analys*)).mp.	23913
9	(cost utility analys* or (cost-utility adj1 analys*)).mp.	5163
10	((cost-effective* adj1 analys*) or "cost adj1 effectiveness adj1 analys*").mp.	22928
11	6 or 7 or 8 or 9 or 10	38797
12	((economic or pharmacoeconomic) adj1 (evaluation or assessment or analys?s or stud*)).mp.	26545
13	("CEA" or "CMA" or "CBA" or "CUA" or "CCA").mp.	7169
14	exp Decision Trees/	920
15	decision tree.mp.	2038
16	economic model.mp. or exp Models, Economic/	2473
17	(markov or deterministic).mp.	5925
18	((transition adj1 probabilit*) or (health adj1 stat*) or (sensitivity adj1 analys*) or (health adj1 outcome)).mp.	50743

#	Searches	Results
19	((patient level or patient-level or discrete event or discrete-event) adj1 simulat*).mp.	179
20	exp Patient Preference/	1333
21	(Patient* adj2 preferen*).mp.	6825
22	discrete choice*.mp.	309
23	(incremental-cost or incremental cost).mp.	9391
24	("ICER" or "QALY" or "DALY" or "WTP" or "TTO").mp.	8421
25	12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24	82436
26	11 or 25	96066
27	5 and 26	664

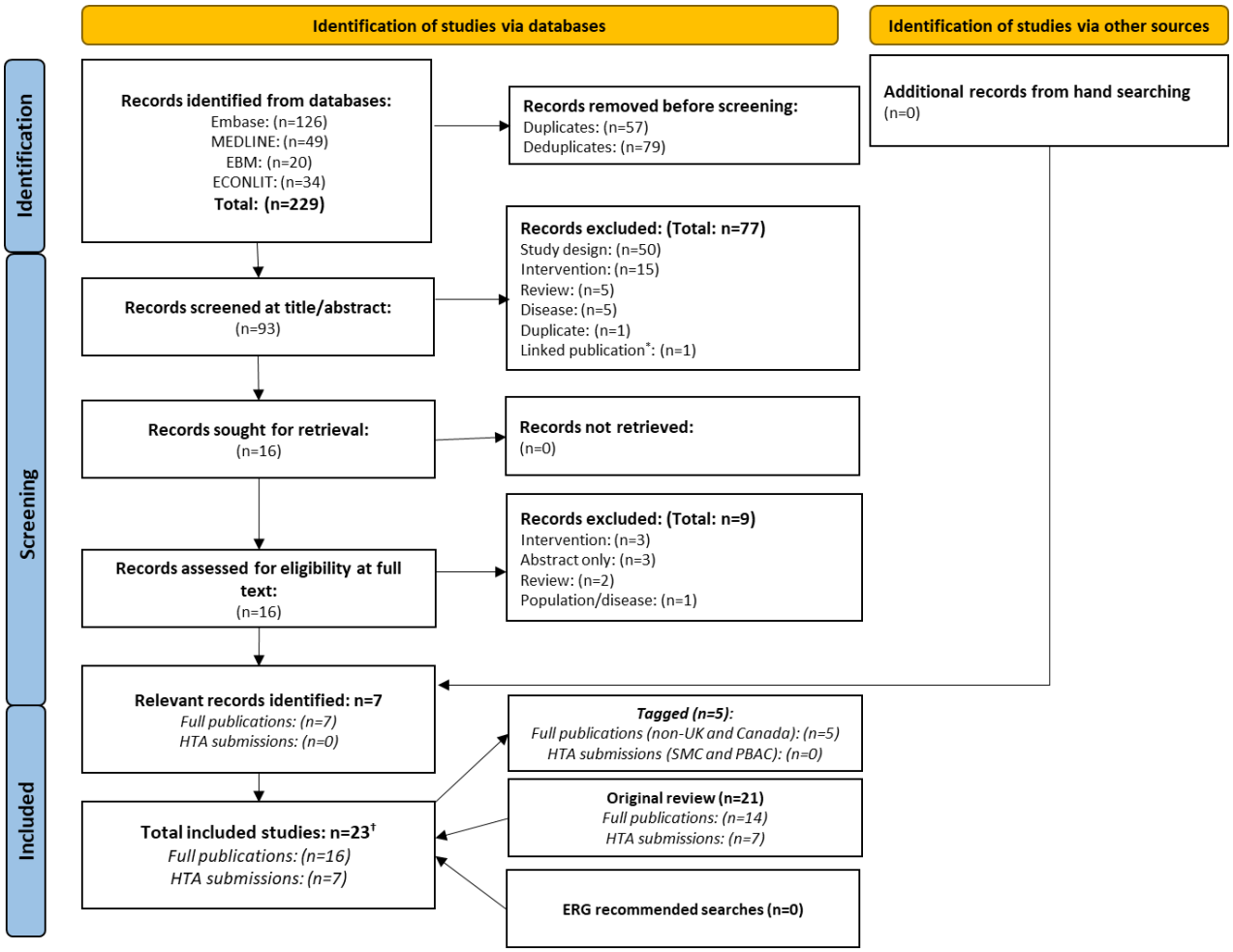
3.2 PRISMA flow diagrams for the additional ERG search

Figure 30: ERG search PRISMA flow diagram for the economic evaluation SLR



Abbreviations: EBM, Evidence based medicine; SLR, systematic literature review.

Figure 31: Overall PRISMA flow diagram for the economic evaluation SLR



Abbreviations: CADTH, Canadian Agency for Drugs and Technologies in Health; EBM, evidence-based medicine; HTA, health technology assessment; NICE, National Institute for Health and Care Excellence; PBAC, Pharmaceutical Benefits Advisory Committee; SLR, systematic literature review; SMC, Scottish Medicines Consortium; UK, United Kingdom.
†The review focussed on identified full publications from the UK and Canada, and NICE and CADTH HTA submissions.
*Linked publications are abstracts that have been superseded by full publications.

NICE National Institute for Health and Care Excellence

Patient organisation submission

Olaparib for adjuvant treatment of high-risk HER2-negative, BRCA-positive early breast cancer after chemotherapy [ID3893]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Breast Cancer Now
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Breast Cancer Now is the UK charity that's steered by world-class research and powered by life-changing care. We provide support for today and hope for the future.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	No comparators are listed on the appraisal matrix and Breast Cancer Now has not received any funding from the manufacturer (AstraZeneca) of this technology in the last 12 months (April 2021-April 2022).

If so, please state the name of manufacturer, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None.
5. How did you gather information about the experiences of patients and carers to include in your submission?	At Breast Cancer Now we utilise our various networks of those affected by breast cancer to gather information about patient experience, for example via our online forum and through our support services. For this appraisal this has included speaking to people with experience of this particular type of breast cancer, as well as patients who have taken olaparib in this indication through the drug company's early access scheme.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	A diagnosis of breast cancer can cause considerable anxiety to the patient as well as their family and friends. The initial diagnosis can be extremely shocking and impact on people's emotional wellbeing, whilst in the longer-term, the fear of breast cancer returning or spreading to other parts of the body (such as the bone, liver, lung and brain) which is known as secondary breast cancer and is incurable can be extremely frightening and distressing for patients. Breast cancer patients tell us about the impact of the disease on their lives, for example the side effects of treatments and visits to hospital taking a significant toll on their general wellbeing, everyday activities, ability to work and relationships.

	It is estimated that BRCA mutations are found in approximately 5% of breast cancer patients. BRCA mutations can be associated with more aggressive tumours, such as triple negative breast cancer. The risk of triple negative breast cancer returning and spreading to other parts of the body in the first few years after treatment is higher than it is for other breast cancers. Patients who are BRCA positive also tell us they can feel guilty and fearful about whether their children or other family members could also carry this mutation. They can also live with the fear of having a higher risk of developing ovarian cancer and deciding about whether they want risk-reducing treatment. A patient with BRCA positive, primary triple negative breast cancer told us: "It's daunting to know that your breast cancer is less common and more aggressive than other types of breast cancer, with a higher risk of returning in the years immediately following treatment – but at the same time there are fewer treatment options available to reduce that risk." Another patient with BRCA positive, primary triple negative breast cancer explains: "It was very worrying being diagnosed with BRCA positive, triple negative primary breast cancer. It's hard having to live with this information for life, even if you get the all clear, it's constantly in the back of my mind. My mum and other family members have passed away from cancer – I don't know if my Mum had the gene, I don't think she was tested. And now it's me. It's very scary, I try not to think about it. When the doctor told me I unfortunately had that gene, I was thought oh my goodness, they say it with sadness which is frightening"
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Treatment for primary breast cancer is usually a combination of surgery, radiotherapy and chemotherapy. Patients with hormone-receptor positive breast cancer will receive endocrine (hormone therapy). There are currently no drug treatments specifically targeted at patients who are BRCA positive. Currently chemotherapy remains the mainstay of drug treatment for BRCA positive triple negative breast cancer patients.

	Patients with this type of breast cancer generally feel that there have been fewer advances in the treatment options available to them on the NHS to reduce the risk of local recurrence and breast cancer spreading to other parts of the body. They desperately want to see new effective treatments which could significantly reduce the risk of recurrence and provide them with reassurance that their cancer is less likely to return or progress to incurable secondary breast cancer. For patients who are BRCA positive, hormone receptor positive, HER2 negative primary breast cancer, in line with the NICE early and locally advanced guideline, men and premenopausal women may be offered tamoxifen as an adjuvant endocrine therapy. Premenopausal women could also be offered an aromatase inhibitor with ovarian suppression. An aromatase inhibitor (letrozole, anastrozole, exemestane) may be offered as the initial endocrine therapy for postmenopausal women with ER positive breast cancer who are at high risk. Extended endocrine therapy (of up to ten years) may also be considered. This treatment has remained unchanged for many years. However, it should be noted that there is an ongoing NICE appraisal of adjuvant abemaciclib for hormone-receptor positive, HER2 negative, node-positive primary breast cancer, therefore, questions may arise about the optimal way to use olaparib and abemaciclib for any overlapping patients.
8. Is there an unmet need for patients with this condition?	Yes, there is a need for more effective adjuvant treatments that can reduce the risk of recurrence, including the risk of the breast cancer spreading to other parts of the body where it becomes incurable. For example, currently for patients with triple negative breast cancer there has been little progress made on the treatments available on the NHS. New treatment options that can improve outcomes are welcomed by patients. A patient currently receiving olaparib via the drug company's early access programme explains "I feel incredibly lucky to have been given the opportunity to benefit from olaparib. Given the significant reduction in the risk of breast cancer recurring that olaparib provides I feel it is absolutely vital that other women with early breast cancer that have a BRCA mutation are able to benefit from olaparib too."

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Evidence shows that for eligible patients one year of taking olaparib can reduce the risk of recurrence, including progression to secondary cancer where the cancer becomes incurable and improve overall survival. Data from the phase 3 OlympiA trial (published in June 2021) has shown that invasive disease-free survival was significantly longer for patients taking olaparib compared to placebo, with 85.9% of patients alive and free of invasive disease-free survival at 3 years, compared to 77.1% of patients in the placebo group. Distant disease-free survival was also significantly longer among those patients who received olaparib (87.5% versus 80.4%). We know that the fear of recurrence and 'living under its shadow' can have a significant impact on the quality of lives of people after they finish their treatment for primary breast cancer. To have a new treatment option in olaparib, which is known to be generally well-tolerated, and could significantly reduce the risk of recurrence, including the risk of secondary breast cancer and the associated need for on-going and complex treatments could have a significantly positive impact on people's wellbeing. In addition to reducing the risk of recurrence, updated results from the trial (published in March 2022) have now shown a significant survival benefit with olaparib. After a median 3.5 years of follow-up, it was shown that adjuvant olaparib can improve overall survival for this group of patients, with a 32% reduction in the risk of death versus placebo. A patient currently receiving olaparib explains that "The clear benefit of olaparib for me is the significant reduction in the risk of my cancer recurring. Compared to other extended adjuvant treatments I am aware of for breast cancer, the reduction is much bigger. As I had triple negative breast cancer the risk of it recurring in the years immediately following treatment is higher." Another patient receiving olaparib explains: "I've been on olaparib since mid-August 2021. It definitely has a big positive mental impact – I feel better knowing I'm having a treatment which shows positive survival

	results. It makes me feel more protected and makes a big difference to my life. An additional year of being on a treatment is worth it because looking at the statistics about the effectiveness of the treatment and knowing the benefits is so crucial for patients from a mental wellbeing perspective” Another important factor to take into consideration with this treatment is its administration method. Olaparib is an oral tablet which is taken at home twice daily which is a very important factor for patients, as it can result in less disruption to their day to day lives, in terms of travel time to the hospital and the associated financial impact of travel and potentially taking time away from work. A patient explains: “olaparib is very easy to take – just two tablets twice a day with a glass of water. Obviously much easier than having to go into hospital for IV or subcutaneous treatment and the time that takes out of your day”. For eligible patients with a BRCA mutation, knowing a drug is targeted to their mutation can be very powerful and have a positive emotional impact as they feel they are then on the most optimum treatment for their particular type of breast cancer. This can therefore be seen as more personalised type of treatment.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	Every treatment for breast cancer has some side effects and each patient’s situation will be different, with side effects affecting some patients more than others. Patients’ willingness to undertake treatments will vary, however, as long as all the side effects are clearly discussed with the patient, they can weigh up the benefits and risks with their healthcare team. Patients may experience side effects with olaparib, which could potentially have a negative impact on some patient’s quality of life. For example, common side effects reported in the trial included nausea, fatigue, anaemia, sickness, headaches, diarrhoea. Importantly, side effects in the trial were largely of grade 1 or 2. However, side effects of grade 3 toxicity that occurred in more than 1% of the patients included anaemia (in 8.7% of patients, decreased neutrophil count (4.8%) and fatigue (1.8%). These side effects are known to healthcare professionals and it is reported that dose interruptions and reductions

	were effective management strategies during the trial. A patient currently taking olaparib explains that “I am tired and go to bed earlier, but not as tired as I was on chemotherapy and I believe that this tiredness is not just down to the olaparib. I am working full time and have also been able to start running again which is great.” Another patient who is taking olaparib explains: “Taking the tablet is very easy, it was something I worried about to begin with but it’s fine. The only little negatives are, at first I had quite a metallic taste but drinking a lot of water helped with this. Also I feel it does affect my bones. I have some problems with my jaw, back, arm and knees. I am sometimes stressed if my cancer is coming back but know that pain can be a side effect. I find movement is really helping, so I run on a treadmill. My nose can also get dry and bleed sometimes if I touch it. There are other possible side effects of the drug which I don’t get, such as sickness or diarrhoea. In my opinion, I feel much better on olaparib than I did when I was receiving chemotherapy.” For eligible patients whose breast cancer is triple negative, adding olaparib into standard treatment would increase the amount of time a patient is receiving treatment for, as well as being required to be reviewed by the treatment team. However, patients we have spoken to have said the benefits that olaparib can offer them in terms of reducing the risk of recurrence outweigh any burden of needing to take this adjuvant treatment and the additional hospital appointments required. Also anecdotally, having additional hospital appointments can be a benefit for some patients as they are still connected to healthcare professionals for support. For patients with hormone-receptor positive breast cancer, there may not be an additional burden as olaparib may be taken concurrently with their endocrine treatment and it is important to consider that patients with this type of breast cancer may then need to manage side effects from both olaparib and the endocrine treatment.
Patient population	

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	- This study looked particularly at people who were 'high-risk'. Please see comment below regarding definition of 'high-risk'.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	- One of the groups of patients who may be eligible for olaparib are those who are triple negative and BRCA positive. Triple negative breast cancer is more common in black women and women under 40.
Other issues	
13. Are there any other issues that you would like the committee to consider?	1. Genetic testing: It is crucial that genetic testing pathway processes are in place to allow for streamlined genetic testing to identify patients in a timely manner for this treatment. Whilst we understand that the genetic testing pathway is not within the remit of this appraisal, it is important that any issues relating to testing are acknowledged and considered by the appraisal committee.

	2. 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. The risk of recurrence is higher among patients with certain risk factors, such as large tumour size and higher number of positive lymph nodes.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission:

- A diagnosis of primary breast cancer can cause considerable anxiety to patients as well as their family and friends, including fear of recurrence or it spreading to other parts of the body where it becomes incurable.
- Adjuvant olaparib has been shown to improve invasive disease-free survival, distant disease-free survival and overall survival, compared to placebo. With the risk of recurrence often looming over this group of patients, having a new treatment which could help reduce this and increase the ‘rate of cure’ could have a significant impact on their quality of life.
- Olaparib is generally well tolerated by patients and is convenient to take due to it being an oral tablet.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

……

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

……

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Olaparib for adjuvant treatment of high-risk HER2-negative, BRCA-positive early breast cancer after chemotherapy ID3893

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**NCRI-ACP-RCP-RCR**

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	**No**

If so, please state the name of manufacturer, amount, and purpose of funding.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Up to 5% of unselected breast cancer patients carry a pathogenic germline mutation in either the *BRCA1* or *BRCA2* gene. Those with a *BRCA1* mutation have a tendency to develop triple negative breast cancers, whereas *BRCA2* mutation carriers generally develop oestrogen receptor positive, HER2-negative tumours (1). The intent of adjuvant therapy in women preventing with early breast cancer and a germline *BRCA1/2* mutation is curative. However, there are limited treatment options available for women with triple negative disease (cytotoxic chemotherapy and surgery are the mainstays of treatment), and although those with ER+ disease may be additionally treated with endocrine therapy, there remains a significant risk of distant relapse and death from breast cancer, particularly in higher risk patient groups. There is a good underlying biological rationale to suggest that PARP inhibitors will be efficacious in patients with germline *BRCA1/2* mutated breast cancer, where tumours have an innate DNA damage repair deficiency. Consistent with this, previous studies in advanced *BRCA*-mutated breast cancer have shown a benefit for PARP inhibition (2). Indeed, a randomised phase 3 trial in advanced *BRCA*-mutated breast cancer confirmed a progression-free survival benefit of 2.8 months for Olaparib over physician's choice of

	chemotherapy (3). The pivotal trial in early breast cancer, however, is the OlympiA trial (4). This double-blind phase 3 trial randomised 1836 patients with high-risk HER2-ve early breast cancer with *BRCA1/2* pathogenic mutations to either 1 year of adjuvant Olaparib or placebo following completion of standard therapy. High-risk status in OlympiA was determined by one of the following: • Triple negative breast cancer (TNBC) – **either** incomplete response to neoadjuvant chemotherapy with residual disease in the breast and/or axilla, **or** either node-positive disease or a primary tumour >2cm in maximum diameter if receiving adjuvant chemotherapy • ER positive HER2-ve breast cancer – **either** incomplete response after neoadjuvant chemotherapy with a CPS+EG score of ≥3 **or** at least 4 pathologically confirmed positive lymph nodes after surgery if receiving adjuvant chemotherapy. The primary end point was invasive disease-free survival, and at 3 years there was an absolute benefit of 8.8% (85.9% versus 77.1%) in favour of patients treated with Olaparib (HR 0.58, p<0.001). When considering secondary end points, there was a statistically significant improvement in distant disease-free survival (87.5% versus 80.4%, difference 7.1%, HR 0.75, p<0.001) in favour of Olaparib. Although fewer deaths were reported in the Olaparib arm (59 versus 86, HR 0.68, p=0.02) but this did not cross a prespecified boundary for statistical significance. Updated data from a second interim analysis of OlympiA has recently been presented (ESMO plenary session, March 2022) and at 4 years the absolute difference in OS was 3.4% favouring Olaparib, with a stratified HR of 0.68 and p=0.009, crossing the pre-specified significance boundaries. However, this data is not yet available in peer-reviewed published form, although this is expected later in 2022.
7. What do you consider a clinically significant treatment response? (For example, a	Given the limited treatment options and relatively poor prognosis for these patient groups, the absolute improvement in invasive disease-free survival of 8.8% at 3 years reported in the OlympiA study with 12 months of adjuvant Olaparib represents both a statistically and clinically significant (and clinically meaningful) treatment response. It should be noted that in the control group in OlympiA, the 3 year IDFS was 77.1%, underscoring the relatively poor prognosis of these patients in the absence of additional

reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	targeted therapies. Similarly, the 7.1% absolute benefit in terms of distant disease-free survival reported by Tutt *et al* represents clinically significant improvement in outcome for these patients (4). While the initial report of the OlympiA trial did suggest an overall survival benefit with adjuvant Olaparib, the absolute benefit was 3.8% and did not reach statistical significance according to the pre-specified statistical analysis plan for the study. However, an updated interim analysis of the trial data has recently been presented (ESMO plenary session, March 2022) and at 4 years the absolute difference in OS was 3.4% favouring Olaparib, with a stratified HR of 0.68 and p=0.009, crossing the pre-specified significance boundaries. There is therefore little doubt that the benefits associated with adjuvant Olaparib are both statistically and clinically significant and clinically meaningful in a high-risk patient group with limited treatment options.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. As outlined above, outcomes for this high-risk patient group remain poor, with a 3-year IDFS of 77.1%. At present, for TNBC there are no targeted therapies that can be employed, and thus there is a real need for additional therapeutic approaches, and this data confirms that there is a group of patients who can be identified using a biomarker (*BRCA1/2* sequencing) who will benefit from this treatment.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	There is currently considerable heterogeneity in the treatment of TNBC in the NHS. Patients with T2 and above tumours will generally be treated with neoadjuvant chemotherapy, as will node positive patients, who constitute the high-risk patient groups that are included in the OlympiA trial (4). There is variation in practice nationally in the selection of chemotherapy regimens, with the majority of patients receiving anthracycline-taxane combinations. However, a proportion of patients will receive platinum-containing regimens (~25% in a UK prospective audit from 2017-18; unpublished data). It is likely

	with time that this proportion is increasing although there is no UK data available regarding contemporary practice. Importantly, in the OlympiA study, the benefit of Olaparib was seen in both those patients receiving both non-platinum and platinum containing chemotherapy regimens (although the number of patients in the latter group was small and the hazard ratio of 0.77 had wide confidence intervals (0.49-1.22). Patients with TNBC who do not achieve a pathological complete response to neoadjuvant therapy may be considered for capecitabine following definitive breast surgery (see below regarding pathway of care).
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Current NICE guidance [NG101] recommends offering neoadjuvant chemotherapy for ER negative breast cancer as an option to reduce tumour size; the guidance for TNBC suggests consideration of a neoadjuvant chemotherapy regimen containing both platinum and anthracycline. International guidelines (St Gallen) recommend neoadjuvant systemic therapy as the preferred initial approach for women with stage 2/3 TNBC
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Generally, the pathway of care is well-defined, and the majority of clinicians would agree with the guidance/treatment pathways outlined above. However, there is clearly heterogeneity in the types of neoadjuvant chemotherapy agents used (+/-platinum agents), with some centres routinely giving platinum agents and others not. In addition, treatment of patients with TNBC who do not achieve pCR with neoadjuvant chemotherapy is non-standardised. If pCR is not achieved, the addition of further adjuvant therapy with capecitabine following breast surgery may be considered, and improved disease-free survival has been reported with this approach (5), although the evidence for this is equivocal (6). If capecitabine is given in the post-neoadjuvant setting, however, there is no clear biomarker to identify which patients with TNBC are likely to benefit; in contrast with Olaparib, where there is a clearly defined subgroup of patients (germline BRCA mutation carriers) who will benefit from this treatment approach.

• What impact would the technology have on the current pathway of care?	This would extend the current pathway of care for these patients, with adjuvant treatment with oral Olaparib as an outpatient lasting 12 months after surgery.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Olaparib is not in current use for the treatment of early breast cancer in NHS practice.
• How does healthcare resource use differ between the technology and current care?	As above – PARP inhibitors are not currently in routine use in the treatment of early breast cancer.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist clinics should deliver systemic anti-cancer therapy, as is currently the case.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Most chemotherapy units are now familiar with giving olaparib due to its use in advanced ovarian cancer, so with respect to training there should be minimal additional training required. Pharmacies will be familiar with handling the drug due to its use in this context.
11. Do you expect the technology to provide clinically	Yes

meaningful benefits compared with current care?	
• Do you expect the technology to increase length of life more than current care?	Yes – as discussed above there is data from a large phase 3 RCT confirming benefits in invasive disease-free survival, distant disease-free survival and overall survival for Olaparib.
• Do you expect the technology to increase health-related quality of life more than current care?	No - but equally data from the OlympiA trial presented at the San Antonio Breast Cancer Symposium in December 2021 showed that there were no significant differences in quality of life scores between patients on Olaparib and those on placebo so there was no associated adverse impact on quality of life with extended treatment.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Yes – this treatment approach would only be appropriate in patients with a confirmed pathogenic *BRCA1/2* mutation and with high-risk disease, in keeping with the entry criteria for the OlympiA trial. There is no trial data to suggest a treatment benefit for Olaparib in unselected HER2 negative breast cancer, nor in *BRCA1/2* mutation carriers with lower risk disease.
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare	Treatment with adjuvant Olaparib in this setting will extend the duration of treatment for patients. However this is an oral treatment given in the outpatient setting. Anaemia and neutropaenia (1.8% and 1.0%

professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	respectively) were reported in OlympiA and therefore haematological monitoring will be required during treatment.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Eligible patients would be those carrying a germline BRCA mutation. Criteria for testing breast cancer patients for germline BRCA mutations are set out in the NHS National Genomic test Directory (https://www.england.nhs.uk/publication/national-genomic-test-directories/). It is therefore anticipated that appropriate patients should already be being tested for BRCA mutations as per these criteria.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the	No

quality-adjusted life year (QALY) calculation?	
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes. Currently there are no targeted therapies available for patients within this group. Patients with TNBC have no additional options following completion of cytotoxic chemotherapy at present (other than adjuvant capecitabine, as discussed above), and patients with ER+ HER2 negative disease have only the option of endocrine therapy. There is therefore a clear unmet need in this setting, and Olaparib delivers a significant and clinically meaningful improvement for patients with high-risk disease, relatively poor outcomes and few current treatment options.
• Is the technology a 'step-change' in the management of the condition?	Yes (see above)
• Does the use of the technology address any particular unmet need of the patient population?	Yes (see above)
17. How do any side effects or adverse effects of the technology affect the	In OlympiA, there was no significant increase in the rate of serious adverse events in the Olaparib arm compared with placebo (8.7% versus 8.4%). There was no significant increase in the rate of adverse events of special interest such as pneumonitis, myelodysplastic syndrome, acute myeloid leukaemia or

management of the condition and the patient's quality of life?	other second primary cancer although a median follow-up of 2.5 years is relatively short in respect of these latter toxicities. As noted above, there were no adverse quality of life outcomes associated with Olaparib.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes – the treatment approaches and regimens used in OlympiA are reflective of current UK practice. At the time of the OlympiA trial adjuvant capecitabine for non-pCR TNBC patients was not routine practice and this was not permitted in the study. Dose reductions were required in 25% of patients on Olaparib and treatment was discontinued in 9.9%.
• If not, how could the results be extrapolated to the UK setting?	N/A
• What, in your view, are the most important outcomes, and were they measured in the trials?	The most important outcomes in the adjuvant setting for early breast cancer are invasive disease-free survival, distant disease-free survival and overall survival, all of which were assessed in the OlympiA trial.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
• Are there any adverse effects that were not	No

apparent in clinical trials but have come to light subsequently?	
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance?	No
21. How do data on real-world experience compare with the trial data?	No relevant real-world data exist for the use of adjuvant Olaparib.
Equality	
22a. Are there any potential equality issues that should be	No

taken into account when considering this treatment?	
22b. Consider whether these issues are different from issues with current care and why.	N/A

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.

- Patients with high-risk germline BRCA mutated breast cancer have a relatively poor prognosis and currently have limited treatment options.
- Adjuvant Olaparib in these high-risk patients has been shown to significantly improve outcomes in terms of IDFS, DDFS and OS.
- Adjuvant Olaparib did not significantly impact on quality of life when compared with placebo and had a manageable toxicity profile.
- Breast cancer patients should be tested for BRCA mutations according to the existing eligibility criteria laid out in the genomic test Directory.
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

1. Da Silva L, Lakhani SR. Pathology of hereditary breast cancer. Mod Pathol. 2010;23 Suppl 2:S46-51.
2. Tutt A, Robson M, Garber JE, Domchek SM, Audeh MW, Weitzel JN, et al. Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and advanced breast cancer: a proof-of-concept trial. Lancet. 2010;376(9737):235-44.
3. Robson M, Im SA, Senkus E, Xu B, Domchek SM, Masuda N, et al. Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation. N Engl J Med. 2017;377(6):523-33.
4. Tutt ANJ, Garber JE, Kaufman B, Viale G, Fumagalli D, Rastogi P, et al. Adjuvant Olaparib for Patients with BRCA1- or BRCA2-Mutated Breast Cancer. N Engl J Med. 2021;384(25):2394-405.
5. Masuda N, Lee S-J, Ohtani S, Im Y-H, Lee E-S, Yokota I, et al. Adjuvant Capecitabine for Breast Cancer after Preoperative Chemotherapy. New England Journal of Medicine. 2017;376(22):2147-59.
6. Lluch A, Barrios CH, Torrecillas L, Ruiz-Borrego M, Bines J, Segalla J, et al. Phase III Trial of Adjuvant Capecitabine After Standard Neo-/Adjuvant Chemotherapy in Patients With Early Triple-Negative Breast Cancer (GEICAM/2003-11_CIBOMA/2004-01). Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2020;38(3):203-13.

CONFIDENTIAL UNTIL PUBLISHED

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

Authors

Penny Whiting, Professor of Clinical Epidemiology, Bristol TAG, Population Health Sciences, Bristol Medical School, University of Bristol, Bristol

Elsa M R Marques, Senior Lecturer in Health Economics, Bristol TAG, Population Health Sciences, Bristol Medical School, University of Bristol, Bristol

Chris Cooper, Research Fellow in Health Technology Assessment and Information Science, Bristol TAG, Population Health Sciences, Bristol Medical School, University of Bristol, Bristol

Eve Tomlinson, Research Associate in Evidence Synthesis, Bristol TAG, Population Health Sciences, Bristol Medical School, University of Bristol, Bristol

Rachel James, Research Associate in Evidence Synthesis, Bristol TAG, Population Health Sciences, Bristol Medical School, University of Bristol, Bristol

Nicky Welton, Professor of Statistical and Health Economic Modelling, Bristol TAG, Population Health Sciences, Bristol Medical School, University of Bristol, Bristol

Hugo Pedder, Senior Research Associate in Statistical Modelling, Bristol TAG, Population Health Sciences, Bristol Medical School, University of Bristol, Bristol

Thomas Strawson-Smith, Consultant Clinical Oncologist Breast and Lower GI, University Hospitals Bristol and Weston NHS Foundation Trust, Bristol

Lara S Gibbs, Consultant Medical Oncologist Breast and Germ Cell Cancers, Bristol Haematology and Oncology Centre, Bristol

Howard Thom, Senior Lecturer in Health Economics, Bristol TAG, Population Health Sciences, Bristol Medical School, University of Bristol, Bristol

Correspondence to Penny Whiting, Professor of Clinical Epidemiology, Bristol TAG, Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, BS8 2PS

Date completed 29/6/2022

Source of funding: This report was commissioned by the National Institute for Health and Care Research (NIHR) Evidence Synthesis Programme as project number 13/55/84.

Declared competing interests of the authors:
None of the authors has any conflicts of interest to declare.

Acknowledgements
We would like to thank Tracie Miles (Associate Director of Nursing and Midwifery) and Rachel Palmer (Lead Genomics Pharmacist) from the NHS South West Genomic Medicine Service Alliance for clinical advice regarding BRCA testing. We would also like to thank Charlene Wisdom-Trew, Bristol TAG, for providing administrative support.

Rider on responsibility for report
The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:
Whiting P, Marques EMR, Cooper C, Tomlinson E, James R, Welton N, Pedder H, Strawson-Smith T, Gibbs L S, Thom H. Olaparib for adjuvant treatment of high-risk HER2-negative,

BRCA-positive early breast cancer after chemotherapy: A Single Technology Appraisal. Bristol TAG, 2022.

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

1 EXECUTIVE SUMMARY 12
1.1 Overview of the EAG's key issues 12
1.2 Overview of key model outcomes 13
1.3 The decision problem: summary of the EAG's key issues 13
1.4 The clinical and cost effectiveness evidence: summary of the EAG's key issues 14
1.5 Other key issues: summary of the EAG's view 16
1.6 Summary of EAG's preferred assumptions and resulting ICER 17
2 INTRODUCTION AND BACKGROUND 19
2.1 Critique of the company's proposed place of the technology in the treatment pathway and intended positioning of the intervention. 19
2.2 Critique of company's definition of decision problem 20
3 CLINICAL EFFECTIVENESS 24
3.1 Critique of the methods of review(s) 24
3.2 Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these) 24
3.2.1 Study design 24
3.2.2 Patients 26
3.2.3 Interventions 28
3.2.4 Outcomes 29
3.2.5 Protocol deviations 33
3.2.6 Trial results 33
3.3 Conclusions of the clinical effectiveness section 41
3.3.1 Is there evidence of clinical effectiveness? 41
3.3.1 Are estimates that feed into the economic model reliable and appropriate to the scope? 41
3.3.2 Have the most appropriate estimates been selected to feed into the economic model? 41
4 COST EFFECTIVENESS 42
4.1 EAG comment on company's review of cost-effectiveness evidence 42
4.2 Summary and critique of the company's submitted economic evaluation by the EAG 42
4.2.1 NICE reference case checklist 42
4.2.2 Model structure 44
4.2.3 Population 46
4.2.4 Interventions and comparators 46
4.2.5 Perspective, time horizon and discounting 46
4.2.6 Treatment effectiveness and extrapolation 47
4.2.7 HRQoL 57
4.2.8 Resources and costs 61
5 COST EFFECTIVENESS RESULTS 65

5.1 Company's cost effectiveness results 65
5.2 Company's sensitivity analyses 66
5.2.1 Company's deterministic sensitivity analysis 66
5.2.2 Company's probabilistic sensitivity analysis 67
5.2.3 Company's scenario analyses 69
5.3 Model validation and face validity check 71
5.3.1 Company validation and face validity check 71
5.3.2 EAG validation and face validity check 72
6 EVIDENCE ASSESSMENT GROUP'S ADDITIONAL ANALYSES 73
6.1 Exploratory and sensitivity analyses undertaken by the EAG 73
6.1.1 Increasing the number of PSA samples for base case results 73
6.1.2 Varying the transition probabilities assumptions: 73
6.1.3 Varying the cost assumptions: 73
6.1.4 Varying the utility assumptions: 73
6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the EAG 74
6.3 EAG's preferred assumptions 74
6.4 EAG's cost-effectiveness results 76
6.4.1 EAG base case deterministic and probabilistic sensitivity analyses 78
6.4.2 EAG base case with company scenario analyses 81
6.4.3 EAGs additional scenario analyses 83
6.5 Conclusions of the cost effectiveness section 85
7 Severity and Innovation 86
8 REFERENCES 86
9 APPENDICES 92
9.1 Appendix 1: Risk of bias in the systematic review (SR)(12) conducted for the company submission assessed using a modified version of the ROBIS tool.(74) 92
9.2 Appendix 2: Risk of bias in the OlympiA trial assessed using the Cochrane Risk of Bias Tool v 2.0(17) 98
9.2.1 Risk of bias in the effect of **assignment** to intervention 98
9.2.2 Risk of bias in the effect of **adhering** to intervention 100

LIST OF TABLES

Table 1 Summary of key issues 12
Table 2 Summary of EAG's preferred assumptions in TNBC* 17
Table 3 Summary of EAG's preferred assumptions in HR+/HER2-* 17
Table 4 Summary of decision problem 21
Table 5 Risk of Bias in OlympiA Trial assessed separately for each outcome 25
Table 6 NGTD BRCA testing eligibility criteria 28
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 29
Table 8 Overview of AE groupings and definitions 32

Table 9 Summary of OlympiA primary and key secondary endpoints, DCO1 and DCO2 (FAS), reproduced from company's response to clarification questions.(6) 34
Table 10 iDFS results stratified according to HR status 38
Table 11 Results of Safety Analyses for DC01 and DC02 40
Table 12 NICE reference case checklist 43
Table 13 Data and assumptions used for cost-effectiveness model transition probabilities .47
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. 52
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) 55
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) 56
Table 17 Company deterministic base case results (TNBC, olaparib PAS price) (From Company Clarification Responses Table 30)(6) 65
Table 18 Company deterministic base case results (HR+/HER2-, olaparib PAS price) (From Company Clarification Responses Table 31)(6) 65
Table 19 Company probabilistic base case results using 1000 samples (TNBC) (From Company Clarification Responses Table 32)(6) 65
Table 20 Company probabilistic base case results using 1000 samples (hr+/her2-) (from company clarification responses table 33)(6) 66
Table 21 Company scenario analysis results (discounted, TNBC & HR+/HER2- analyses) (From Company Clarification Responses Table 34)(6) 69
Table 22 EAG's preferred model assumptions. 75
Table 23 EAG deterministic base case results (TNBC, olaparib PAS price) 77
Table 24 EAG deterministic base case results (HR+/HER2-, olaparib PAS price) 77
Table 25 EAG probabilistic base case results (TNBC, olaparib PAS price). Using 10,000 samples. 77
Table 26 EAG probabilistic base case results (HR+/HER2-, olaparib PAS price). Using 10,000 samples. 77
Table 27 EAG base case with company scenario analysis results (discounted, TNBC & HR+/HER2- analyses) (Based on Company Clarification Responses Table 34) 81
Table 28 EAG Deterministic Scenario analysis results modifying from EAG preferred base case (discounted, TNBC & HR+/HER2- analyses) 83

LIST OF FIGURES

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) 20
Figure 2 Kaplan–Meier plot of iDFS in OlympiA, DCO2 (FAS) reproduced from Figure 7 in the company response to request for clarification.(6) 36

Figure 3 Kaplan−Meier plot of dDFS in OlympiA, DCO2 (FAS) reproduced from Figure 8 in the company response to request for clarification.(6) 37
Figure 4: Kaplan−Meier plot of OS in OlympiA, DCO2 (FAS) reproduced from Figure 9 in the company response to request for clarification.(6) 37
Figure 5 Cost-effectiveness model structure reproduced from figure 15 of cs document b(1) 45
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).....51
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) 54
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).....55
Figure 9 Deterministic one-way sensitivity analyses for company base case (TNBC) (Reproduced from Company Clarification Responses Figure 28)(6) 66
Figure 10 Deterministic one-way sensitivity analyses for company base case (HR+/HER2-) (Reproduced from Company Clarification Responses Figure 29)(6) 67
Figure 11 Company Cost-effectiveness acceptability curve, olaparib vs. placebo samples (“watch & wait”) using 1000 (TNBC) (From Company Clarification Responses Figure 25)(6).68
Figure 12 company cost-effectiveness acceptability curve, olaparib vs. Placebo (“watch & wait”) using 1000 samples (HR+/HER2-) (from company clarification responses figure 27)(6) 69
Figure 13 EAG Base case cost-effectiveness acceptability curve, olaparib vs. Placebo ("watch & wait") (TNBC). Using 10,000 samples.....78
Figure 14 EAG base case cost-effectiveness plane (TNBC). Using 10,000 samples.....79
Figure 15 DETERMINISTIC ONE-WAY SENSITIVITY ANALYSES FOR EAG BASE CASE. (TNBC)...79
Figure 16 EAG BASE CASE COST-EFFECTIVENESS ACCEPTABILITY CURVE, OLAPARIB VS. PLACEBO ("WATCH & WAIT") (HR+/HER2-). Using 10,000 samples.....80
Figure 17 EAG Base case cost-effectiveness plane (HR+/HER2-). Using 10,000 samples. 80
Figure 18 DETERMINISTIC ONE-WAY SENSITIVITY ANALYSES FOR EAG BASE CASE (HR+/HER2-) 81

LIST OF ISSUES

Issue 1 Immaturity of data 14
Issue 2 Potential risk of bias in estimates of HRQoL 15
Issue 3 HRQoL measures used in the economic model 15
Issue 4 Access to BRCA testing in HR+/HER2- 16

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

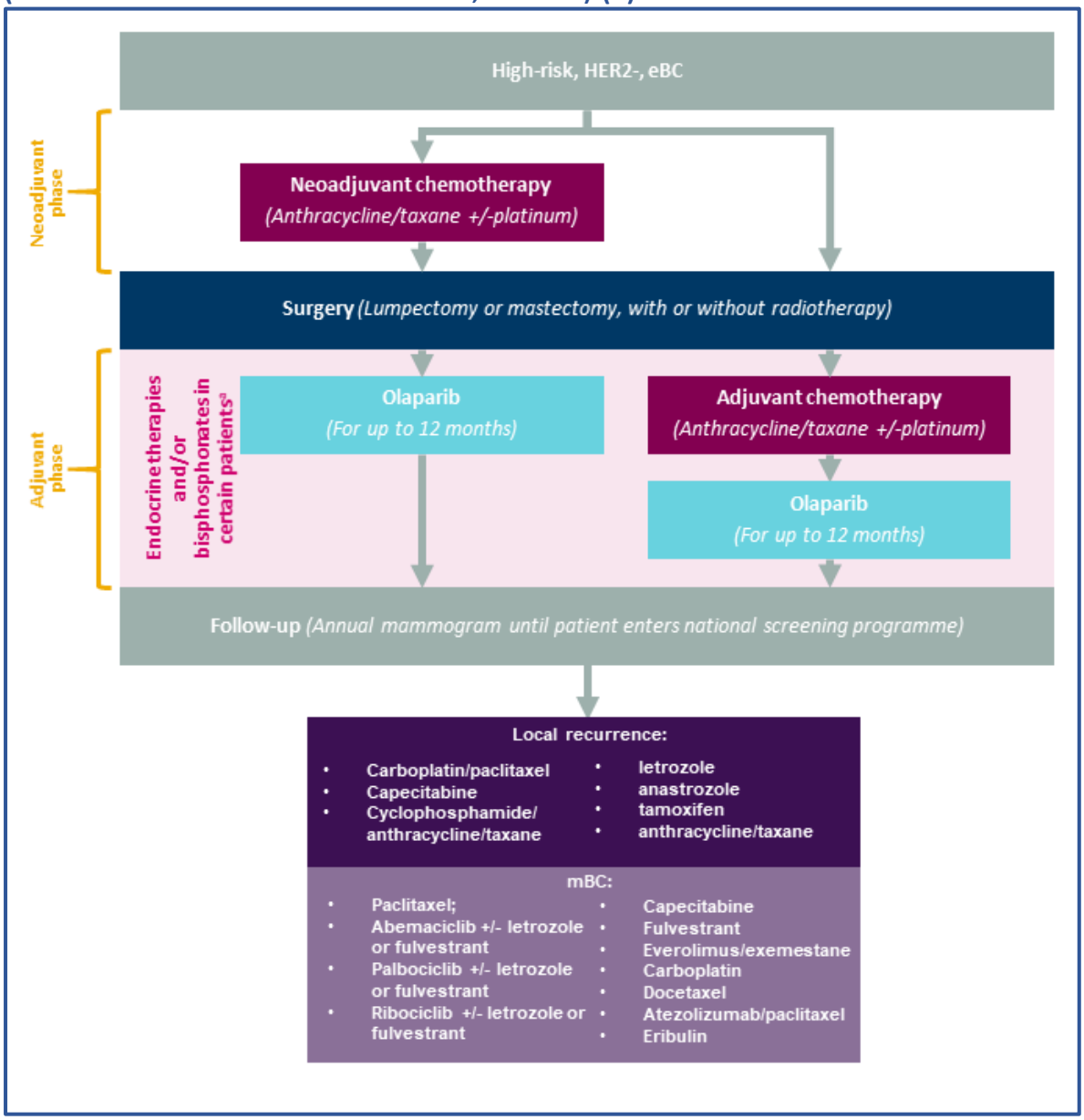
This report provides a critique of the evidence submitted by the company (AstraZeneca) in support of adjuvant treatment of high-risk Human Epidermal Growth Factor Receptor 2 (HER2)-negative, Breast Cancer Susceptibility Gene (BRCA)-positive early breast cancer after chemotherapy. It considers the company 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%)

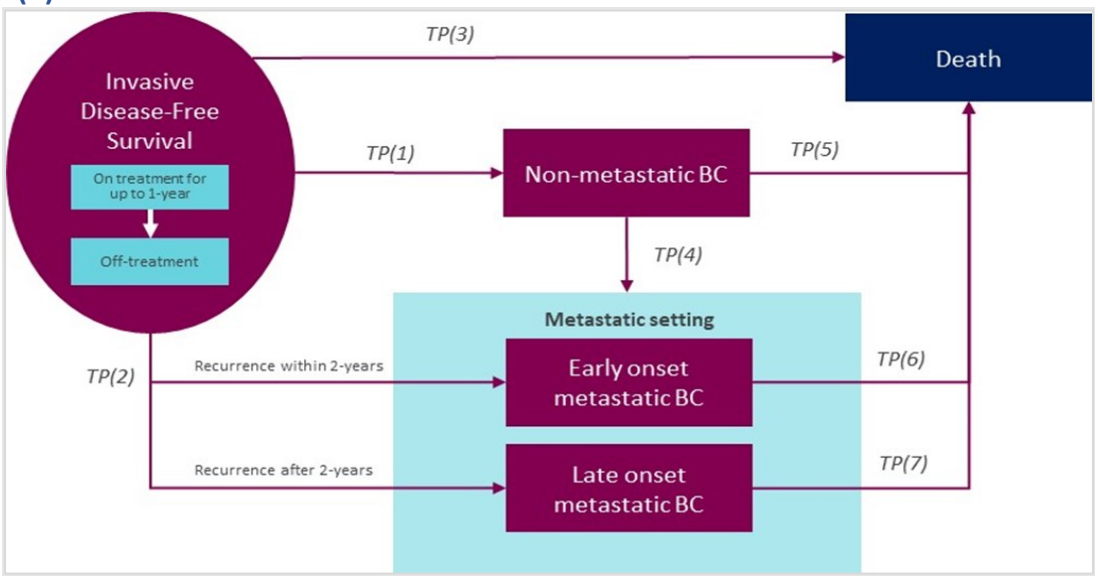
Element of health technology assessment	Reference case	EAG comment on company's submission
PSS, personal social services; QALYs, quality-adjusted life years; EQ-5D, EuroQol questionnaire, NICE recommended instrument to measure generic health-related quality of life, valued using UK societal preference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

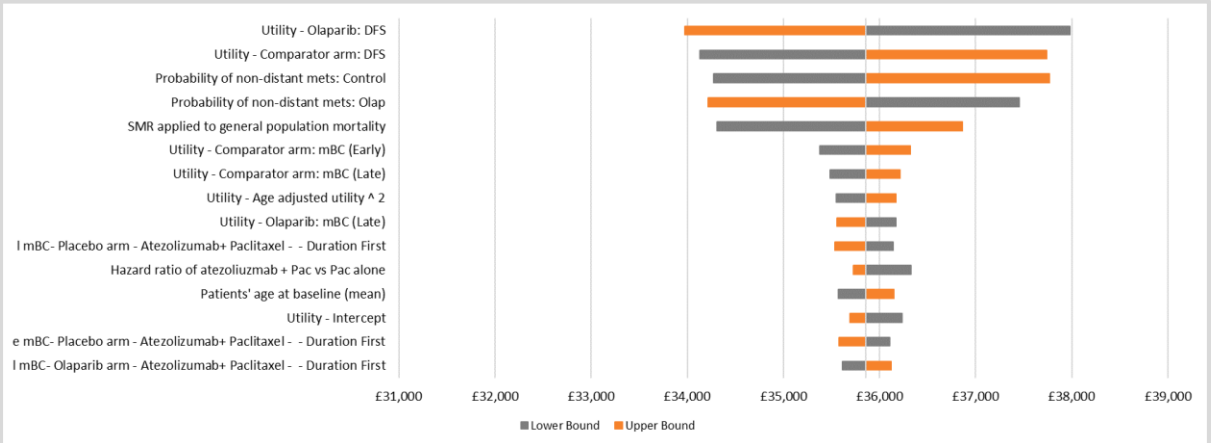
5.2 Company's sensitivity analyses

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)

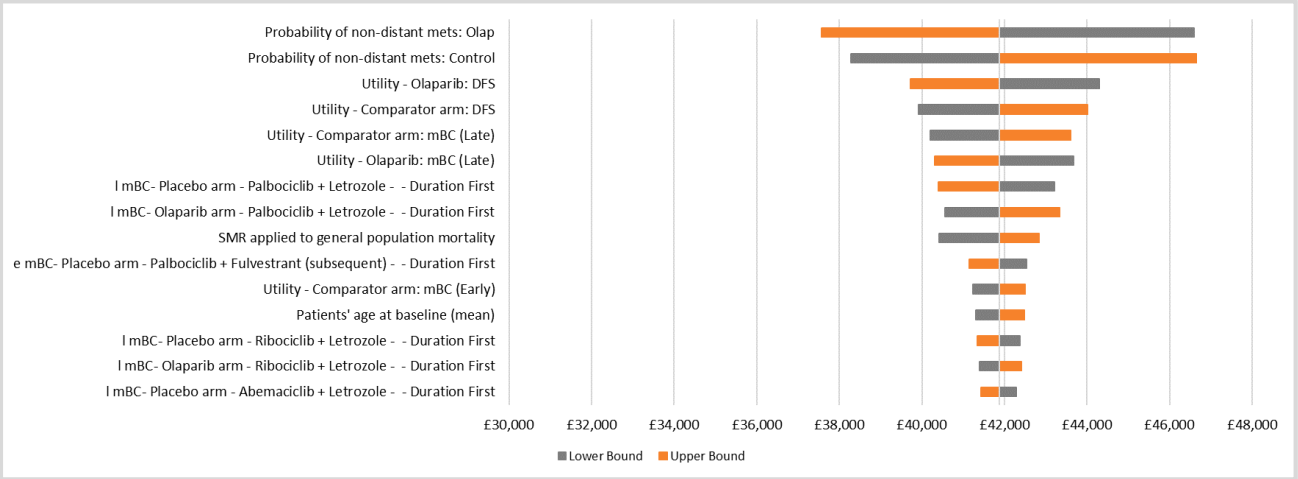


Abbreviations: DFS: disease-free survival; e-mBC: 'early onset' metastatic breast cancer; l-mBC: 'late onset' metastatic breast cancer; SMR: standardised mortality ratio; TNBC: triple negative breast cancer

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.

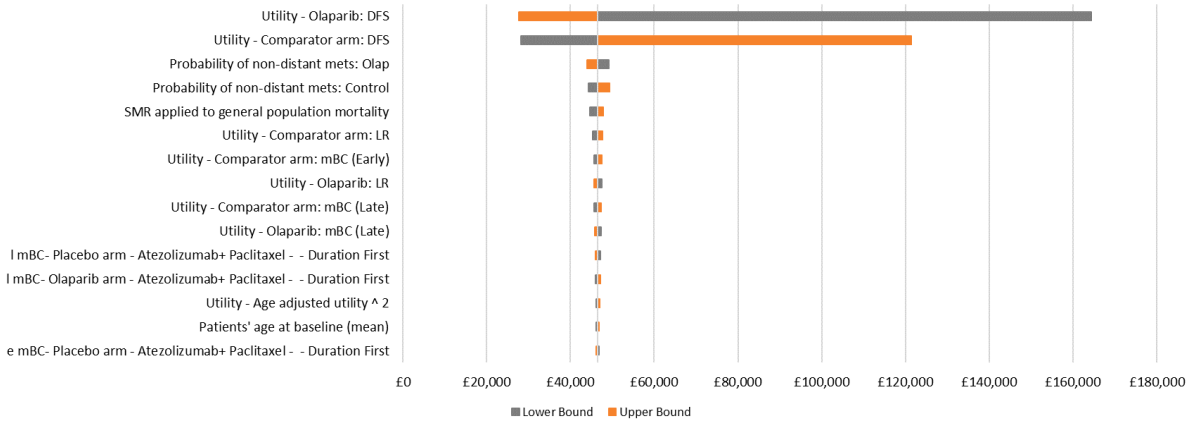
FIGURE 13 EAG BASE CASE COST-EFFECTIVENESS ACCEPTABILITY CURVE, OLAPARIB VS. PLACEBO ("WATCH & WAIT") (TNBC). USING 10,000 SAMPLES.

[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).



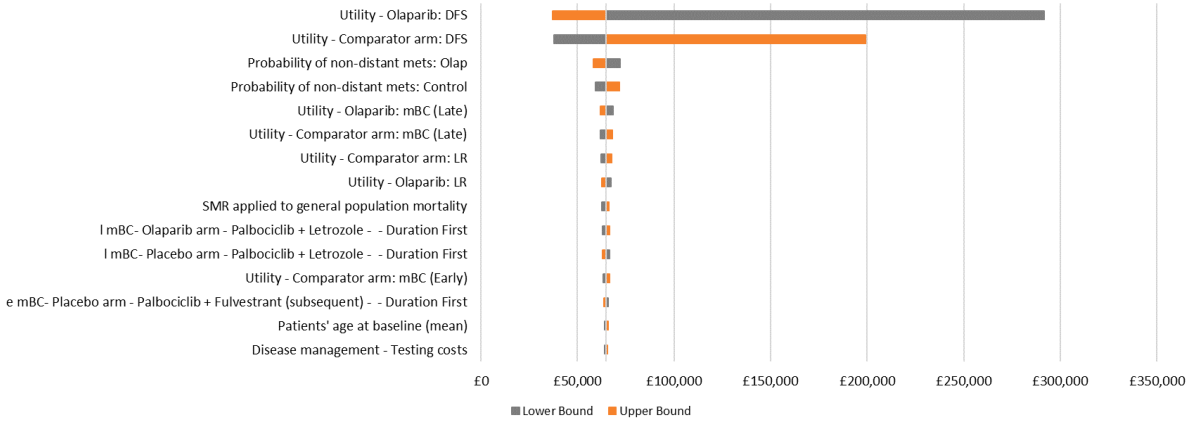
The cost-effectiveness results for the HR+/HER2- population reflect the additional uncertainty around this population. The CEAC using 10,000 samples for the EAG base case in HR+/HER2- is presented in Figure 16. If the NHS is willing to pay between £20,000 and £30,000 per additional QALY, the probability 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.

8 REFERENCE

1. AstraZeneca. Document B: Olaparib for adjuvant treatment of high-risk HER2-negative, BRCA-positive early breast cancer after chemotherapy [ID3893]. Company evidence submission. 2022.
2. National institute for health and care excellence (NICE). Olaparib for adjuvant treatment of high-risk HER2-negative, BRCA-positive early breast cancer after chemotherapy: Final Scope 2022. Available from: https://www.nice.org.uk/guidance/gid-ta10903/documents/final-scope. [Accessed 01 May 2022];
3. ClinicalTrials.gov. NCT02032823 . Olaparib as Adjuvant Treatment in Patients With Germline BRCA Mutated High Risk HER2 Negative Primary Breast Cancer (OlympiA) 2022. Available from: https://www.clinicaltrials.gov/ct2/show/NCT02032823?term=NCT02032823&draw=2&rank=1. [Accessed 01 May 2022];
4. Gray LA, Hernandez Alava M, Wailoo AJ. Mapping the EORTC QLQ-C30 to EQ-5D-3L in patients with breast cancer. BMC Cancer. 2021;21(1):1237.
5. Gray LA, Hernandez Alava M, Wailoo AJ. Correction to: Mapping the EORTC QLQ-C30 to EQ-5D-3L in patients with breast cancer. BMC Cancer. 2022;22(1):112.
6. AstraZeneca. Olaparib for adjuvant treatment of high-risk HER2-negative, BRCA-positive early breast cancer after chemotherapy [ID3893]. Company Response to Clarification Questions 2022.
7. National Institute for Health and Care Excellence (NICE). [NG101] Early and locally advanced breast cancer: diagnosis and management 2018 Available from: https://www.nice.org.uk/guidance/ng101/chapter/Recommendations#referral-diagnosis-and-preoperative-assessment. [Accessed 01 May 2022];
8. National Institute for Health and Care Excellence (NICE). The British National Formulary: Carboplatin 2022. Available from: https://bnf.nice.org.uk/drugs/carboplatin/ [Accessed 23 June 2022];

9. National Institute for Health and Care Excellence (NICE). The British National Formulary: Abemaciclib 2022. Available from: https://bnf.nice.org.uk/drugs/abemaciclib/ [Accessed 23 June 2022];
10. mtech access. Pharmacological therapies in non-metastatic, primary, invasive her2-negative breast cancer. 2022.
11. Tutt ANJ, Garber JE, Kaufman B, Viale G, Fumagalli D, Rastogi P, et al. Adjuvant Olaparib for Patients with BRCA1- or BRCA2-Mutated Breast Cancer. NEJM. 2021;384(25):2394-405.
12. AstraZeneca. OlympiA: Clinical Study Report. 2021.
13. Committee for Medicinal Products for Human Use (CHMP). Guideline on the clinical evaluation of anticancer medicinal products 2019. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-evaluation-anticancer-medicinal-products-man-revision-6_en.pdf. [Accessed 01 May 2022];
14. Centre for Reviews and Dissemination (CRD). CRD's guidance for undertaking reviews in health care. Centre for Reviews and Dissemination. York: University of York 2009. Available from: https://wwwyorkacuk/media/crd/Systematic_Reviewspdf. [Accessed 01 May 2022];
15. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898.
16. AstraZeneca. Appendices: Olaparib for adjuvant treatment of high-risk HER2-negative, BRCA-positive early breast cancer after chemotherapy [ID3893]. Company evidence submission 2022.
17. Patient organisation submission. Olaparib for adjuvant treatment of high-risk HER2-negative, BRCA-positive early breast cancer after chemotherapy ID3893 [Accessed 01 May 2022];
18. NHS England. National Genomic Test Directory 2021. Available from: https://www.england.nhs.uk/publication/national-genomic-test-directories/. [Accessed 01 May 2022];
19. AstraZeneca. Clinical study report: A Randomised, Double-Blind, Parallel Group, Placebo-Controlled Multi-Centre Phase III Study to Assess the Efficacy and Safety of Olaparib Versus Placebo as Adjuvant Treatment in Patients With Germline BRCA1/2 Mutations and High Risk HER2 Negative Primary Breast Cancer Who Have Completed Definitive Local Treatment and Neoadjuvant or Adjuvant Chemotherapy. 2021.
20. British National Formulary (BNF). Olaparib: Medicinal forms 2022. Available from: https://bnf.nice.org.uk/drugs/olaparib/medicinal-forms/. [Accessed 01 May 2022];
21. Hudis CA, Barlow WE, Costantino JP, Gray RJ, Pritchard KI, Chapman J-AW, et al. Proposal for Standardized Definitions for Efficacy End Points in Adjuvant Breast Cancer Trials: The STEEP System. J Clin Oncol. 2007;25(15):2127-32.
22. EORTC Quality of Life. EORTC QLQ-C30. Available from: https://qol.eortc.org/questionnaire/eortc-qlq-c30/. [Accessed 15 May 2022];
23. FACIT.org. FACIT-F. Functional Assessment of Chronic Illness Therapy – Fatigue. 2021. Available from: https://www.facit.org/measures/FACIT-F. [Accessed 01 May 2022];
24. EORTC Quality of Life Group. EORTC QLQ BR23 1994. Available from: https://www.eortc.org/app/uploads/sites/2/2018/08/Specimen-BR23-English-1.1.pdf. [Accessed 01 May 2022];

25. Bjelic-Radisic V, Cardoso F, Cameron D, Brain E, Kuljanic K, da Costa RA, et al. An international update of the EORTC questionnaire for assessing quality of life in breast cancer patients: EORTC QLQ-BR45. Ann Oncol. 2020;31(2):283-8.
26. EuroQol Group. EuroQol - a new facility for the measurement of health-related quality of life. Health Policy. 1990;16(3):199-208.
27. U.S. Department of health and human services. Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 2009. Available from: https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf. [Accessed 01 May 2022];
28. AstraZeneca. OlympiA: Clinical Study Protocol. 2020.
29. National Institute for Health and Care Excellence (NICE). [TA107] Trastuzumab for the adjuvant treatment of early-stage HER2-positive breast cancer. 2006. [Accessed 14 June 2022];
30. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, Goldhirsch A, Untch M, Smith I, et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Engl J Med. 2005;353(16):1659-72.
31. National Institute for Health and Care Excellence (NICE). TA424: Pertuzumab for the neoadjuvant treatment of HER2-positive breast cancer [ID767]. Committee Papers 2016. Available from: https://www.nice.org.uk/guidance/ta424/documents/committee-papers-2 [Accessed 01 May 2022];
32. National Institute for Health and Care Excellence (NICE). TA569: Pertuzumab for adjuvant treatment of HER2-positive early breast cancer [ID1192]. Committee Papers 2018. Available from: https://www.nice.org.uk/guidance/ta569/evidence/appraisal-consultation-1-committee-papers-pdf-6720470173 [Accessed 01 May 2022];
33. National Institute for Health and Care Excellence (NICE). TA612: Neratinib for extended adjuvant treatment of hormone receptor-positive, HER2-positive early stage breast cancer after adjuvant trastuzumab 2019. Available from: https://www.nice.org.uk/guidance/ta612. [Accessed 01 May 2022];
34. National Institute for Health and Care Excellence (NICE). TA632: Trastuzumab emtansine for adjuvant treatment of HER2-positive early breast cancer. 2020. Available from: https://www.nice.org.uk/guidance/ta632 [Accessed 01 May 2022];
35. McKenzie HS, Maishman T, Simmonds P, Durcan L, Eccles D, Copson E. Survival and disease characteristics of de novo versus recurrent metastatic breast cancer in a cohort of young patients. Br J Cancer. 2020;122(11):1618-29.
36. Breast Cancer Now. Facts and statistics 2021. Available from: https://breastcancernow.org/about-us/media/facts-statistics. [Accessed 01 May 2022];
37. Copson E, Eccles B, Maishman T, Gerty S, Stanton L, Cutress RI, et al. Prospective Observational Study of Breast Cancer Treatment Outcomes for UK Women Aged 18–40 Years at Diagnosis: The POSH Study. J Natl Cancer Inst 2013;105(13):978-88.
38. Copson ER, Maishman TC, Tapper WJ, Cutress RI, Greville-Heygate S, Altman DG, et al. Germline *BRCA* mutation and outcome in young-onset breast cancer (POSH): a prospective cohort study. Lancet Oncol. 2018;19(2):169-80.

39. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet. 2005;365(9472):1687-717.
40. Pan H, Gray R, Braybrooke J, Davies C, Taylor C, McGale P, et al. 20-Year Risks of Breast-Cancer Recurrence after Stopping Endocrine Therapy at 5 Years. NEJM. 2017;377(19):1836-46.
41. Mai PL, Chatterjee N, Hartge P, Tucker M, Brody L, Struewing JP, et al. Potential excess mortality in BRCA1/2 mutation carriers beyond breast, ovarian, prostate, and pancreatic cancers, and melanoma. PLoS One. 2009;4(3):e4812-e.
42. Levi F, Randimbison L, Te VC, La Vecchia C. Long-term mortality of women with a diagnosis of breast cancer. Oncology. 2002;63(3):266-9.
43. AstraZeneca Data on File. Early breast cancer clinical interviews March 2022 (Data on File Number: GB-35540). 2022.
44. Reddy SM, Barcenas CH, Sinha AK, Hsu L, Moulder SL, Tripathy D, et al. Long-term survival outcomes of triple-receptor negative breast cancer survivors who are disease free at 5 years and relationship with low hormone receptor positivity. Br J Cancer. 2018;118(1):17-23.
45. Clèries R, Buxó M, Vilardell M, Ameijide A, Martínez JM, Font R, et al. No Excess Mortality up to 10 Years in Early Stages of Breast Cancer in Women Adherent to Oral Endocrine Therapy: A Probabilistic Graphical Modeling Approach. Int J Environ Res. 2022;19(6):3605.
46. Louwman WJ, Klokman WJ, Coebergh JW. Excess mortality from breast cancer 20 years after diagnosis when life expectancy is normal. Br J Cancer. 2001;84(5):700-3.
47. McCrea C, Hettle R, Gulati P, Taneja A, Rajora P. Indirect treatment comparison of olaparib and talazoparib in germline BRCA-mutated HER2-negative metastatic breast cancer. J Comp Eff Res. 2021;10(13):1021-30.
48. Gennari A, André F, Barrios CH, Cortés J, de Azambuja E, DeMichele A, et al. ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. Ann Oncol. 2021;32(12):1475-95.
49. Robson ME, Tung N, Conte P, Im SA, Senkus E, Xu B, et al. OlympiAD final overall survival and tolerability results: Olaparib versus chemotherapy treatment of physician's choice in patients with a germline BRCA mutation and HER2-negative metastatic breast cancer. Ann Oncol. 2019;30(4):558-66.
50. Robson ME, Ruddy KJ, Im S-A, Senkus E, Xu B, Domchek SM, et al. Patient-reported outcomes in patients with a germline BRCA mutation and HER2-negative metastatic breast cancer receiving olaparib versus chemotherapy in the OlympiAD trial. Eur J Cancer. 2019;120:20-30.
51. Dakin H, Abel L. Health Economics Research Centre (HERC) database of mapping studies, Version 8.0. 2020. [Accessed;
52. Crott R, Briggs A. Mapping the QLQ-C30 quality of life cancer questionnaire to EQ-5D patient preferences. Eur J Health Econ. 2010;11(4):427-34.
53. Longworth L, Yang Y, Young T, Mulhern B, Hernández Alava M, Mukuria C, et al. Use of generic and condition-specific measures of health-related quality of life in NICE decision-making: a systematic review, statistical modelling and survey. Health Technol Assess. 2014;18(9):1-224.

54. Crott R, Versteegh M, Uyl-de-Groot C. An assessment of the external validity of mapping QLQ-C30 to EQ-5D preferences. Qual Life Res. 2013;22(5):1045-54.
55. Crott R. Direct Mapping of the QLQ-C30 to EQ-5D Preferences: A Comparison of Regression Methods. PharmacoEconomics - Open. 2018;2(2):165-77.
56. Young TA, Mukuria C, Rowen D, Brazier JE, Longworth L. Mapping Functions in Health-Related Quality of Life: Mapping from Two Cancer-Specific Health-Related Quality-of-Life Instruments to EQ-5D-3L. Med Decis Making. 2015;35(7):912-26.
57. Lidgren M, Wilking N, Jönsson B, Rehnberg C. Health related quality of life in different states of breast cancer. Qual Life Res. 2007;16(6):1073-81.
58. Verrill M, Wardley AM, Retzler J, Smith AB, Bottomley C, S ND, et al. Health-related quality of life and work productivity in UK patients with HER2-positive breast cancer: a cross-sectional study evaluating the relationships between disease and treatment stage. Health Qual Life Outcomes. 2020;18(1):353.
59. National Institute for Health and Care Excellence (NICE). TA563: Abemaciclib with an aromatase inhibitor for untreated advanced hormone receptor positive, HER2-negative breast cancer [ID1227]. Committee Papers 2018. Available from: https://www.nice.org.uk/guidance/ta563/documents/committee-papers-2. [Accessed 01 May 2022];
60. Nafees B, Stafford M, Gavriel S, Bhalla S, Watkins J. Health state utilities for non small cell lung cancer. Health Qual Life Outcomes. 2008;6:84.
61. Morice P-M, Leary A, Dolladille C, Chrétien B, Poulain L, González-Martín A, et al. Myelodysplastic syndrome and acute myeloid leukaemia in patients treated with PARP inhibitors: a safety meta-analysis of randomised controlled trials and a retrospective study of the WHO pharmacovigilance database. Lancet Haematol. 2021;8(2):e122-e34.
62. Madley-Dowd P, Hughes R, Tilling K, Heron J. The proportion of missing data should not be used to guide decisions on multiple imputation. J Clin Epidemiol. 2019;110:63-73.
63. Bruce J, Mazuquin B, Mistry P, Rees S, Canaway A, Hossain A, et al. Exercise to prevent shoulder problems after breast cancer surgery: the PROSPER RCT. 2022;26:15.
64. Manchanda R, Sun L, Patel S, Evans O, Wilschut J, De Freitas Lopes AC, et al. Economic Evaluation of Population-Based BRCA1/BRCA2 Mutation Testing across Multiple Countries and Health Systems. Cancers (Basel). 2020;12(7).
65. NHS. The NHS Long Term Plan 2019. Available from: https://www.longtermplan.nhs.uk/. [Accessed 01 May 2022];
66. NHS. Improving Outcomes Through Personalised Medicine. Available at: https://www.england.nhs.uk/wp-content/uploads/2016/09/improving-outcomes-personalised-medicine.pdf (accessed 06/03/2022). 2016.
67. UK Government. Genome UK: The Future of Healthcare 2020. Available from: https://www.gov.uk/government/publications/genome-uk-the-future-of-healthcare [Accessed 01 May 2022];
68. Sun L, Cromwell D, Dodwell D, Horgan K, Gannon MR, Medina J, et al. Costs of Early Invasive Breast Cancer in England Using National Patient-Level Data. Value in Health. 2020;23(10):1316-23.
69. Velikova G, Absolom K, Hewison J, Holch P, Warrington L, Avery K, et al. Programme Grants for Applied Research. Electronic self-reporting of adverse events for patients

undergoing cancer treatment: the eRAPID research programme including two RCTs. Southampton (UK): NIHR Journals Library; 2022.
70. Earl H, Hiller L, Vallier AL, Loi S, McAdam K, Hughes-Davies L, et al. Six versus 12 months' adjuvant trastuzumab in patients with HER2-positive early breast cancer: the PERSEPHONE non-inferiority RCT. Health Technol Assess. 2020;24(40):1-190.
71. Stein RC, Dunn JA, Bartlett JM, Campbell AF, Marshall A, Hall P, et al. OPTIMA prelim: a randomised feasibility study of personalised care in the treatment of women with early breast cancer. Health Technol Assess. 2016;20(10):xxiii-xxix, 1-201.
72. Hall PS, Hamilton P, Hulme CT, Meads DM, Jones H, Newsham A, et al. Costs of cancer care for use in economic evaluation: a UK analysis of patient-level routine health system data. Br J Cancer. 2015;112(5):948-56.
73. Luta X, Diernberger K, Bowden J, Droney J, Howdon D, Schmidlin K, et al. Healthcare trajectories and costs in the last year of life: a retrospective primary care and hospital analysis. BMJ Support Palliat Care. 2020:bmjspcare-2020-002630.
74. Whiting P, Savović J, Higgins JPT, Caldwell DM, Reeves BC, Shea B, et al. ROBIS: A new tool to assess risk of bias in systematic reviews was developed. J Clin Epidemiol. 2016;69:225-34.

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.

Response to factual accuracy check and confidential information check

Olaparib for adjuvant treatment of high-risk HER2-negative, BRCA-positive early breast cancer after chemotherapy [ID3893]

Factual Errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Definition of high-risk disease			
Page 27: Note that "The OlympiA trial used an expert consensus process consisting of two rounds of interviews with UK clinicians to determine whether the definition of "high risk" used in the trial could be applied to the UK population. This is detailed in section B.1.3.1.5 of the CS.(1)"	Propose to update to: "AstraZeneca has 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."	**Factual error:** The EAG phrasing suggests that the validation interviews formed part of the OlympiA trial. However, these were a separate validation exercise conducted specifically to establish generalisability of the OlympiA population to the UK for the purpose of UK HTA appraisals. Furthermore, the EAG phrasing also conflates two separate workstreams (the clinical validation interviews to establish generalisability of OlympiA data to UK practice, [redacted]	The EAG are happy with the amendment and have changed this in the report.
Health related quality of life			

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 60: Note that "After recurrence, completing quality of life measurements at the OlympiA trial was no longer mandatory."	Propose to update to: "Quality of life questionnaires were completed at baseline (prior to randomisation) and every 6 months for a period of 2 years. When these questionnaires were analysed according to recurrence status, it was noted that in the post-recurrence state more patients in the control arm…."	**Factual error:** the existing statement insinuates that quality of life questionnaires were mandatory until patients experienced recurrence. However, this was actually time-based, with data collected routinely for 2 years, irrespective of recurrence events.	The company submission doc B, section B.3.4.1. of page 58 describes how data *"(…) were only routinely collected every 6 months up to recurrence or for a maximum of 2 years"*, to justify using health utilities for recurrence health-states from external sources. The EAG have changed the report to reflect the words used by the company in their submission: Page 59 and 63: "Quality of life measurements for the OlympiA trial were collected routinely every

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
			6 months up to recurrence or for a maximum of 2 years, (…)."
Typos/minor factual inaccuracies			
Page 12: Note that "… parametric model for survival following early non-metastatic recurrence…"	Propose to update to: "… parametric model for survival following early metastatic recurrence…"	**Typo:** one of the key differences between the company's preferred assumptions and the EAG's preferred assumptions is the choice of the parametric model for survival following early *metastatic* recurrence (TP6), not *non-metastatic* recurrence (TP4 & TP5).	Thank you for spotting this typo. We have changed to the suggested wording.
Page 16: Note that "… mapping EORTC QLQ-C30 scores onto EQ-5D utilities for the DF states…"	Propose to update to: "… mapping EORTC QLQ-C30 scores onto EQ-5D utilities for the DF state…"	**Typo:** there is only one DF health state.	Thank you for spotting this typo. We have changed to the suggested wording.
Pages 17-18: Note that "… using Crott & Briggs (2010) for	Propose to update to: "… using Crott & Briggs (2010) for the DF and non-metastatic health states	**Minor factual inaccuracy:** in the company base case the mapped OlympiA utility value for the DF health state using the	Thank you for this correction. We have changed to the

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
progression free plus Lidgren (2007) for metastatic" in Tables 2 and 3.	and Lidgren (2007) for the metastatic health states."	Crott & Briggs (2010) mapping algorithm was also used for the non-metastatic health state.	suggested wording in Tables 2 and 3.
Pages 17-18: Note that "Utility values in non-metastatic recurrence set to mid-point of progression-free and metastatic recurrence (company base case assumed them the same)."	Propose to update to: "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)."	**Lack of clarity:** it is unclear in the current sentence whether in the company base case the HSUV for the non-metastatic state is set equal to the HSUV for the DF or metastatic health states.	Thank you for this suggestion. We have changed to the suggested wording in Tables 2 and 3.
Page 19: Note that "… all but two of the treatments listed (carboplatin and abemaciclib) are listed in the British National Formula (BNF) and include breast cancer among the treatment indications."	Propose to update to: "…all are listed in the BNF, and all but one treatment (carboplatin) includes breast cancer amongst the BNF-listed treatment indication."	**Factual inaccuracy:** both treatments are listed in the BNF: • bnf.nice.org.uk/drugs/carboplatin • bnf.nice.org.uk/drugs/abemaciclib Abemaciclib does list "locally advanced or metastatic breast cancer" as an indication.	The EAG are happy with the amendment and have changed this in the report.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 47 & 53 Note that "Levi 2001"	Propose to update to: "Levi et al. (2002)"	**Typo:** the publication year of the Levi et al. study is 2002, not 2001 (see the reference below): *Levi F, Randimbison L, Te VC, La Vecchia C. Long-term mortality of women with a diagnosis of breast cancer. Oncology. 2002;63(3):266-9. doi:10.1159/000065475*	Agree and have used the suggested wording. We also changed this on page 72.
Page 50: Note that "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. 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."	Remove one of the two sentences.	**Typo:** sentence duplication.	Thanks for spotting this typo. We have removed the duplicate sentence.

Misleading Statements

Description of problem	Description of proposed amendment	Justification for amendment	EAG RESPONSE
DCO1 timing			
Page 34: Note that "The EAG queried this with the manufacturer but there was no clear explanation for why the analysis was conducted at this time point rather than the specified time point."	Propose to remove this statement and instead acknowledge the response which we provided to question A2 in clarification questions.	We provided a comprehensive explanation for the timing of DCO1 as part of our response to clarification questions (question A2). In this response we explained that the timing of the interim analysis was protocolled to occur based on a number of events in the "mature cohort", but that the analysis itself would be performed on both the "mature cohort" as well as "all patients". This detail from the statistical analysis plan fully explains the perceived discrepancy in event numbers which the EAG highlight in their report.	The EAG apologise for misinterpreting the response to the clarification questions. Having revisited this issue we appreciate that the response did explain the reasoning behind the time point at which the interim analysis took place. We have edited the report a follows: 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 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

Description of problem	Description of proposed amendment	Justification for amendment	EAG RESPONSE
			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." We have deleted other text raising this as a potential issue.
Health-related quality of life			

Description of problem	Description of proposed amendment	Justification for amendment	EAG RESPONSE
Page 16: Note that "In the absence of estimates from a suitable mapping algorithm, the EAG suggests applying utility scores from the literature, derived from responses to the EQ-5D questionnaires in good quality studies in a similar patient group at the different health states of the model." **Page 84:** Note that "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."	For the sentence on page 16, we propose to rephrase to: "In the absence of QoL estimates from the OlympiA trial using a more suitable mapping algorithm such as the one from Gray et al. (2014), the EAG suggests applying utility scores from external literature, derived from responses to the EQ-5D questionnaires in good quality studies in a relatively similar patient group at the different health states of the model." For the sentence on page 84, propose to rephrase to: "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, or alternatively the mapped EQ-5D utilities	**Misleading statement:** the current sentences insinuate that there is no other suitable mapping algorithm available that could replace Crott & Briggs (2010) and as such, the EAG have *only* suggested applying utility scores from Verrill et al. (2020). However, it is in our understanding based on Section 4.2.7 of the report that the EAG would consider applying the mapped OlympiA QoL data for the DF health state if the Gray et al. (2014) mapping algorithm is used instead of the algorithm from Crott & Briggs (2010).	The EAG believes that Crott & Briggs (2010) is not a suitable algorithm to produce unbiased mapped estimates. There are more recent alternative algorithms, for example, but not exclusively Gray (2021) and more from Longworth's team (Meunier 2022), which attempt to overcome the issues of OLS-based algorithms and would warrant further exploration. It is possible that these newer algorithms will also be proven unsuitable in future validations studies. Furthermore, none of these newer algorithms are developed for the specific cancer type being evaluated. Estimates from these newer algorithms could be explored in further sensitivity analyses. The EAG feels there is too much uncertainty about which algorithm would be the most appropriate for mapping OlympiA trial patients

Description of problem	Description of proposed amendment	Justification for amendment	EAG RESPONSE
	from the OlympiA data (DCO2) using the Gray et al. (2021) algorithm."		HRQoL scores to EQ-5D utilities. In the absence of a fully externally validated unbiased algorithm available, the EAG believes that estimates from Verril 2020, reporting EQ-5D utilities, would best reflect the true HRQoL state of this patient group. The EAG would therefore amend the report to reflect this additional explanation Page 16 "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 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

Description of problem	Description of proposed amendment	Justification for amendment	EAG RESPONSE
			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." Page 87: "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"
Page 16: Note that "It is expected that direct EQ-5D data from OlympiA would more closely	We kindly ask the EAG to clarify what is meant by this sentence: does it mean that if direct EQ-5D data from OlympiA would be used the	**Lack of clarity**	Yes, the company have understood correctly. We agree that the sentence is confusing and not informative and therefore have

Description of problem	Description of proposed amendment	Justification for amendment	EAG RESPONSE
align with the EAG's preferred base case…"	HSUVs would more closely align with the EAG's preferred base case using the Verrill et al. (2020) utility values?		decided to remove this from the report on page 16.
Page 16: Note that "… with sensitivity analysis around other algorithms…"	We kindly ask the EAG to clarify which 'other' algorithms are being referenced in this sentence; are the ones by Crott & Briggs (2010) and Longworth et al. (2014) still considered?	**Lack of clarity**	We agree that the EAG was not very clear on this point. We have therefore reworded to state: "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, 6)" Given the uncertainty around external validation of the newer algorithms, the EAG believes it is still not appropriate to consider any mapping algorithm as the preferred base-case at this stage.

Description of problem	Description of proposed amendment	Justification for amendment	EAG RESPONSE
Page 39: Note that "A limitation with the HRQoL data is that completion of these questionnaires was poor." **And Page 15:** Note that "The missing data was caused by low completion rates of HRQoL questionnaires"	Propose to update to: "As with many clinical trials, a limitation of the HRQoL data is the drop-off in questionnaire response rate over time."	**Misleading statement:** the existing phrasing is excessively negative. The HRQoL response rate in OlympiA was in line with that expected in clinical trials in this setting, with response rates [redacted] at baseline, dropping [redacted] at 24 months. A recent 2021 study of PRO completion rates in clinical trials after discontinuation of the study drug showed that the mean response rate in the breast cancer setting was ~71% (range ~50-100%),[1] indicating that the OlympiA trial is [redacted]	We respectfully disagree with this suggestion. The fact that other HRQoL studies also have this limitation does not reduce the importance of the OlympiA HRQoL data missingness.
Page 58: Note that "They provide the lowest utility values that the company considered in sensitivity analysis" and "… Lidgren's estimates, although	We kindly ask the EAG to specify whether these two statements specifically refer to the HSUV for the DF health state? For example, the HSUV for the metastatic state (0.685) from Lidgren et al. (2007) is not the lowest utility	**Lack of clarity**	Thank you for highlighting this issue. We have clarified that we were referring to utilities for the DF and non-metatastic recurrence states, with the latter set equal to DF in all scenarios. We have also now noted that the Lidgren scenario gives the least difference

Description of problem	Description of proposed amendment	Justification for amendment	EAG RESPONSE
the lowest considered by the company…"	value that the company considers in sensitivity analysis for this health state.		between these states and the metastatic recurrence states.
Page 58: Note that "…Lidgren's estimates, although the lowest considered by the company, are still overvalued."	We kindly ask the EAG to clarify whether they are making the argument that the 0.779 HSUV for the DF state from Lidgren et al. (2007) is also considered too low for this patient population?	**Unclear and misleading statement:** no rationale or justification given as to why the DF HSUV from Lidgren et al. (2007) is 'overvalued'.	We agree that the term is incorrect, the EAG will reword it to "overestimated" for some of the health-states where Lidgren 2007 set negative EQ-5D values to zero, inflating the mean utility estimate for the patients in i) "First year after primary BC" (used by the company to inform DF) and iii) "Second and following years after primary BC/recurrence" (used by the company to inform non-metastatic recurrence). We therefore further clarify that this overestimation occurs in the health states of DF and "They provide the lowest utility values for the DF and non-metastatic recurrence states that

Description of problem	Description of proposed amendment	Justification for amendment	EAG RESPONSE
			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 estimates for these health states, may therefore be overestimated."
Page 59: Note that "… 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."	We kindly ask the EAG to provide additional rationale and justification to support the choice of applying an 0.703 utility value for the DF health state from Verrill et al. (2020).	**Unclear and misleading statement:** the 0.703 DF HSUV from Verrill et al. (2020) is significantly lower than similar DF utility values from recent empirical literature on patient reported HRQoL in eBC such as Kaur et al. (2022) (~0.9) and Criscitiello et al. (2021) (~0.872), as well as DF HSUVs (~0.8) accepted in previous eBC appraisals (TA725, TA632, TA612 & TA569). Furthermore, in previous NICE appraisals for	The EAG has made an error extracting the Verrill et al (2020) utility estimates. The correct value to be applied to the DF state is 0.732 (as per supplementary table 5). The EAG has re-estimated all their base-case and sensitivity-analysis results to reflect the correct value for the DF state and the non-mBC utility which is the midpoint between the DF and mBC utility values. The ICERs for both

		metastatic breast cancer, including TA495 (palbociclib for untreated metastatic HR+/HER2- BC) and TA639 (atezolizumab PD L1-positive, advanced TNBC), a utility value of ~0.7 was accepted for the progression free health state. Using a 0.703 DF HSUV in an eBC setting thus seems excessively conservative and lacks validation.	cancer types are accordingly lowered by approximately £3,000. The EAG carefully considered multiple sources for utility estimates, weighting their various pros and cons. Kaur's new systematic review (Jul 2022) reports estimates derived using a multitude of utility estimation methods, including direct methods, and indirect methods of standard gamble and visual analogue scales which are not recommended by NICE. The one study with a large sample size (>1,000 patients) for breast cancer specific utilities using indirect valuations of the EQ-5D, "consistently found the early breast cancer health states to be between 0.58 and 0.81". These valuations were also on HER+ breast cancer Dutch patients and unclear whether UK preference-based tariffs were used. In Figure 5 of Kaur 2022, the mean utility value for disease free

			BC, using a multitude of valuations (most of them not recommended in the NICE reference case) is also between 0.7 and 0.8. Criscitiello 2021 includes 1,083 completed EQ-5Ds but has a number of methodological limitations. The greatest limitation is that it includes patients from a multitude of countries, where EQ-5D questionnaire responses were valued using their own country-specific valuations. Only 63 of 1,083 patients included in the analyses were based in the UK and had their responses valued using UK preference-based tariffs. These valuations are therefore dominated by non-UK valuations and not compliant with the NICE reference case. Previous valuations for metastatic breast cancer concern a different patient group and a different problem and therefore not relevant for this evaluation.

			When mapping algorithms were ruled out as unbiased sources of utility estimates, the EAG considered the two next best external sources of utilities which used a UK preference value set were Lidgren (2007) and Verrill et al (2020). Verrill 2020 estimates were derived from the EQ-5D-5L questionnaire, with two additional levels of attributes compared to the 3L version, and is designed to pick up smaller differences in quality of life. The questionnaires were administered to 299 adult UK patients with ages 55-57, younger than the patients on most other BC alternative studies, and valued using UK preference based tariffs using Van Hout's crosswalk values, the NICE recommended valuation at the time for the 5L questionnaire. Limitations of Verrill 2020 include: a) the study population is HER+ and it is possible that utilities for the HER- population were lower than

			those estimated for the HER+. All other studies (such as Lidgren, or even the mapping algorithms developed) use a conjunction of HER+ and HER- breast cancer patients, where HER+ is the most prevalent type. b) it is an industry-sponsored study, and does not control raw utilities for patient characteristics (they were considered balanced). We do not believe these are likely to bias the results. In the absence of direct EQ-5D estimates from the OlympiA trial patients, the EAG feels that Verrill 2020 utility valuations are preferrable to Lidgren (2007) as they are from a UK population (Lindgren is from a Swedish population), use a more sensitive questionnaire (5L vs 3L of Lidgren), and being more recent study (2021 vs 2007) reflect a more up-to-date health state of the BC population.

Description of problem	Description of proposed amendment	Justification for amendment	EAG RESPONSE
Immaturity of the clinical effectiveness data			
Page 12: The first key issue in Table 1: "Clinical effectiveness data are immature" **Page 46:** Note that "However, NICE also specifies that there must be confidence about the gains, which is not true for olaparib given the immaturity of trial data." **Page 84:** Note that "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	We kindly ask the EAG to specify in the sentences on pages 12 and 46 *which* clinical effectiveness data from the OlympiA trial are immature, i.e., survival modelling for the HR+/HER2- subgroup analysis. For the sentence on page 84, we propose to rephrase to: "The immaturity of data (Key Issue 1) meant there is uncertainty regarding the long-term risk of recurrence in TNBC and the appropriate distribution for recurrence in HR+/HER2-."	**Misleading statements:** the current statements insinuate that *all* of the OlympiA clinical effectiveness data is immature, which is not the case, e.g., as highlighted on page 54 certain clinical data (survival following early metastatic recurrence) from OlympiA is already relatively mature.	This statement is correct as we consider all clinical effectiveness data to be immature as explained on page 37 section 3.2.6.1

Description of problem	Description of proposed amendment	Justification for amendment	EAG RESPONSE
for survival following early metastatic recurrence."			
Page 14: In the table on Issue 1 it is noted that that "… there is the risk of very rare but serious adverse events that were not picked up in the trial patients (small sample and short follow-up) …" **Page 15:** Note that "An increased risk of additional serious adverse events may impact the ICER further through a change in QALYs …" **Page 84:** Note that "There is also a risk that very rare but serious adverse events (e.g., leukaemia) would not have been detected during the	Propose to remove positioning the risk of very rare but serious adverse events as a key issue throughout the report.	**Misleading statements:** on page 60 the EAG agrees with the company that "… the inclusion of potential very rare but serious adverse events such as leukaemia is unlikely to impact on the ICER." We would therefore argue it is not necessary to repeatedly highlight this as a key issue/risk throughout the report.	We remain concerned about the minimal inclusion of adverse events in the model, given the low sample sizes for estimating rates of such rare events, if not necessarily the duration of follow-up. However, we agree that adverse events should not be included in the key issue of the immaturity of data due the minimal likely impact on the ICER. We have removed text related to adverse events from this section.

Description of problem	Description of proposed amendment	Justification for amendment	EAG RESPONSE
OlympiA trial, due to small sample and short follow-up."			
BRCA testing			
Page 23: Note that "Testing for *BRCA* mutations is not routinely performed in the NHS."	Propose to update to: "Testing for BRCA mutations is not yet routinely available on the NHS for all patients potentially eligible for olaparib in this setting."	**Misleading statement**: the current phrasing insinuates that *BRCA* testing is not routinely available for any eBC patients. However, based on current testing eligibility criteria from the National Genomic Test Directory (NGTD), the majority of the target population for olaparib in the OlympiA indication would already be eligible, particularly considering that patients with *BRCA* mutations are generally diagnosed younger than the wider eBC population.	The EAG are happy with the amendment and have changed this in the report.
Treatment effectiveness and extrapolation			
Page 47:	Propose to rephrase to:	**Misleading statement:** the current sentence could be interpreted that that the treatment benefit is	Agree and have used the suggested wording.

Description of problem	Description of proposed amendment	Justification for amendment	EAG RESPONSE
Note that "The lognormal model assumes the treatment benefit is maintained in the long-run."	"The lognormal model assumes the treatment benefit is maintained over a longer period of time."	maintained across the entire model time horizon with the lognormal model. This is not the case.	
Page 47: Note that "Levi 2001 provides an alternative source for SMR…"	Propose to rephrase to: "Levi et al. (2002) provides an alternative although outdated and possibly unreliable source for SMR…"	**Misleading statement**: the current statement insinuates that the SMR from Levi et al. (2002) is an appropriate source to consider for scenario analyses, which is not the case. The study by Levi et al. (2002) is highly outdated and does not analyse a population remotely comparable to the OlympiA population of interest. The reported SMR is therefore not a reliable and accurate reference when validating the SMR used in the OlympiA economic analysis and is likely highly conservative given the improvements in BC treatments and management of cancer-related comorbidities today.	We agree with the company that Levi 2002 is a poor estimate of the SMR. However, we still have concerns about the SMR reported by Mai 2009 (See response below). To balance Levi 2002, we have included a new scenario analysis using the indicated SMR of 1.00 from Clèries 2022, which found no evidence of excess mortality in patients disease-free over time. We have also clarified our reasoning for including these scenarios (See response below).

Description of problem	Description of proposed amendment	Justification for amendment	EAG RESPONSE
Page 53: Note that "However, we include a new scenario analysis assuming an SMR of 2.00 as reported by Levi 2001."	Considering that the study by Levi et al. (2002) is highly outdated and does not analyse a population comparable to the OlympiA population of interest, we would kindly ask the EAG to not consider this SMR of 2.00 in a scenario analysis.	**Misleading statement:** rationale for choosing the SMR from Levi et al. (2002) is not given.	We have edited Section 4.2.6.3 to include the following text explaining our reservations about Mai 2009: "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." We have also added our rationale for the two scenario analyses: However, due to our concerns about the reliability of Mai 2009, we include new scenario analyses assuming an SMR of 1.00 as

Description of problem	Description of proposed amendment	Justification for amendment	EAG RESPONSE
			indicated by Clèries 2022 and 2.00 as reported by Levi et al. (2002).
Other			
Page 83: Note that "The EAG has concerns about the data and assumptions underlying both models, as described in the Key Issues noted in Section 1.4."	Propose to use slightly softer language: "The EAG has some concerns about the data and assumptions underlying both models, as described in the Key issues noted in Section 1.4."	**Slightly misleading statement:** the current sentence insinuates that the EAG has major concerns across most of the data and assumptions underlying both models, even though this does not appear to be the case.	Our apologies as we did not intend the insinuation. We have "concerns" that are neither "minor" nor "major". We have left the wording as it is.

Further clarification

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Health-related quality of life and utilities			
Page 15: Conclusion that "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."	No specific amendments suggested, but AstraZeneca would like to provide additional clarification to support preparations for technical engagement.	AstraZeneca question the EAGs suggestion to use multiple imputation methods. In its standard form, this method assumes that the data are missing at random (whereas we understand that the EAG consider it to be non-random). Whilst multiple imputation methods can be modified to handle data that are missing not at random, these methods typically require assumptions and are complex to handle. We therefore feel that such methods would introduce additional uncertainties and may not meaningfully inform decision-making.	Whilst we acknowledge the limitations of multiple imputation methods, especially when data are not missing at random, with the levels of missing data we consider that some form of sensitivity analysis to investigate the impact of missing data would be of interest. Some understanding as to the effect of this missingness on the ICER would be helpful to inform the Committee of its potential impact. An alternative approach could be to use a threshold anlaysis that assumes different plausible HRQoL

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
			values for the missing data and demonstrates their impact on the ICER. We have edited the text to add this alternative option.
BRCA testing			
Page 16: Conclusion that "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" and **Page 27:** Note that "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."	As above.	AstraZeneca acknowledge the uncertainty relating to the timelines relating to *BRCA* testing for availability of *BRCA* testing in the HR+/HER2- group. To provide additional clarity and reassurance on the fact that we anticipate that this will be available in time for the launch of olaparib in the OlympiA indication later this year, we have provided the EAG with a copy of the NGTD desirables list below. This document can be sourced via a direct request to Genomics England.	The EAG acknowledge the NGTD desirables list provided by the Company and have amended the text accordingly. Revised text: Page 27: 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

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
			included BRCA1/2 testing for breast cancer patients.
Page 22: Note that "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."	As above	Although AstraZeneca acknowledge the rationale for this conclusion, we would like to reiterate that we anticipate that *BRCA* testing will be routinely reimbursed in the HR+/HER2- group in time for launch (as above). Furthermore, we would like to reiterate that expansion of *BRCA* testing is not solely related to establishing eligibility for olaparib and provides additional benefits for the patient and their family as outlined in section B.1.3.1 of the CS, such as tailoring of surgical approach for the patient, and informing	The company make a valid point that BRCA testing is not only needed for Olaparib and could allow tailoring of surgical approach for the patient and informing prophylactic management for the affected relative. However, this is additional value of BRCA testing and not a justification for its exclusion in Olaparib prescribing. The company are free to argue the additional value of introducing BRCA testing but as it's not currently routine, it has to be

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		prophylactic management for affected relatives. Therefore, AstraZeneca do not feel that it is appropriate to include these costings in the base case economic analysis.	included in the cost of Olaparib as it can't be prescribed without the testing. We have recognised this argument in Section 4.2.8.1.1 with the text: "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. "
Safety profile			

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 14: Conclusion that "there is the risk of very rare but serious adverse events that were not picked up in the trial patients (small sample and short follow-up) but could still occur when this treatment is provided more widely on the NHS (e.g., an increased risk of leukaemia was observed in other cancer types where olaparib has been used) (3)."	As above.	Although AstraZeneca acknowledge the EAG's concern, we would like to reiterate that given that such events would inherently be very rare, their impact on the economic analysis would be expected to be minor, and not sufficient to meaningfully impact decision making. We also note that the EAG also reached this conclusion on page 60 of the report. Furthermore, in a recent study of patients treated with PARP inhibitors across several tumour types, it was noted that the median latency period of myelodysplastic syndrome and acute myeloid leukaemia from first exposure to a PARP inhibitor was 17·8 months (IQR 8·4–29·2)[(2)], indicating that the majority of such events would actually have been identified by the time of OlympiA DCO2, at	See above. We have removed the key issue around AEs in recognition of the company's query.

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
		which point median follow up was around [redacted]	
Page 25/26: Conclusions that "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	As above.	On page 60 of the report the EAG acknowledge that the incidence of other grade ≥3 AEs, or cases of leukaemia are so low that they would be unlikely to significantly impact the ICER. AstraZeneca therefore considers that this issue should have no meaningful impact on decision-making.	We acknowledge that this is unlikely to have had a major impact on the ICER and for that reason have not highlighted this as a key issue.

Confidentiality highlighting

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
Page 14: Company preferred and EAG preferred base-case deterministic and probabilistic ICERs	No need to highlight CIC.	As long as no cost or QALY/LY incrementals are given for either the deterministic or probabilistic ICERs, the confidential PAS price for olaparib cannot be back calculated. These ICERs therefore do not need to be highlighted CIC.	Thank you for the clarification. We have removed the highlighting.
Page 16: CIC highlighting of "… approximately £10,000/QALY…"	No need to highlight CIC	See above.	We have removed the highlighting.
Page 16: Deterministic and probabilistic ICERs for the HR+/HER2- subgroup analysis including the cost of *BRCA* testing	No need to highlight CIC	See above.	We have removed the highlighting.
Pages 17-18: Deterministic ICERs in Tables 2 and 3	No need to highlight CIC	See above.	We have removed the highlighting.

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
Pages 64-66: Deterministic and probabilistic ICERs and the increase/decrease in ICER based on the tornado diagrams in Figures 9 and 10	No need to highlight CIC	See above.	We have removed the highlighting.
Pages 68-70: Deterministic ICERs for each scenario analysis in Table 21	No need to highlight CIC	See above.	We have removed the highlighting.
Pages 73-75: Changes from the base-case ICERs and scenario analysis ICERs as presented in Table 22	No need to highlight CIC	See above.	We have removed the highlighting.
Pages 76-83: Deterministic and probabilistic ICERs	No need to highlight CIC	See above.	We have removed the highlighting.
Page 84: Deterministic and probabilistic ICERs and changes from the	No need to highlight CIC	See above.	We have removed the highlighting.

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
base-case ICER for different scenario analyses			
Page 38: Table 10	All results in table 10 should be marked AIC	These results relate to DCO2 data which is not yet in the public domain.	This has been corrected.
Page 75: Mapped OlympiA HSUVs	No need to highlight CIC.	The mapped OlympiA HSUVs are not commercially or academically confidential.	We have removed the highlighting.

References:

1. Kaur MN, Yan J, Klassen AF, David JP, Pieris D, Sharma M, Bordeleau L, Xie F. A Systematic Literature Review of Health Utility Values in Breast Cancer. Med Decis Making. 2022 Jul;42(5):704-719. doi: 10.1177/0272989X211065471. Epub 2022 Jan 18. PMID: 35042379; PMCID: PMC9189726.

2. King-Kallimanis BL et al. Patient-Reported Outcomes After Treatment Discontinuation: Commercial Clinical Trial Data From Four Cancer Types. Value in Health. Volume 24, Issue 9, September 2021, Pages 1302-1307. https://www.sciencedirect.com/science/article/pii/S109830152101528X#appsec1

3. Meunier A, Soare A, Chevrou-Severac H, Myren KJ, Murata T, Longworth L. Indirect and Direct Mapping of the Cancer-Specific EORTC QLQ-C30 onto EQ-5D-5L Utility Scores. Appl Health Econ Health Policy. 2022 Jan;20(1):119-131. doi: 10.1007/s40258-021-00682-0. Epub 2021 Sep 23. PMID: 34554442.

4. Morice PM et al. Myelodysplastic syndrome and acute myeloid leukaemia in patients treated with PARP inhibitors: a safety meta-analysis of randomised controlled trials and a retrospective study of the WHO pharmacovigilance database. Lancet Haematol. 2021 Feb;8(2):e122-e134. doi: 10.1016/S2352-3026(20)30360-4. Epub 2020 Dec 18. Erratum in: Lancet Haematol. 2021 Feb;8(2):e105. PMID: 33347814.

NICE National Institute for Health and Care Excellence

Technical engagement response form

Olaparib for adjuvant treatment of high-risk HER2-negative, BRCA-positive early breast cancer after chemotherapy [ID3893]

As a stakeholder you have been invited to comment on the external assessment group (EAG) report for this appraisal.

Your comments and feedback on the key issues below are really valued. The EAG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAG report that are likely to be discussed by the committee. The key issues in the EAG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAG report.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAG report that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Deadline for comments by **5pm** on **Tuesday 23 August 2022.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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

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

Technical engagement response form

Olaparib for adjuvant treatment of high-risk HER2-negative, BRCA-positive early breast cancer after chemotherapy [ID3893]

1 About you

Table 1: About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	AstraZeneca UK – stakeholder
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**Nothing to disclose**

2 Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAG report.

Table 2: Key issues

Key Issue	Does this response contain new evidence, data or analyses?	Response
Issue 1: Immaturity of trial data	No	Although it is acknowledged that the clinical data from OlympiA are somewhat immature, this is an inherent challenge when studying adjuvant treatments for use in early stages of disease, often when there is no known residual disease after surgery. This limitation has been acknowledged and accepted in prior appraisals (e.g., TA810,[1] where the lack of statistically significant OS benefit was acknowledged to relate to the treatment setting). In such early-stage trials, it can take decades to reach the median for certain time-to-event efficacy outcomes, particularly OS. Generally, such clinical trials do not continue follow-up indefinitely, given the associated costs, and the burden which this would impose on participating patients, so median values may never be reached. Despite olaparib being an adjuvant therapy in an early disease setting, and unlike many other trials in the eBC setting (including the MonarchE trial which informed TA810)[1], **the OlympiA trial has already demonstrated a statistically significant OS benefit; this is a remarkable result in this setting**. At DCO2 of the OlympiA trial, the ITT iDFS data were 18.6% mature (341 events/1,836 patients).[2] This is higher than the maturity of the iDFS data which were used to inform TA810 (at the AFU1 analysis, iDFS data were 10.0% mature (565 events/5,637 patients).[1] Given these considerations, the OlympiA data should be considered sufficiently mature to inform decision-making, particularly in the TNBC subgroup. We acknowledge the EAG's concern regarding the higher uncertainty in the HR+/HER2- subgroup, given the smaller number of patients recruited, as well as the shorter follow-up in

		this group. This resulted in fewer iDFS events in the HR+/HER2- group and meant that the use of ITT data as a proxy for the HR+/HER2- subgroup in the economic model was the most appropriate approach. Although we have validated the related assumptions with clinical experts to minimise uncertainty as much as possible, we agree with the EAG assessment that a degree of unresolvable uncertainty remains. Longer follow-up from the OlympiA trial is anticipated to resolve this uncertainty in the coming years, with DCO3 expected [redacted]. AstraZeneca suggest that the HR+/HER2- subgroup could be [redacted] to resolve this specific uncertainty.
Issue 2: Potential risk of bias in estimates of HRQoL	Yes	Although we acknowledge the EAG's concern of potential bias in the OlympiA trial HRQoL estimates and the uncertainty regarding the choice of mapping algorithm that is applied, we firmly believe that the OlympiA trial provides the set of utility values that are most relevant to the current decision problem. We believe that the key issue that should ultimately be addressed is which **HRQoL data source most appropriately reflects the utility** experienced by patients in the OlympiA indication, specifically those who are and remain progression-free. For this reason, we have structured and combined our response to Key Issues 2 and 3 as follows: 1. Demonstrating the relevance and appropriateness of the OlympiA HRQoL data 2. A critique of the EAG's preferred HSUVs from Verrill et al. (2020) 3. A discussion of the face validity of the EAG's preferred HSUVs and ultimately what value best reflects the HRQoL of patients who are progression-free in this eBC indication **<u>1. Relevance and appropriateness of the OlympiA HRQoL data</u>** The EAG's main concern around the OlympiA HRQoL data is that potentially non-random missing data resulting from low completion rates of the HRQoL questionnaires could have

		impacted, and thereby biased, the trial's HRQoL estimates. Although we do not contend that there is missing data, we would like to point out that: • A certain level of missing data in HRQoL questionnaires is present in all clinical trials and **does not directly infer that the data itself is biased**. As presented in our response to the factual accuracy check, the HRQoL response rate in OlympiA was in line with that expected in clinical trials in this setting, with response rates of [redacted] at baseline, dropping to only [redacted] at 24 months[3] (please refer to Appendix A [Table A1] for an overview of the OlympiA HRQoL questionnaire response rates over time). • More importantly, as demonstrated in Appendix A (Table A2), the EORTC QLQ-C30 scores in OlympiA remain [redacted]. If the majority of missing observations were not random and attrition bias was therefore present, there would be an expectation that the average utility score would increase over time as the remaining sample would consist of healthier patients. Therefore, even if there was some level of attrition bias as a result of more severe patients not completing the questionnaires, evidence suggests that the **magnitude of this potential bias on the HRQoL estimates is negligible**. In addition to the concern around biased HRQoL estimates, the EAG also argue that it is not appropriate to consider any algorithm to map the OlympiA EORTC QLQ-C30 data to HSUVs, stating that none of the available algorithms are unbiased and fully externally validated. However, by making this conclusion and thus recommending an external study (Verrill et al., 2020)[4] as the main HRQoL reference for the economic model, the EAG discards the most robust and applicable source of HSU data for the patient population relevant to this appraisal. Although the SLR described in Section B.3.4.3 of Document B identified 5 studies which reported on HSUVs in eBC (including Verrill et al., 2020)[4], none of the studies are representative of the specific population considered within the current decision problem, as all studies lacked information on *BRCA* mutation or risk of recurrence status. The **OlympiA trial therefore represents the most robust and applicable source of HRQoL data for**

		patients with g*BRCA*m, high-risk eBC. Furthermore, the HRQoL data collected in OlympiA can be considered more robust than the HSU evidence from Verrill et al. (2020) for several reasons (further critique given under Point 2, below): • The OlympiA trial includes a large pool of patients, with the PRO analysis set comprising n=1,751 patients (out of 1,836 patients in total).[3] A total of [redacted] questionnaires ([redacted] in the olaparib and placebo arms, respectively) were completed over the first 2 years of follow-up.[5] This is a significantly larger and more relevant cohort than in the study by Verrill et al. (2020), which only recruited 108 patients in Group 2 (patients with HER2+ eBC who had completed treatment and were in remission).[4] • One of the key strengths of the OlympiA trial is that it captures the HRQoL of patients across multiple time points (completed at baseline before randomisation and every six months for a period of two years),[3] whereas the report by Verrill et al. (2020) is based on a cross-sectional study.[4] As such, it does not allow for an assessment and consideration of the temporal relationship between disease/treatment stage and impact on HRQoL, which is something that the HRQoL data from OlympiA does reflect. Furthermore, we have provided additional sensitivity analyses to address the EAG's critique of potential bias in the mapping algorithms through the application of different algorithms, including those from Longworth et al. (2014),[6] Crott and Briggs (2010)[7] and Gray et al. (2021);[8] the latter having been newly submitted as part of this response (Appendix C [Table C1]). We have also provided an additional UK analysis of the OlympiA EORTC QLU-C10D (see UK value set here) which, although not aligned with NICE's preferred measure of HRQoL, presents another set of sensitivity analysis around the mapping algorithms. As demonstrated in Table 2-1, the mapped utility scores for the PF health state from the three different algorithms and the EORTC QLU-C10D analysis fall significantly and meaningfully above (+~0.07) the utility scores from Verrill et al. (2020). These results also

show that the **choice of algorithm is not a key driver of the mapped utility estimates from OlympiA** as there is a reasonable amount of consistency between the different values.

Table 2-1: Summary of the company and EAG's HSUVs for the PF state

Source	HSUV (PF state)
Crott & Briggs (2010) mapping algorithm[7]	0.869
Gray et al. (2021) mapping algorithm[8]	0.815
OlympiA EORTC QLU-C10D analysis	[redacted]
Longworth et al. (2014) mapping algorithm[6]	0.802
Verrill et al. (2020)[4]	0.732

Abbreviations: DCO: data cut-off; EORTC: European Organisation for Research and Treatment of Cancer; HSUV: health state utility value; PF: progression-free.

2. A critique of the EAG's preferred HSUVs from Verrill et al. (2020)

We appreciate that the EAG has provided additional rationale and justification for choosing the HSUVs from Verrill et al. (2020) in their base-case economic analysis as part of their response to the factual accuracy check. However, we would like to stress that the **respective HSUV of 0.732 for the PF state lacks face validity** and the study is subject to significant limitations. We further elaborate on the face validity argument under Point 3 (below), but first would like to make the following comments about the study by Verrill et al. (2020):

- The study by Verrill et al. (2020) is **not representative of a younger *BRCA* population** due to its older mean age of 57.7 years in Group 2 (vs. 43.3 years in OlympiA).[3, 4] Feedback from KEEs has indicated that the demographics of the patient population in OlympiA better align with the patient group clinicians anticipate would receive olaparib in clinical practice. Caution should therefore be taken when interpreting the health utilities from Verrill et al. (2020).
- A second important critique of Verrill et al. (2020) is that the study was cross-sectional with patients recruited based on their physician's referral. Specifically, almost half of

		the patients in Group 2 (48.1%) were unemployed and their questionnaires were collected on average ~4 years after their initial diagnosis, which **indicates a potential selection bias**. Patients with a 'normal' HRQoL are likely to have returned to work at this point if they remain progression-free, have an improved quality of life, and are therefore unlikely to have completed the questionnaire in the study. The measured health utility of 0.732 from Verrill et al. (2020) for Group 2 is therefore likely to be negatively biased, and thus not applicable and relevant to the general demographics of the OlympiA patient population. Overall, the bias inherent in the HRQoL scoring from Verrill et al. (2020) cannot be easily elucidated or explored within the economic model. The differing age, selection bias from recruitment and the lack of g*BRCA*m and TNBC patients in the study are likely to impart **bias in the utility results and limit its generalisability to OlympiA patients.** **3. Discussion of the appropriate HSUVs to use in the economic model** As discussed in the Technical Engagement call, we believe that the discussion should not primarily centre around the potential bias of the HRQoL data from OlympiA or the appropriateness of the mapping algorithms, but ultimately **which HSUVs best reflect the HRQoL of UK patients with g*BRCA*m, high-risk eBC**. Importantly, we believe that assigning a **utility value of 0.732** to a young patient group who have early-stage, treatable BC and are in remission **lacks face validity** for several reasons: • First, the UK general population utility for women aged 43.3 years (mean age in OlympiA) is 0.877. Considering that patients in the PF state are in remission, with a significant proportion of patients expected to achieve long-term remission, these patients are not expected to experience any significant continuing BC-related symptoms or AEs from treatment, especially given the strong safety profile of olaparib. Therefore, there is **no clear rationale as to why the utility value assigned to these patients should be significantly lower than the values of the age-matched UK general population**.

		• This argument can be further supported by comparing the different mapped OlympiA PF HSUVs and the HSUV from Verrill et al. (2020) with utility values from previous NICE appraisals in the early and metastatic BC settings and relevant empirical literature, as presented in Table 2-2. It is clear from this overview that **there is no precedent of either accepting or concluding such a low utility value** for eBC patients who are in (long-term) remission. Specifically, in all previous NICE appraisals in eBC, including two appraisals (TA632 and TA424)[9, 10] which covered a 'high-risk' patient population (with the latter also focusing on locally advanced disease), values significantly above Verrill et al. (2020) were continuously accepted as the appropriate HSUV for the DF health state. • Furthermore, although we acknowledge that the patient groups and decision problem of the two mBC NICE appraisals differ slightly from those currently under consideration, we disagree with the EAG that these do not provide a relevant reference for this appraisal. Instead, considering that patients with newly diagnosed mBC are shown to have a utility value of ~0.73, it is **highly unrealistic to assume that such a utility value would also apply to patients with early-stage disease**, specifically those individuals who remain progression-free for a long period of time. • This finding was also confirmed during interviews with UK clinical oncologists, who unanimously commented that the HRQoL of eBC patients will become similar to the age-matched general population over time. It is therefore highly reasonable to assume that the **'true' HSUV for (long-term) disease-free patients with high-risk, g*BRCA*m early disease ranges between 0.8–0.877**.

Table 2-2: An overview of different sources and appraisals on utility values for patients with eBC who are disease-free

Health state	Utility values	Source	Population specifics
General population *Never had BC*	0.877	Ara & Brazier (2010)[11]	Mean value, UK population norms for women aged 43.3 years
iDFS in eBC *Patient treated for eBC and currently disease-free*	0.872	Criscitiello et al (2021)[12]	HR+/HER2- eBC, either receiving adjuvant treatment or under post-adjuvant surveillance, UK cohort
	0.802–0.869	OlympiA	Based on 3 different mapping algorithms
	0.837	NICE TA612 (November 2019): Neratinib (ExteNET)[13]	Extended adjuvant treatment of HR+/HER2+ eBC after adjuvant trastuzumab-based treatment <1 year ago
	0.822[a]	NICE TA569 (March 2019): Pertuzumab + IV trastuzumab +ChT (APHINITY)[14]	Adjuvant treatment of HER2+ eBC with lymph node-positive disease
	0.788[a]	NICE TA632 (June 2020): Trastuzumab emtansine (KATHERINE)[9]	Adjuvant treatment of HER2+ eBC with residual invasive disease after neoadjuvant treatment

			0.779[b]	NICE TA424 (December 2016): Pertuzumab + IV trastuzumab +ChT (NeoSphere, TRYPHAENA)[10]	Neoadjuvant treatment of HER2+ locally advanced, inflammatory or eBC at high risk of recurrence
			0.779	Lidgren et al (2007)[15]	Patients with BC, in the second and following years after primary BC/recurrence, Swedish study
			0.732	Verrill et al (2020)[4]	HER2+ eBC patients who completed treatment and were in remission, UK study
		PFS in mBC *Patient treated for mBC and currently progression-free*	0.72–0.77	NICE TA495 (December 2017): Palbociclib + aromatase inhibitor (PALOMA-1 & 2)[16]	HR+/HER2- locally advanced or metastatic BC as initial endocrine-based treatment
			0.726	NICE TA639 (July 2020): Atezolizumab with nab-paclitaxel (IMpassion130)[17]	Unresectable, locally advanced or metastatic TNBC with PD-L1 ≥1% and no prior ChT for mBC

Footnotes: [a]In some cases, slightly different utility values were used for patients on and off treatment – in these cases, the off-treatment values are presented here to represent the long-term; [b]This appraisal uses different values for the first year and beyond the first year. The value presented here is for beyond the first year.
Abbreviations: BC: breast cancer; ChT; chemotherapy; DCO: data cut-off; eBC: early breast cancer; HER2: human epidermal growth factor 2; HR: hormone receptor; iDFS: invasive disease-free survival; IV: intravenous; mBC: metastatic breast cancer; NICE: National Institute for Health and Care Excellence; PFS: progression-free survival; TA: technology appraisal; TNBC: triple negative breast cancer; UK: United Kingdom.

Therefore, we firmly believe that the **utility values applied in the company's base-case analysis represent a set of estimates that better reflect the HRQoL** of patients for the specific indication addressed in this appraisal. However, we also accept that there is uncertainty regarding the most appropriate choice of mapping algorithm to utilise, and that the approach adopted in the company's base-case analysis resulted in the highest possible utility value for the DF state. Therefore, to mitigate against this uncertainty, we have selected the HSUV for the DF state from the Gray et al. (2021) mapping algorithm[8] (0.815) in an additional scenario analysis, which represents a significant reduction in the utility value that is applied in this health state. It should however be noted that this utility estimate is likely still highly conservative considering the feedback from KEEs that the HRQoL of eBC patients who remain disease-free will eventually become similar to the age-matched general population over time. Furthermore, KEEs also commented that TNBC patients who are and remain DF are generally in better health than those with HR+/HER2- disease, simply because they do not receive long-term endocrine therapy which may impact their HRQoL. The DF HSUV for these patients should therefore realistically be higher as well. For this reason, we have provided another scenario analysis choosing a midpoint HSUV for the DF state of 0.842 ([0.869-0.815]/2) to reflect this feedback and to further support the committee's decision-making. The cost-effectiveness results from both scenario analyses are presented in Table 2-3.

Table 2-3: Additional DF HSUV scenario analysis results (discounted)

	HSUV DF state	ICER TNBC	ICER HR+/HER2-
Base-case (Crott & Briggs, 2010)	0.869	£35,855	£41,879
Scenario analysis 1 (Gray et al., 2021)	0.815	£38,324	£44,780
Scenario analysis 2 (midpoint approach)	0.842	£36,910	£43,127

		Footnotes: Please note that in both scenario analyses we have kept the HSUV for the metastatic states as 0.685 taken from Lidgren et al. (2007)[15] and the HSUV for the locoregional health state as the midpoint between the DF and metastatic HSUVs (0.75 and 0.7635 for scenario analysis 1 and 2 respectively). **Abbreviations:** DF: disease-free; HER2: human epidermal growth factor receptor 2; HR: hormone receptor; HSUV: health state utility value; ICER: incremental cost-effectiveness ratio; TNBC: triple negative breast cancer.
Issue 3: HRQoL measures used in the economic model	Yes	Please see our response to Key Issue 2 above.
Issue 4: Access to *BCRA* testing in HR+/HER2 population	Yes	**Overarching comment on *BRCA* testing:** The EAG highlight that *BRCA* testing is currently limited to only a proportion of the HR+/HER2- population, based on the current testing eligibility criteria laid out in the National Genomic Test Directory (NGTD). However, we contend that the vast majority of HR+/HER2- patients who are potentially eligible for olaparib in this indication, would already be identified if current testing criteria were uniformly implemented in clinical practice, particularly given the expansion of these criteria which occurred in April 2022. This is because the OlympiA trial exclusively recruited patients at high risk of recurrence, and many of the prognostic factors associated with an increased risk of recurrence overlap with those associated with an increased risk of testing positive for a *BRCA* mutation. To illustrate this point, an analysis of current NGTD *BRCA* testing criteria, compared to the demographic data of the HR+/HER2- subgroup in the OlympiA trial is provided in Table 2-4. **Table 2-4: Comparison of NGTD *BRCA* testing criteria with OlympiA HR+/HER2- subgroup**

NGTD criteria[18]	Relevant demographic data from the HR+/HER2- subgroup of the OlympiA trial[19]
Breast cancer (age <40 years, excluding grade 1 breast cancers)	Median age was [redacted] years, and [redacted] of patients were under the age of 40.

		Bilateral breast cancer (age <50 years)	[redacted] of patients who received neoadjuvant chemotherapy had bilateral disease, as well as [redacted] of those who received adjuvant chemotherapy.
		Male breast cancer (any age)	[redacted] of patients were male.
		Breast cancer (age <45 years) and a first degree relative with breast cancer (age <45 years)	Although family history was not analysed specifically in the HR+/HER2- subgroup, this was reported in the full analysis set. A high proportion of patients had a 1st degree relative with breast cancer diagnosed under the age of 50 ([redacted] and [redacted] had an affected female relative in the olaparib and placebo arms, respectively).
		Pathology-adjusted Manchester score ≥15 or CanRisk score ≥10%	This is unknown as Manchester score and CanRisk score were not specifically recorded. However, these scales are strongly influenced by factors such as family history, and tumour pathology (e.g., grade 3 disease in the Manchester score).[20, 21] • Grade: [redacted] of patients who received neoadjuvant chemotherapy, and [redacted] of those who received adjuvant chemotherapy had histological grade 3 disease. • Family history: a significant proportion of patients have a positive family history of either breast and / or ovarian cancer (see Appendix B, Table B4 for details).
		Ashkenazi Jewish ancestry and breast cancer at any age	[redacted] of patients had Ashkenazi Jewish ancestry.

Footnotes: Full demographic data are presented in Appendix B.
Abbreviations: BRCA: breast cancer susceptibility gene; HER2: human epidermal growth factor 2; HR: hormone receptor; NGTD: National Genomic Test Directory.

		Therefore, if the existing NGTD criteria were uniformly implemented in clinical practice, a substantial majority of the relevant HR+/HER2- patients would already be identified. However, AstraZeneca understand that in current clinical practice many such patients may not be tested despite meeting the NGTD eligibility criteria, as clinicians feel that there is limited clinical value in knowing the *BRCA* status of such patients when there are currently no targeted treatments available. However, it is anticipated that testing rates would increase after the launch of olaparib in this indication, as we anticipate a move towards a test-to-treat mindset in the clinical community. Furthermore, broader genetic testing is expected in the coming years given the evolving NHS policy landscape and wider NHS objectives, including a move towards improved outcomes through personalised medicine,[22, 23] and an ambition to be the world's most advanced genomic healthcare ecosystem via the Genome UK strategy.[24] Section 4.4.15 of the NICE methods guide states that consideration should be given for situations where there is an established plan to change practice or service delivery in the NHS, and where introducing the new technology will lead to identifiable benefits that are not captured in health technology evaluations.[25] Both such considerations apply to *BRCA* testing, particularly considering the wider familial benefits of identifying *BRCA* mutations, and the potential to optimise surgical approach for affected patients, which are not captured in our economic evaluation. **Response to EAG proposed model updates:** Given the above, and reiterating the fact that *BRCA* testing provides additional benefits to a patient beyond just determining eligibility for *BRCA* targeted therapy (e.g., impacting choice of surgical approach, as well as informing familial testing and risk-reducing strategies), AstraZeneca maintain that it is inappropriate to include the cost of *BRCA* testing in the base case for the HR+/HER2- subgroup. As such, testing costs are included in scenario analyses only.

3 Additional issues

All: Please use the table below to respond to additional issues in the EAG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (for example, at the clarification stage).

Table 3: Additional issues from the EAG report

Issue from the EAG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: The EAG's suggestion to use an alternative distribution for recurrence in the HR+/HER2- subgroup analysis	Sections 1.4 (The Clinical and Cost-Effectiveness Evidence: Summary of the EAG's Key Issues) and 4.2.6 (Treatment Effectiveness and Extrapolation)	No	In Section 4.2.6 of the EAG report, the suggestion is made to apply the generalised gamma instead of the lognormal distribution to extrapolate DFS for patients in the HR+/HER2- analysis; this is on the basis that the generalised gamma indirectly incorporates a conservative waning of the treatment effect at 5.4 years (vs 14.5 years with the lognormal function). However, we would like to argue that: 1. Although we acknowledge that both distributions have very similar AIC/BIC and long-term extrapolations, the lognormal was consistently selected as the preferred parametric model by UK KEEs considering it generates slightly more pessimistic 10- and 20-year iDFS estimates ([redacted] and [redacted]) vs the generalised gamma ([redacted] and [redacted]), which was argued to better reflect the continuing long-term risk of recurrence and thus survival outcomes of patients with HR+/HER2- disease.

2. Furthermore, there is no precedent from other eBC NICE appraisals (TA632, TA612, TA810)[1, 9, 13] or historical trial data in eBC to assume a treatment waning effect of <7.5 years. For example, the 10-year follow-up data from the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial in HR+ eBC patients showed a continuing level of treatment effect beyond 8 years.[26] Although we acknowledge the differing mechanism of action of endocrine therapy or the technologies in the appraisals above vs PARP inhibitors, the lasting treatment effect which has been observed and accepted in these appraisals indicates the existence of a lasting treatment effect in eBC that is not derived from one specific mechanism of action and is independent of the specific treatment received.

For these reasons, we disagree with the EAG's suggestion to select the generalised gamma distribution for the iDFS extrapolations; however, to address the inherent uncertainty about long-term treatment effects, we have provided two additional scenario analyses with the base-case lognormal distribution, applying a treatment waning effect at 7.5 and 10 years (Table 3-1).

Table 3-1: Treatment waning scenario analysis results (discounted, HR+/HER2- analysis)

Scenario	ICER HR+/HER2-
Base-case analysis: TP1/2 distribution: lognormal	£41,879

			<table><tr><td>TP1/2 distribution: lognormal with a 7.5 years waning of the treatment effect of olaparib</td><td>£42,211</td></tr><tr><td>TP1/2 distribution: lognormal with a 10 years waning of the treatment effect of olaparib</td><td>£43,075</td></tr></table> **Abbreviations:** HR: hormone receptor; HER2: human epidermal growth factor receptor 2; ICER: incremental cost-effectiveness ratio; TP: transition probability.
Additional issue 2: Innovation	Section 7 – Severity and Innovation.	No	The EAG report states that the company is "not making a case for severity or innovation". Although we have not requested formal consideration within our cost-effectiveness model relating to severity or innovation, we would nonetheless consider olaparib to be innovative in the eBC setting, considering both a broader clinical definition of innovation, as well as the narrow definition of innovation referred to in Section 2.2.24 of the NICE process and methods manual,[25] which focusses on the potential for health-related benefits which are unlikely to be captured in the economic model. Olaparib represents the first personalised treatment option for HR+/HER2- eBC patients with a *BRCA* mutation, targeting the underlying genetic driver of their disease to deliver a statistically significant and clinically meaningful OS benefit.[2] This is a remarkable outcome in this treatment setting. Furthermore, there are wider benefits of introducing olaparib in the eBC setting which are not captured in our

			economic model. Specifically, a move towards more personalised treatment of eBC patients, and a greater focus on the genetic drivers of disease may drive more consistent application of the NGTD *BRCA* testing criteria, and thus more frequent identification of such mutations. Family members of affected patients will benefit from early identification via cascade testing, potential risk-reducing interventions, and genetic counselling, all of which may ultimately reduce the incidence of breast, ovarian, and prostate cancers in affected families.
Additional issue 3: Considering the application of a 1.5% discount rate	Section 4.2.5 – Perspective, Time Horizon, and Discounting	No	The EAG conclude in their report that a discount rate of 3.5% is most appropriate for olaparib in the OlympiA indication, citing immaturity of the clinical trial results. We acknowledge that this conclusion may be true for the HR+/HER2- subgroup; however, we argue that the TNBC population clearly supports application of the lower 1.5% discount based on the criteria outlined in the Methods Guide. Therefore although we maintain the 3.5% value in our base-case, we defend the relevance of a scenario analysis using the 1.5% rate for the TNBC population, as presented in Table 3-2. In the NICE process and methods manual (Section 4.5),[25] non-reference-case discounting at a 1.5% rate may be considered by the committee if all three of the following criteria are met: • Criteria 1: The technology is for people who would otherwise die or have a very severely impaired life.

			• Criteria 2: It is likely to restore them to full or near-full health. • Criteria 3: The benefits are likely to be sustained over a very long period. Criteria 1 is true for a significant proportion of the high-risk g*BRCA*m TNBC patients in the OlympiA trial who, without olaparib therapy, would experience a distant recurrence and progress to metastatic disease. The 5-year survival rate of women with mBC in England (at diagnosis) is only 26.2%.[27] Criteria 2 is also true for such patients; patients who do not experience a recurrence would be expected to eventually regain a similar functional status and HRQoL as they had before their breast cancer diagnosis. This is particularly true when considering the long-term picture for such patients, once they have fully recovered from surgery, completed all endocrine therapy, and mentally recovered from the shock and anxiety associated with a breast cancer diagnosis. Criteria 3 is also true for many patients. Clinical experts have stated that the risk of recurrence progressively falls as patients remain disease-free for longer, and that this effect is particularly pronounced in TNBC patients.[28, 29] Therefore avoiding recurrence in the years immediately following treatment of their primary breast cancer is expected to result in long-term cure for some patients.

Finally, we would like to highlight that during the NICE methods review process, it was concluded that the evidence suggests there is a case to change the reference-case discount rate to 1.5%, but that this was not implemented. Given this conclusion, we feel that it is appropriate to consider the 1.5% discount rate as a non-reference case analysis for this appraisal for the TNBC subgroup; the results of such an analysis are presented in Table 3-2.

Table 3-2: Discount rate scenario analysis

Scenario	ICER TNBC
Base-case: discount rate 3.5%	£35,855
Scenario analysis: discount rate 1.5%	£25,287

Abbreviations: HER2: human epidermal growth factor receptor 2; HR: hormone receptor; ICER: incremental cost-effectiveness ratio; TNBC: triple negative breast cancer.

4 Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4: Changes to the company's cost-effectiveness estimate

Key issue(s) in the EAG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
N/A – no changes made to base case	N/A – no changes made to base case	N/A – no changes made to base case	N/A – no changes made to base case

Sensitivity analyses around revised base case

N/A – no changes made to base case

5 References

1. NICE. TA810: Abemaciclib with endocrine therapy for adjuvant treatment of hormone receptor-positive, HER2-negative, node-positive early breast cancer at high risk of recurrence. 2022. Available from: https://www.nice.org.uk/guidance/ta810 (accessed 16/08/2022).
2. AstraZeneca Data on File. OlympiA Efficacy Analysis (DCO2). 2022.
3. AstraZeneca Data on File. OlympiA Clinical Study Report. 2021.
4. Verrill M, Wardley AM, Retzler J, et al. Health-related quality of life and work productivity in UK patients with HER2-positive breast cancer: a cross-sectional study evaluating the relationships between disease and treatment stage. Health Qual Life Outcomes 2020;18:353.
5. AstraZeneca Data on File. OlympiA PRO Analysis (DCO2). 2022.
6. Longworth L, Yang Y, Young T, et al. Use of generic and condition-specific measures of health-related quality of life in NICE decision-making: a systematic review, statistical modelling and survey. Health Technol Assess 2014;18:1-224.
7. Crott R, Briggs A. Mapping the QLQ-C30 quality of life cancer questionnaire to EQ-5D patient preferences. Eur J Health Econ 2010;11:427-34.
8. Gray LA, Hernandez Alava M, Wailoo AJ. Mapping the EORTC QLQ-C30 to EQ-5D-3L in patients with breast cancer. BMC cancer 2021;21:1-10.
9. NICE. TA632: Trastuzumab emtansine for adjuvant treatment of HER2-positive early breast cancer [ID1516]. Committee Papers. 2020. Available at: https://www.nice.org.uk/guidance/ta632/evidence/committee-papers-pdf-8771187997 (accessed 31/05/2022).
10. NICE. TA424: Pertuzumab for the neoadjuvant treatment of HER2-positive breast cancer [ID767]. Committee Papers. 2016. Available at: https://www.nice.org.uk/guidance/ta424/documents/committee-papers-2 (accessed 31/05/2022).
11. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. Value Health 2010;13:509-18.
12. Criscitiello C, Spurden D, Piercy J, et al. Health-Related Quality of Life Among Patients With HR+/HER2- Early Breast Cancer. Clin Ther 2021;43:1228-1244.e4.
13. NICE. TA612: Neratinib for extended adjuvant treatment of hormone receptor-positive, HER2-positive early stage breast cancer after adjuvant trastuzumab [ID981]. Committee Papers. 2019. Available at: https://www.nice.org.uk/guidance/ta612/evidence/appraisal-consultation-committee-papers-pdf-6967189694 (accessed 31/05/2022).
14. NICE. TA569: Pertuzumab for adjuvant treatment of HER2-positive early breast cancer [ID1192]. Committee Papers. 2018. Available at: https://www.nice.org.uk/guidance/ta569/evidence/appraisal-consultation-1-committee-papers-pdf-6720470173 (accessed 31/05/2022).
15. Lidgren M, Wilking N, Jönsson B, et al. Health related quality of life in different states of breast cancer. Quality of life research 2007;16:1073-1081.
16. NICE. TA495: Palbociclib with an aromatase inhibitor for previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer. 2017. Available at: https://www.nice.org.uk/guidance/ta495 (accessed 16/08/2022).

17. NICE. TA639: Atezolizumab with nab-paclitaxel for untreated PD-L1-positive, locally advanced or metastatic, triple-negative breast cancer. 2020. Available at: https://www.nice.org.uk/guidance/ta639 (accessed 09/02/2022).
18. NHS England. National Genomic Test Directory. Available at: https://www.england.nhs.uk/publication/national-genomic-test-directories/ (accessed 06/01/2022), 2021.
19. AstraZeneca Data on File. OlympiA Clinical Study Report (Supplementary Materials 1). 2021.
20. Evans DG, Harkness EF, Plaskocinska I, et al. Pathology update to the Manchester Scoring System based on testing in over 4000 families. Journal of Medical Genetics 2017;54:674-681.
21. CanRisk Knowledgebase. When calculating mutation carrier probabilities, which input data/parameters most strongly influence the resulting probabilities? Available at: https://canrisk.atlassian.net/wiki/spaces/FAQS/pages/1947729925/When+calculating+mutation+carrier+probabilities+which+input+data+parameters+most+strongly+influence+the+resulting+probabilities. Accessed: 16/08/2022. 2021.
22. NHS. The NHS Long Term Plan. 2019.
23. NHS. Improving Outcomes Through Personalised Medicine. Available at: https://www.england.nhs.uk/wp-content/uploads/2016/09/improving-outcomes-personalised-medicine.pdf (accessed 06/03/2022). 2016.
24. UK Government. Genome UK: The Future of Healthcare. Available at: https://www.gov.uk/government/publications/genome-uk-the-future-of-healthcare (accessed 12/01/2022). 2020.
25. NICE. PMG36. NICE health technology evaluations: the manual. 2022. Available at: https://www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technology-evaluation (accessed 12/04/2022).
26. Howell A, Cuzick J, Baum M, et al. Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. Lancet 2005;365:60-2.
27. Cancer Research UK. Breast cancer survival statistics. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer/survival (accessed 12/03/2022), 2021.
28. AstraZeneca Data on File. Early breast cancer clinical interviews March 2022 (Data on File Number: GB-35540). 2022.
29. AstraZeneca Data on File. Early breast cancer clinical interviews December 2021 (Data on File Number: GB-35535). 2022.

6 Appendices

Appendix A OlympiA HRQoL questionnaires longitudinal response rates

Tables A1 and A2 present an overview of the OlympiA HRQoL questionnaire response rates and OlympiA EORTC-QLC-C30 scores overtime, respectively.

Table A1: Status of HRQoL questionnaires received by treatment group and visit (PRO analysis set)

	Olaparib 300 mg bd (N=876)			Placebo (N=875)		
	Forms expected, n[a]	Forms received	Expected forms received, %	Forms expected, n[a]	Forms received, n	Expected forms received, %
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: DCO2: 12 July 2021. [a]Form is expected for all visits for all patients who complete baseline questionnaire and initiate study medication. Once patients experience a disease recurrence or a second primary cancer they are not expected to continue with the PRO assessments.
Abbreviations: bd: twice daily; DCO: data cut-off; HRQoL: health-related quality of life; PRO: patient-reported outcome.
Source: AstraZeneca Data on File (OlympiA DCO2: PRO Analyses).[5]

Table A2: Summary of EORTC QLQ-C30 scores in OlympiA (PRO analysis set; DCO2)

	Olaparib (N=876)			Placebo (N=875)		
	n	Mean (SD)	Median	n	Mean (SD)	Median
Patients with prior neoadjuvant treatment (olaparib: n=440; placebo: n=435)						
EORTC QLQ-C30 Global Health Status QoL						
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Olaparib (N=876)			Placebo (N=875)		
	n	Mean (SD)	Median	n	Mean (SD)	Median
Change from Baseline to 6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from Baseline to 12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from Baseline to 18 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from Baseline to 24 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EORTC QLQ-C30 Nausea and Vomiting Symptom Scale						
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from Baseline to 6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from Baseline to 12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from Baseline to 18 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from Baseline to 24 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EORTC QLQ-C30 Diarrhoea Symptom Scale						
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from Baseline to 6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from Baseline to 12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from Baseline to 18 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from Baseline to 24 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients with prior adjuvant treatment (olaparib: n=436; placebo: n=440)						
EORTC QLQ-C30 Global Health Status QoL						
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Olaparib (N=876)			Placebo (N=875)		
	n	Mean (SD)	Median	n	Mean (SD)	Median
Change from Baseline to 6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from Baseline to 12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from Baseline to 18 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from Baseline to 24 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EORTC QLQ-C30 Nausea and Vomiting Symptom Scale						
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from Baseline to 6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from Baseline to 12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from Baseline to 18 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from Baseline to 24 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EORTC QLQ-C30 Diarrhoea Symptom Scale						
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from Baseline to 6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from Baseline to 12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from Baseline to 18 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from Baseline to 24 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: DCO2: 12 July 2021. All EORTC QLQ-C30 scales range in score from 0 to 100. Higher score indicates better QoL/functioning or worse symptom severity.
Abbreviations: DCO: data cut-off; EORTC QLQ-30: European Organisation for Research and Treatment of Cancer quality of life questionnaire; PRO: patient reported outcome; SD: standard deviation; QoL: quality of life.
Source: AstraZeneca Data on File (OlympiA DCO2: PRO Analyses).[5]

Appendix B Demographic and baseline patient characteristics for the OlympiA HR+/HER2- subgroup

Tables B1, B2, B3 and B4 present demographic and baseline patient characteristics for the OlympiA HR+/HER2- subgroup (DCO1; 27 March 2020), and are limited to those characteristics which are considered relevant to the EAG Key Issue 4 relating to eligibility for BRCA testing.

Table B1: Demographic characteristics for HR+/HER2- patients (DCO1; full analysis set)

	Olaparib 300 mg bd (N=168)	Placebo (N=157)	Overall (N=325)
Age (years)[a]			
Mean	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Min	[redacted]	[redacted]	[redacted]
Max	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]
Age groups			
<30 years	[redacted]	[redacted]	[redacted]
30-39 years	[redacted]	[redacted]	[redacted]
40-49 years	[redacted]	[redacted]	[redacted]
50-59 years	[redacted]	[redacted]	[redacted]
60-69 years	[redacted]	[redacted]	[redacted]
≥70 years	[redacted]	[redacted]	[redacted]

Missing	[redacted]	[redacted]	[redacted]
Sex			
Female	[redacted]	[redacted]	[redacted]
Male	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]
Ashkenazi Jewish descent			
Ashkenazi Jewish	[redacted]	[redacted]	[redacted]
Not Ashkenazi Jewish[b]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]

Footnotes: DCO1: 27 March 2020. [a]Age is calculated as the patient's age at randomisation; [b]Not Ashkenazi Jewish can mean that the patient is either Jewish but not Ashkenazi Jewish, not Jewish or descent recorded as unknown.
Abbreviations: bd: twice daily; DCO: data cut-off; G: Grade; HER2: human epidermal growth factor 2; HR: hormone receptor; SD: standard deviation.
Source: AstraZeneca Data on File (OlympiA CSR [Supplementary Materials 1]).[19]

Table B2: Pathological characteristics of primary breast cancer at baseline for HR+/HER2- patients who received neoadjuvant chemotherapy (DCO1; full analysis set)

	Olaparib 300 mg bd (N=104)	Placebo (N=92)	Overall (N=196)
Bilateral invasive breast cancer			
No	[redacted]	[redacted]	[redacted]
Yes	[redacted]	[redacted]	[redacted]
Histological grade			
Gx: Cannot be assessed/not done	[redacted]	[redacted]	[redacted]
G1: Well differentiated	[redacted]	[redacted]	[redacted]

G2: Moderately differentiated	[redacted]	[redacted]	[redacted]
G3: Poorly differentiated/undifferentiated	[redacted]	[redacted]	[redacted]
Not done	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]
Nuclear grade			
Gx: Cannot be assessed/not done	[redacted]	[redacted]	[redacted]
G1: Well differentiated	[redacted]	[redacted]	[redacted]
G2: Moderately differentiated	[redacted]	[redacted]	[redacted]
G3: Poorly differentiated/undifferentiated	[redacted]	[redacted]	[redacted]
Not done	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]

Footnotes: DCO1: 27 March 2020.
Abbreviations: bd: twice daily; DCO: data cut-off; G: Grade; HER2: human epidermal growth factor 2; HR: hormone receptor.
Source: AstraZeneca Data on File (OlympiA CSR [Supplementary Materials 1]).[19]

Table B3: Pathological characteristics of primary breast cancer at baseline for HR+/HER2- patients who received adjuvant chemotherapy (DCO1; full analysis set)

	Olaparib 300 mg bd (N=64)	Placebo (N=65)	Overall (N=129)
Bilateral invasive breast cancer			
No	[redacted]	[redacted]	[redacted]
Yes	[redacted]	[redacted]	[redacted]
Histological grade			
Gx: Cannot be assessed/not done	[redacted]	[redacted]	[redacted]
G1: Well differentiated	[redacted]	[redacted]	[redacted]

G2: Moderately differentiated	[redacted]	[redacted]	[redacted]
G3: Poorly differentiated/undifferentiated	[redacted]	[redacted]	[redacted]
Not done	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]
Nuclear grade			
Gx: Cannot be assessed/not done	[redacted]	[redacted]	[redacted]
G1: Well differentiated	[redacted]	[redacted]	[redacted]
G2: Moderately differentiated	[redacted]	[redacted]	[redacted]
G3: Poorly differentiated/undifferentiated	[redacted]	[redacted]	[redacted]
Not done	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]

Footnotes: DCO1: 27 March 2020.
Abbreviations: Data cut-off; G: Grade; HER2: human epidermal growth factor 2; HR: hormone receptor.
Source: AstraZeneca Data on File (OlympiA CSR [Supplementary Materials 1]).[19]

Table B4: Family history of cancer (DCO1; full analysis set)[a]

Treatment Group	Sex of relative	Age group of relative	Breast		Ovarian		Other	
			1st degree relative	2nd degree relative	1st degree relative	2nd degree relative	1st degree relative	2nd degree relative
Olaparib 300 mg bd (N=921)	Male	≤50 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		>50 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Any	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Female	≤50 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		>50 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

		Any	[redacted]					
Placebo (N=915)	Male	≤50 years	[redacted]					
		>50 years	[redacted]					
		Any	[redacted]					
	Female	≤50 years	[redacted]					
		>50 years	[redacted]					
		Any	[redacted]					

Footnotes: DCO1: 27 March 2020. [a]A patient can have more than one relative in any age or indication category under a given degree of relatedness. However, the patient will only be counted once in each category. The denominator for the percentages is the number of patients in the full analysis set in each treatment group.
Abbreviations: bd: twice daily; DCO: data cut-off.
Source: AstraZeneca Data on File (OlympiA CSR [Supplementary Materials 1]).[19]

Appendix C OlympiA mapping analysis using the Gray et al. (2021) algorithm

Table C1 presents the summary statistics for the mapped HSU values using the Gray et al. (2021) algorithm by arm and study period based on the OlympiA DCO2 data.

Table C1: Summary statistics for the mapped HSU values using the Gray et al. (2021) algorithm by arm and study period (OlympiA DCO2 data)

Time period	Arm	n	Mean	SD	Median	Min	Max
All visits	Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	All	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline	Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	All	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-recurrence	Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	All	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-recurrence	Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	All	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: DCO: data cut-off; HSUV: health state utility; SD: standard deviation.

NICE National Institute for Health and Care Excellence

Clinical expert statement and technical engagement response form

Olaparib for adjuvant treatment of high-risk HER2-negative, BRCA-positive early breast cancer after chemotherapy [ID3893]

Thank you for agreeing to comment on the external assessment group (EAG) report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The EAG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the EAG report that are likely to be discussed by the committee. The key issues in the EAG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAG report (see section 1.4). You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR

- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

Clinical expert statement

Olaparib for adjuvant treatment of high-risk HER2-negative, BRCA-positive early breast cancer after chemotherapy [ID3893]

Deadline for comments by **5pm** on **Tuesday 23 August 2022.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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

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

NICE National Institute for Health and Care Excellence

Part 1: Treating HER2-, BRCA+ early breast cancer and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Andrew Tutt
2. Name of organisation	The Institute of Cancer Research and Kings Collge London
3. Job title or position	
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with early breast cancer? ☒ A specialist in the clinical evidence base for early breast cancer or this technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A

8. What is the main aim of treatment for HER2-, BRCA+ early breast cancer after surgery and neoadjuvant or adjuvant chemotherapy? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	To improve invasive disease free survival (IDFS) and overall survival (OS) in breast cancer. Please note this is group of patients in whom we expect 70-75% of patients to survive their breast cancer without invasive breast cancer recurrence with current standard of care treatment and therefore improve overall survival over longer follow up.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Improvement in Invasive disease free survival by >30% equating to an hazard ratio of 0.7.
10. In your view, is there an unmet need for patients and healthcare professionals in HER2-, BRCA+ early breast cancer after surgery and neoadjuvant or adjuvant chemotherapy?	Yes. Without doubt. The IDFS of approximately 75% at approximately 3 years after standard of care treatment for patients in this population is unacceptably lowf
11. How is HER2-, BRCA+ early breast cancer after surgery and neoadjuvant or adjuvant chemotherapy currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	Currently patients are treated differently dependent upon whether they have ER+ve HER2 -ve or ER-ve HER2 -ve breast cancer. Patients with ER+ve HER2 -ve breast cancer have adjuvant endocrine therapy with Tamoxifen +/- Zoladex or an aromatase inhibitor. The addition of the CDK4/6 inhibitor abemaciclib has been shown to improve disease free but not overall survival in this group. Post menopausal patients have an aromatase inhibitor but also have adjuvant bisphosphonates ER-ve HER2-ve breast cancer patients have no additional adjuvant systemic therapy other than adjuvant bisphosphonates if they are post-menopausal.

12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	Olaparib would be used in addition to these current therapies. Olaparib would be an additional oral medicine that would be used in the context of a specialist breast cancer oncology clinic. No particular additional facilities, equipment of training would be required
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Yes. The OlympiA trial has indicated that 32% more women with remain alive long term if they receive Olaparib for 12 months even only at 3-4 years follow compared to a double blind placebo control.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	There is no evidence that any subgroup of the OlympiA Trial eligible patients benefited more or less than the overall recruited population.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use?	No. This is an additional treatment but is oral and the gains in overall and invasive and distant disease free survival are achieved with modest side effects and importantly the OlympiA quality of life and Patient Related Outcome data

(For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	show no evidence the impairment to global QoL scores during or after treatment in follow up.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Yes. The patients will require basic monthly blood monitoring of FBC and serum biochemistry as is normal standard of care in any systemic anti-cancer treatment
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	The benefits are in improved overall survival by 32% ie all deaths and I metastatic an local recurrence or new cancers by approximately 40% with attendant improved length of high quality of life in women of high general health status many of whom develop cancer in their 30's and 40's by having years of life they would otherwise not have, without any evidence of detrimental impact on global quality of life.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	Yes this is innovative, entirely novel and improves the unmet need by improving both life threatening recurrence events and overall survival

19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	There are adverse effects but these are mild in comparison with many other agents that improve overall survival in a curative setting in cancer. A very detailed and academically lead quality of life study by an academic global expert in cancer intervention quality of life impacts (Dr Patricia Ganz of UCLA) has shown only transient and mild effects of quality of life during the 12 mth treatment period that improve rapidly when the treatment period is complete and have no detrimental impact on global quality of life scores.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Yes The most important outcomes are invasive disease free, distant disease free survival and overall survival. These were all measured in the OlympiA trial which was conducted, analysed an published independent of AstraZeneca and MSD. This is the single relevant trial that has been conducted in this highly defined patient population No adverse events have come to light subsequently
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. How do data on real-world experience compare with the trial data?	Not applicable

23. NICE considers whether there are any equalities issues at each stage of an appraisal. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this appraisal could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme.	This technology and condition are particularly relevant in young women with breast cancer <50 years of age and in the rare group of men who develop breast cancer who have a high frequency of germline mutations in BRCA1 and BRCA2

Find more general information about the Equality Act and equalities issues here.	

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the EAG report, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAG report. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Issue 1: immature trial data The median follow-up in the OlympiA trial is 3.5 years, however a limited number of events have occurred, with fewer than 50% of participants having experienced events for each of the effectiveness time-to-event outcomes. Due to this there is uncertainty regarding long term effectiveness and assumptions have been made:	This demonstates some lack of understanding by the EAG of the disease group in which the technology is licensed. Those with curable breast cancer are not expected to have events in >50% of the population except in exceptionally high risk of recurrence populations. Please note other technology appraisals for drugs like trastuzumab in HER2 +ve early breast cancer. For TNBC the risk of recurrence after 5 years are very low and approach 0%. I would however estimate 2-3% 5-8 years and 0% after this point.

<u>Triple negative breast cancer (TNBC) population</u> The company assumes a 0% risk of recurrence beyond 5 years The EAG prefers to use literature on non-zero long-term recurrence in TNBC and assumes a risk of recurrence after 5 years of 5% over the following 10 years. 1. which assumption is most plausible? <u>HR+/HER2- population</u> The company and EAG use different distributions to model recurrence (EAG generalised gamma; company lognormal). These have similar extrapolations up to 20 years, but the company's lognormal model assumes the treatment benefit is maintained over a longer period. Due to uncertainty in the long-term estimates, the EAG considers the generalised gamma distribution is the most plausible choice. 2. do the experts have a view on which is most clinically plausible? (see table 14 of EAG report). <u>Both populations</u>	I really don't think there are meaningful difference between the results of the company and EAG approach. Clinically the benefits are in overall survival are already very clear and achieved with very modest short term side effects. The level of benefit in overall survival will most likely further improve and there is no evidence they are weakening in the two analyses reported from the OlympiA trial.

The company and EAG use different distributions to model survival following early metastatic recurrence. The EAG argues that the exponential distribution used by the company is not appropriate when proportional hazards are violated and prefers the Gompertz distribution as this still gives a plausible difference in survival between arms in the long term.	
Issue 2: Risk of bias for health-related quality of life (HRQoL) data The EAG highlights that there are missing HRQoL data in the OlympiA trial, caused by low completion rates of questionnaires. This may have resulted in biased EORTC QLQ-C30 estimates which were then mapped to utility scores for the model. The EAG suggests additional analyses to explore the potential impact of missing data on estimates of HRQoL. The company argues that response rates are in line with those expected in clinical trials ([redacted] at baseline, dropping to [redacted] at 6 and 12 months, [redacted] at 18 months, and [redacted] at 24 months). 3. what are the experts' views on the quality and completeness of the EORTC QLQ-C30 HRQoL data?	A very detailed QoL / PRO study was designed and analysed independent of the funding Pharma AstraZeneca and MSD by Professor Patricia Ganz of UCLA. This has been presented at the international San Antonio Breast Cancer Symposium 2021. Professor Ganz is a world expert on early breast cancer QoL study design and analysis and her declared view is that the selection of QoL assessment tools is optimal and the response rates are very good and the data set is unusually complete in this study. https://ascopost.com/videos/2021-san-antonio-breast-cancer-symposium/patricia-ganz-on-early-breast-cancer-olaparib-chemotherapy-and-quality-of-life/

	A very detailed QoL / PRO study was designed and analysed independent of the funding Pharma AstraZeneca and MSD by Professor Patricia Ganz of UCLA. This has been presented at the international San Antonio Breast Cancer Symposium 2021. Professor Ganz is a world expert on early breast cancer QoL study design and analysis and her declared view is that the selection of QoL assessment tools is optimal and the response rates are very good and the data set is unusually complete in this study. I am not myself an expert on QoL / PRO sub-study design but the independent academic OlympiA QoL/PRO study PI Professor Patti Ganz is an international expert in this field. I would strongly recommend that NICE discuss any EAP key issues with regard QoL analysis with Professor Ganz before concluding that there is inappropriate use of QoL assessment tools or unusually high poor compliance with QoL data acquisition and risk of bias. This has not been raised in any of the review of the OlympiA QoL / PRO sub-study previously. https://ascopost.com/videos/2021-san-antonio-breast-cancer-symposium/patricia-ganz-on-early-breast-cancer-olaparib-chemotherapy-and-quality-of-life/

Issue 4: Access to BCRA testing in HR+/HER2- population 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. BCRA testing for all people with TNBC is expected in the near future, but testing is limited for people with HR+/HER2- cancer and it is unclear when testing will become routine. The EAG suggest adding the costs of BCRA testing to the HR+/HER2- model. 4. how widespread is BCRA testing in the TNBC and HR+/HER2- groups? 5. is BCRA testing likely to be used routinely in the HR+/HER2- population?	I fundamentally disagree with the EAG on this point. In my view it is inappropriate to add the costs of genetic testing in the NHS to this technology assessment. The fact that referral for genetic testing based despite established NHS guidance is underperformed in ER+ve breast cancer is a matter of the need for education of the medical community not a need to test purely and exclusively to meet a marketing authorisation that includes germline pathogenic or likely pathogenic mutation status. The indication for genetic counselling and testing is based on many factors including effects on broader family implications, the survival benefits of risk reducing surgery and eligibility for NHS MRI/mammographic screening programmes that have been independently assessed for NHS cost benefit analysis and approved for NHS funding in both TNBC and ER +ve breast cancer contexts. In my view the costs of genetic counselling and testing should not be added to the cost impacts of this technology assessment.
Are there any important issues that have been missed in EAG report?	Page 99 of the report has a significant error in concluding that the OlympiA study was “unblinded” with regard to treatment allocation to the patient and investigators at sites. The OlympiA trial remains blinded to patients and at sites with regard treatment allocation outside the circumstance of a site recording an IDFS event

	(the primary outcome measure) if the site require the information to appropriately treat the patient in the setting of recurrence. There appears to be a misinterpretation of the fact that it was only the independent study statisticians (independent of the trial sponsor) were unblinded to the patients treatment allocation after IDMC review of the pre-planned interim analysis and recommendation to the OlympiA steering committee so that primary analysis could be conducted as pre-planned stopping criteria had been reached. The risk of bias identified by the EAG is on these pages in erroneous as a result.

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

There is a significant unmet need in the identified patient group that is now readily identified by approved and NHS funded genetic testing policy

A academically controlled and designed double blind placebo controlled trial with appropriate survival primary and secondary endpoints and quality of life study has been conducted by the Breast International Group testing if Olaparib can achieve a target Hazard ratio of <0.7 for IDFS pre-specified and agreed with medicines regulators with secondary endpoints of distant disease free and overall survival with a pre-specified alpha conservation multiple testing plan defined by an independent statistical team and steering committee.

This study has met its primary and secondary endpoints and exceeds the statistical and clinical significance boundaries pre-specified by an independent academically led steering committee and is achieved with what that steering committee believes is modest side effect profile and ack of negative impact on quality of life for a therapy that improves distant disease free and overall survival by >30%.

Published international Early Breast Cancer Cancer Consensus Guideline Groups (NCCN, ASCO, St Gallen, ESMO) recommend use of Olaparib in the now licensed indication as an effective additional adjuvant therapy strategy to meet significant unmet clinical need.

The target population for this technology in this licensed indication are healthy women on average in their mid-forties without significant co-morbidities and high baseline quality of life and social and economic functioning where gains of overall survival are expected to mean main additional women years of high quality of life and wider societal and economic benefits.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Clinical expert statement and technical engagement response form

Olaparib for adjuvant treatment of high-risk HER2-negative, BRCA-positive early breast cancer after chemotherapy [ID3893]

Thank you for agreeing to comment on the external assessment group (EAG) report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The EAG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the EAG report that are likely to be discussed by the committee. The key issues in the EAG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAG report (see section 1.4). You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR

- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

Clinical expert statement

NICE National Institute for Health and Care Excellence

Deadline for comments by **5pm** on **Tuesday 23 August 2022.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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

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

NICE National Institute for Health and Care Excellence

Part 1: Treating HER2-, BRCA+ early breast cancer and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Stuart McIntosh
2. Name of organisation	National Cancer Research Institute
3. Job title or position	Breast Research Group Chair
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with early breast cancer? ☒ A specialist in the clinical evidence base for early breast cancer or this technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

8. What is the main aim of treatment for HER2-, BRCA+ early breast cancer after surgery and neoadjuvant or adjuvant chemotherapy? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	
10. In your view, is there an unmet need for patients and healthcare professionals in HER2-, BRCA+ early breast cancer after surgery and neoadjuvant or adjuvant chemotherapy?	
11. How is HER2-, BRCA+ early breast cancer after surgery and neoadjuvant or adjuvant chemotherapy currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	

• How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	

16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting?	

• What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	
22. How do data on real-world experience compare with the trial data?	
23. NICE considers whether there are any equalities issues at each stage of an appraisal. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this appraisal could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation	

• lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the EAG report, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAG report. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Issue 1: immature trial data The median follow-up in the OlympiA trial is 3.5 years, however a limited number of events have occurred, with fewer than 50% of participants having experienced events for each of the effectiveness time-to-event outcomes. Due to this there is uncertainty regarding long term effectiveness and assumptions have been made: <u>Triple negative breast cancer (TNBC) population</u>	There are several issues here. It is noted that within the OlympA trial, a limited number of events have occurred, with < 50% of participants having experienced events for each of the effectiveness time-to-event outcomes. However, it should be considered that early breast cancer (even high-risk early breast cancer, as in the OlympiA participants) has a relatively good prognosis, with around 60-70% 5 year survival overall (this is borne out by 77% IDFS figure seen in the control arm of OlympiA). Therefore, I would not expect to see, either in the control or experimental arms relapse rates approaching 50%.

Clinical expert statement

The company assumes a 0% risk of recurrence beyond 5 years The EAG prefers to use literature on non-zero long-term recurrence in TNBC and assumes a risk of recurrence after 5 years of 5% over the following 10 years. 1. which assumption is most plausible? <u>HR+/HER2- population</u> The company and EAG use different distributions to model recurrence (EAG generalised gamma; company lognormal). These have similar extrapolations up to 20 years, but the company's lognormal model assumes the treatment benefit is maintained over a longer period. Due to uncertainty in the long-term estimates, the EAG considers the generalised gamma distribution is the most plausible choice. 2. do the experts have a view on which is most clinically plausible? (see table 14 of EAG report). <u>Both populations</u> The company and EAG use different distributions to model survival following early metastatic recurrence. The EAG argues that the exponential distribution used by the company is	Recurrence in TNBC is generally an early event, with the majority occurring in the first 2-3 years following diagnosis. A population based Dutch study (van Rooznedall et al, Br Can Res Treat 2016) (2548 women) confirmed that the median time to any recurrence in TNBC was 1.7 years, with 75% of recurrences occurring within 3 years of diagnosis. This is consistent with other published data supporting the statement that almost all IDFS events occur within 5 years of diagnosis and therefore the assumption that the risk of recurrence approaches 0% after 5 years would seem the most plausible assumption to me (question 1). The group of patients in OlympiA with HR+/HER2- disease are highly selected patients at high risk of relapse (patients were required to have at least 4 positive nodes or a poor response to neoadjuvant chemotherapy (CPS+EG score of 3 or higher) – intended to be at equivalent risk of relapse to the TN population. It is therefore not realistic to compare the risk of relapse in these patients with that in the HR+/HER2- population more broadly as these patients were selected to be at an equivalent level of risk to the TNBC patients in the study (question 2).

not appropriate when proportional hazards are violated and prefers the Gompertz distribution as this still gives a plausible difference in survival between arms in the long term.	
Issue 2: Risk of bias for health-related quality of life (HRQoL) data The EAG highlights that there are missing HRQoL data in the OlympiA trial, caused by low completion rates of questionnaires. This may have resulted in biased EORTC QLQ-C30 estimates which were then mapped to utility scores for the model. The EAG suggests additional analyses to explore the potential impact of missing data on estimates of HRQoL. The company argues that response rates are in line with those expected in clinical trials ([redacted] at baseline, dropping to [redacted] at 6 and 12 months, [redacted] at 18 months, and [redacted] at 24 months). 3. what are the experts' views on the quality and completeness of the EORTC QLQ-C30 HRQoL data?	Completion of HRQoL questionnaires is always dependent on patient compliance. The reported rates of completion are comparable to other studies. The QLQ-C30 is considered a reliable and valid measure to assess quality of life in breast cancer patients and the important thing to note is that the questionnaire return rates were very similar in both arms of the study. As the quality of life comparison should be between the two arms of the trial, it is unlikely that the missing data contributes biases the study findings that there was no difference between QoL in the two study arms (question 3).
Issue 3: Health-related quality of life (HRQoL) measures used in the economic model The EORTC QLQ-C30 HRQoL data in the OlympiA trial do not translate directly to utilities. Instead, these data have to be mapped to EQ-5D utilities, which the company performed but	As noted above, the EORTC QLQ-C30 is a well validated and reliable measure of QoL in breast cancer patients. Given that all patients in OlympiA will be disease-free, and largely not be on active treatment after one year of Olaparib/placebo, it would seem to me that the appropriate comparison for the purposes of this study is a comparison of QoL between the two study arms. I would expect this cohort to

used an older mapping algorithm which has been shown to provide biased estimates, and applied it to only data cut-off 1 (DCO1). In the absence of a fully externally validated unbiased algorithm being available, the EAG recommends using utility data from the literature and exploring alternative mapping algorithms in sensitivity analyses. The EAG recommends using utility data from Verrill et al 2020, a UK study reporting EQ-5D scores in 299 patients with HER2+ early and metastatic breast cancer. However, using these estimates instead of the company's has a large impact on the cost effectiveness results. The company considers that the estimates from Verrill et al are not suitable because they are derived from a HER2+ population that does not have information on BRCA mutation status. 4. what are the experts' views on the mapped EORTC QLQ-C30 HRQoL data used by the company, and of the suitability for this appraisal of the Verrill 2020 data used by the EAG? For information, the utility values used by the company are 0.869 (for progression-free and non-metastatic breast cancer health states) and 0.685 for metastatic breast cancer. The values used by the EAG from Verrill 2020 are 0.732 for the disease-free health state, 0.667 for non-	have a good quality of life with minimal reductions – as they are in a disease-free state and are (for the most part) not receiving active treatment. The most appropriate QoL comparison here is not however with any other inferred utility values but rather should be with the control arm of the study. As an RCT, the two groups should be broadly comparable and the finding that there was no significant difference between the two groups in terms of QOL (Ganz, SABCS 2021) is reassuring. As noted by the company, the data from Verrill *et al* relates to a very different patient group – HER2+ breast cancer, *BRCA1/2* wild type, and with a mean age over 10 years older than the Olympia patient cohort, suggesting that this may not be an appropriate group for comparison (question 4). I'm unable to comment on whether the utilities reported in the Verrill paper are comparable with those reported elsewhere in the literature (question 5). However, I would note that the three groups assessed by Verrill et al are (1) on active treatment, (2) disease-free following completion of treatment and (3) metastatic disease. I would not differentiate between the non-metastatic state and the disease-free state as long as a patient is not on active treatment and therefore, I would agree that similar utility values be assumed for both these states (question 6).

metastatic breast cancer, and 0.603 for metastatic breast cancer. 5. the company argues that the 0.732 utility value from Verrill 2020 for the disease-free health state is significantly lower than similar disease-free utility values from recent empirical literature on patient reported HRQoL in early breast cancer. Do the experts have a view on this? The company assumed that the utility value for the non-metastatic recurrence disease state is the same as the disease-free health state. The EAG however set the utility values for non-metastatic recurrence as the mid-point between progression-free and metastatic recurrence. 6. which of these assumptions is most plausible for the non-metastatic recurrence disease state?	
Issue 4: Access to BCRA testing in HR+/HER2- population 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. BCRA testing for all people with TNBC is expected in the near future, but testing is limited for people with HR+/HER2- cancer and it is	BRCA mutation testing in TNBC is routinely available through GLHs for all patients with TNBC as stated in the current version of the Genomic Test Directory (v 4.0 May 2022). For HR+/HER2- breast cancer, NICE currently recommends (CG164) testing any breast cancer patients with a pre-test carrier probability of 10% (based on family history) so it is fair to say that this is routine practice although not currently for all patients with breast cancer. As noted in the NHS England Clinical Commissioning Policy this is in part aimed at reducing the current variation in access to testing (referred to in the EAG report). Ongoing research (e.g. BRCA-DIRECT) is looking

unclear when testing will become routine. The EAG suggest adding the costs of BCRA testing to the HR+/HER2- model. 7. how widespread is BCRA testing in the TNBC and HR+/HER2- groups? 8. is BCRA testing likely to be used routinely in the HR+/HER2- population?	at the implementation of rapid mainstream testing for all breast cancer patients and it is likely that the use of BRCA mutation testing will increase in this patient group in the future. Additionally, and as noted by the EAG there will be other significant benefits to patients beyond the use of Olaparib from BRCA mutation testing – in terms of tailoring surgery and risk-reduction strategies for affected relatives (with potential future impact in reducing the incidence of breast and ovarian cancer in the population). Although this does not affect the models presented it is an important consideration as the use of Olaparib is only one consideration in the management of patients with BRCA-associated breast cancer.
Are there any important issues that have been missed in EAG report?	

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Patient expert statement and technical engagement response form

Olaparib for adjuvant treatment of high-risk HER2-negative, BRCA-positive early breast cancer after chemotherapy [ID3893]

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments and feedback on the key issues below are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources. The external assessment group (EAG) report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking you about living with, or caring for a patient with, HER2-, BRCA+ early breast cancer. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the EAG report that are likely to be discussed by the committee. The key issues in the EAG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAG report (see section 1.4).

A patient perspective could help either:

- resolve any uncertainty that has been identified OR

- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise. We have given guidance on the issues in which we expect this to be the case and advice on what you could consider when giving your response.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

Patient expert statement

Please note, **part 1** can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

Deadline for comments by **5pm** on **Tuesday 23 August 2022**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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

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

Part 1: Living with this condition or caring for a patient with HER2-, BRCA+ early breast cancer

Table 1 About you, HER2-, BRCA+ early breast cancer, current treatments and equality

1. Your name	Holly Heath
2. Are you (please tick all that apply)	☐ A patient with HER2-, BRCA+ early breast cancer? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with HER2-, BRCA+ early breast cancer? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Breast Cancer Now
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission ☒ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☐ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience:

Patient expert statement

	☒ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with HER2-, BRCA+ early breast cancer? **If you are a carer (for someone with HER2-, BRCA+ early breast cancer) please share your experience of caring for them**	Please see the initial patient organisation submission from Breast Cancer Now.
7a. What do you think of the current treatments and care available for HER2-, BRCA+ early breast cancer on the NHS after surgery and neoadjuvant or adjuvant chemotherapy? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	
8. If there are disadvantages for patients of current NHS treatments for HER2-, BRCA+ early breast cancer after surgery and neoadjuvant or adjuvant chemotherapy (for example, how current treatment is given or taken, side effects of treatment, and any others) please describe these	
9a. If there are advantages of olaparib over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others?	

9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? **9c. Does olaparib help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	
10. If there are disadvantages of olaparib over current treatments on the NHS please describe these. For example, are there any risks with olaparib? If you are concerned about any potential side effects you have heard about, please describe them and explain why	
11. Are there any groups of patients who might benefit more from olaparib or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	
12. Are there any potential equality issues that should be taken into account when considering HER2-, BRCA+ early breast cancer and olaparib? Please explain if you think any groups of people with this condition are particularly disadvantaged Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or	

belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	

Part 2: Technical engagement questions for patient experts

Issues arising from technical engagement

The issues raised in the EAG report are listed in table 2. We welcome your comments on the issues, but you do not have to provide a response to every issue, such as the ones that are technical, that is, cost effectiveness-related issues. We have added a comment to the issues where we consider a patient perspective would be most relevant and valuable. If you think an issue that is important to patients has been missed in the EAG report, please let us know in the space provided at the end of this section.

For information: the patient organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAG report, the patient organisation responses will also be considered by the committee.

Table 2 Issues arising from EAG report

Issue 1: immature trial data The median follow-up in the OlympiA trial is 3.5 years, however a limited number of events have occurred, with fewer than 50% of participants having experienced events for each of the effectiveness time-to-event outcomes. Due to this there is uncertainty regarding long term effectiveness and assumptions have been made:	In terms of the issue raised regarding immature trial data, it is not wholly surprising that we are still awaiting some further long-term data. The immaturity of data is an issue in many technology appraisals for cancer medicines. As previously highlighted the trial has met its primary end point and this treatment would provide a crucially important new treatment option for this group of patients. Data from the phase 3 OlympiA trial (published in June 2021) has shown that invasive disease-free survival was significantly longer for patients taking olaparib compared to placebo, with 85.9% of patients alive and free of invasive disease-free survival at 3 years, compared to 77.1% of patients in the placebo group. Distant disease-free survival was also significantly longer among those patients who received olaparib (87.5% versus 80.4%). Updated results from the trial (March 2022) have also shown that olaparib can result in a 32% reduction in death compared to placebo. We know that the fear of recurrence and 'living under its shadow' can have a significant impact on the quality of lives of people after they finish their treatment for primary breast

Triple-negative breast cancer (TNBC) population The company assumes a 0% risk of recurrence beyond 5 years. The EAG prefers to use literature on non-zero long-term recurrence in TNBC and assumes a risk of recurrence after 5 years of 5% over the following 10 years. 1. which assumption is most plausible? HR+/HER2- population The company and EAG use different distributions to model recurrence (EAG generalised gamma; company lognormal). These have similar extrapolations up to 20 years but the company's lognormal model assumes the treatment benefit is maintained over a longer period. Due to uncertainty in the long-term estimates, the EAG considers the generalised gamma distribution is the most plausible choice. 2. do the experts have a view on which is most plausible? (please see table 14 of EAG report) Both populations The company and EAG use different distributions to model survival following early metastatic recurrence. The EAG argues that the exponential distribution used by the company is not appropriate when proportional hazards are	cancer. To have a new treatment option in olaparib, which is known to be generally well-tolerated, and could significantly reduce the risk of recurrence, including the risk of secondary breast cancer and the associated need for on-going and complex treatments could have a significantly positive impact on people's wellbeing. In terms of uncertainty regarding the long-term risk of recurrence in the TNBC population which assumption regarding TNBC is most plausible, we would suggest that the clinical experts are best placed to respond to this. Although we would note that concrete reliable data on this is lacking. However, we would suggest that it is possibly in between both the company and the EAG's assumption. Women with triple negative breast cancer are more likely to see the breast cancer spread to other parts of the body within 5 years after diagnosis compared to other types of breast cancer.

violated and prefers the Gompertz distribution as this still gives a plausible difference in survival between arms in the long term.	
Issue 2: Risk of bias for health-related quality of life (HRQoL) data The EAG highlights that there are missing data for HRQoL in the OlympiA trial, caused by low completion rates of questionnaires. This may have resulted in biased EORTC QLQ-C30 estimates which were then mapped to utility scores for the model. The EAG suggests additional analyses to explore the potential impact of missing data on estimates of HRQoL. The company argues that response rates are in line with those expected in clinical trials ([redacted] at baseline, dropping to [redacted] at 6 and 12 months, [redacted] at 18 months, and [redacted] at 24 months). 3. what are the experts' views on the quality and completeness of the EORTC QLQ-C30 HRQoL data?	It is not unusual or surprising for there to be a drop off rate for HRQoL questionnaires in trials, especially for the patient population in this trial where the median age was 42 and who may be in employment, have family and caring responsibilities and busy social lives. Therefore, the patient population may feel once they have completed the 1-year course of olaparib that they no longer have the time to complete information related to this treatment. We do not feel that the missing data is suggestive of poorer quality of life. We would like to reiterate here the comments we made in our original patient organisation submission about what patients with experience of olaparib told us. Patients told us they were experiencing fatigue and needing to go to bed early but at the same time they were also continuing with activities, including full-time employment and exercise. Patients also told us that they felt better on olaparib than they did with chemotherapy. Whilst we have not been able to speak to anyone who has completed their course of olaparib, we would point the Committee towards the existing quality of life data from the trial and sub-study presented at the 2021 San Antonio Breast Cancer Symposium that shows while olaparib did lead to increases in the severity of nausea and vomiting it did not continue following the treatment ending and also it has been shown that one year of olaparib did not meaningfully affect the speed of recovery.
Issue 3: Health-related quality of life (HRQoL) measures used in the economic model The EORTC QLQ-C30 HRQoL data in the OlympiA trial do not translate directly to utilities. Instead, these data have to be mapped to EQ-5D utilities, which the company performed but used an older mapping algorithm which has	We recognise that the clinical experts will be best placed to respond to this issue, however, there are a couple of reflections we would like to make: - It should be considered that the population relevant here (and included in the trial) can be younger than other breast cancer populations and that other breast cancer quality of life data may not simply be able to be mapped onto this population group and have the same relevance.

been shown to provide biased estimates, and applied it to only data cut-off 1 (DCO1). In the absence of a fully externally validated unbiased algorithm being available, the EAG recommends using utility data from the literature and exploring alternative mapping algorithms in sensitivity analyses. The EAG recommends using utility data from Verrill et al 2020, a UK study reporting EQ-5D scores in 299 patients with HER2+ early and metastatic breast cancer. However, using these estimates instead of the company's has a large impact on the cost effectiveness results. The company considers that the estimates from Verrill et al are not suitable because they are derived from a HER2+ population that does not have information on BRCA mutation status. 4. what are the experts' views on the mapped EORTC QLQ-C30 HRQoL data used by the company, and of the suitability for this appraisal of the Verrill 2020 used by the EAG? For information, the utility values used by the company are 0.869 (for progression-free and non-metastatic breast cancer health states) and 0.685 for metastatic breast cancer. The values used by the EAG are 0.732 for the disease-free health state, 0.667 for non-metastatic	- The values used by the EAG for the non-metastatic and metastatic state do seem to be very similar. There is a difference between these two 'states' which need to be recognised here. In the non-metastatic state, for this population group we have heard from patients on olaparib who are continuing in full-time employment and their social activities, including exercising, meeting friends for dinner and holidays. Whilst there will be some changes in patients quality of life, such as experiencing fatigue and nausea which will improve post-treatment and those who are HR+ve may experience side effects from their endocrine therapy, it is not sufficient to account for very similar utility values between these two states where metastatic patients will be on a constant cycle of treatments which could have a significant and sustained impact on their quality of life and day to day activities. .

Patient expert statement

breast cancer, and 0.603 for metastatic breast cancer. 5. the company argues that the 0.732 utility value from Verrill 2020 for the disease-free health state is significantly lower than similar disease-free utility values from recent empirical literature on patient reported HRQoL in early breast cancer. Do the experts have a view on this? The company assumed that the utility value for the non-metastatic recurrence disease state is the same as the disease-free health state. The EAG however set the utility values for non-metastatic recurrence as the mid-point between progression-free and metastatic recurrence. 6. which of these assumptions is most plausible for the non-metastatic recurrence disease state?	
Issue 4: Access to BCRA testing in HR+/HER2- population 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. BCRA testing for all people with TNBC is expected in the near future, but testing is limited	The testing and timeliness of BRCA testing is crucial to ensure that if olaparib is approved by NICE for use on the NHS, that all eligible patients are being identified. Current recommendations can be found in NHS England's National Genomic Test Directory. We are aware that for HR+ve/HER-ve, the current criteria may not be fully applied for patients or there is lack of awareness that BRCA testing is available beyond triple negative breast cancer as well as the change in age criteria for TNBC patients. In terms of discussions around widening criteria, we would suggest that NICE urgently engages with the genomics team at NHS England to see what current discussions there

for people with HR+/HER2- cancer and it is unclear when testing will become routine. The EAG suggest adding the costs of BCRA testing to the HR+/HER2- model. 7. How widespread is BCRA testing in the TNBC and HR+/HER2- groups? 8. Is BCRA testing likely to be used routinely in the HR+/HER2- population?	are about broadening the BRCA testing eligibility so it is relevant for the olaparib population.
Are there any important issues that have been missed in EAG report?	In the scope there was consideration given to the definition of high risk in clinical practice in England and the EAG appears happy with the company's submission. We would like to note the relevance of a definition of 'high risk' in light of a recent NICE approval of another adjuvant treatment, and the ongoing assessment of two other adjuvant treatments where there could be some patient overlap.

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Please see key messages in Breast Cancer Now's patient organisation submission.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see NICE's privacy notice.

NICE National Institute for Health and Care Excellence

Patient expert statement and technical engagement response form

Olaparib for adjuvant treatment of high-risk HER2-negative, BRCA-positive early breast cancer after chemotherapy [ID3893]

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments and feedback on the key issues below are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources. The external assessment group (EAG) report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking you about living with, or caring for a patient with, HER2-, BRCA+ early breast cancer. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the EAG report that are likely to be discussed by the committee. The key issues in the EAG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAG report (see section 1.4).

A patient perspective could help either:

- resolve any uncertainty that has been identified OR

Patient expert statement

- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise. We have given guidance on the issues in which we expect this to be the case and advice on what you could consider when giving your response.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

Patient expert statement

Please note, **part 1** can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

Deadline for comments by **5pm** on **Tuesday 23 August 2022**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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

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

Part 1: Living with this condition or caring for a patient with HER2-, BRCA+ early breast cancer

Table 1 About you, HER2-, BRCA+ early breast cancer, current treatments and equality

1. Your name	Melanie Sturtevant
2. Are you (please tick all that apply)	☒ A patient with HER2-, BRCA+ early breast cancer? ☒ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with HER2-, BRCA+ early breast cancer? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	Breast Cancer Now
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience:

Patient expert statement

	☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☒ I have not completed part 2 of the statement
6. What is your experience of living with HER2-, BRCA+ early breast cancer? **If you are a carer (for someone with HER2-, BRCA+ early breast cancer) please share your experience of caring for them**	I was diagnosed with triple negative (HER2-, ER-, PR-) early breast cancer in March 2021. Knowing that you have one of the least common but more aggressive types of breast cancer which has a higher risk of recurring in the years immediately following treatment, and that there are fewer treatment options available to reduce this risk, is obviously daunting. Because my breast cancer was triple negative and I am under 60 I was referred for genetic testing. In the meantime, I had a lumpectomy followed by chemotherapy - epirubicin and cyclophosphamide (EC) every 2 weeks for 4 cycles, followed by 12 weekly sessions of paclitaxel. After I had finished chemotherapy, I received the results of the genetic testing and discovered that I had a BRCA1 mutation, which was something of a shock given there is no history of breast (or ovarian) cancer in my family. As well as having an estimated lifetime risk of around 65% of developing a new breast cancer, and around a 45% risk of developing ovarian cancer, I was also really worried that other members of my family may have the BRCA1 mutation and be at significantly increased risk of developing these types of cancer and felt guilty for bringing this possibility into their lives. Being told that you have a BRCA mutation comes with a whole new set of decisions to make. Rather than move onto radiotherapy, as originally planned, I chose to have a double mastectomy with immediate breast reconstruction which has reduced my lifetime risk of developing a new breast cancer to between around 5 and 10%. I was also told that I was eligible for olaparib, which clinical trial results showed reduced

	the risk of recurrence and improved survival, and feel really lucky to have been able to access it through the early access scheme put in place by the company. I started taking olaparib in December 2021.
7a. What do you think of the current treatments and care available for HER2-, BRCA+ early breast cancer on the NHS after surgery and neoadjuvant or adjuvant chemotherapy? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	There are currently no treatments available for early triple negative breast cancer – the type of breast cancer I had - on the NHS after surgery and neoadjuvant or adjuvant chemotherapy.
8. If there are disadvantages for patients of current NHS treatments for HER2-, BRCA+ early breast cancer after surgery and neoadjuvant or adjuvant chemotherapy (for example, how current treatment is given or taken, side effects of treatment, and any others) please describe these	There are currently no treatments available for early triple negative breast cancer - the type of breast cancer I had - on the NHS after surgery and neoadjuvant or adjuvant chemotherapy.
9a. If there are advantages of olaparib over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does olaparib help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	Whilst I am obviously aware that olaparib is an additional, rather than alternative, treatment to neo/adjuvant chemotherapy it is worth setting out how olaparib compares to chemo as a drug treatment. Olaparib is taken orally, as tablets, twice a day, so there is no need to go into hospital for treatment – not just for the chemotherapy itself but also to have your bloods done prior to chemo, and your PICC (or other) line if you have one, maintained – beyond the need for an appointment every four weeks for bloods and monitoring, the frequency of which drops after 6 cycles of olaparib. This is obviously much more convenient and a lot less time consuming than chemo and means I have had to take a lot less time off work.

	Whilst I feel I got off relatively lightly on the side effects from chemo - with the main ones I experienced being dizziness for several days after EC chemo, hair loss, and fatigue - the only issue I have experienced whilst taking olaparib is fatigue. And given that I have been working full time, whilst also getting back into running, and have recently had further surgery to reduce my risk of developing ovarian cancer, I do not believe that the fatigue is solely due to olaparib. I manage the fatigue by doing a bit less than I used to – particularly after work – and going to bed earlier. Lastly, but most importantly, the significant reduction in the risk of recurrence and improved survival that olaparib provides for this type of breast cancer is a huge advantage. I know that I have now done everything I possibly can to reduce the risk of my cancer recurring – as well as developing a new cancer – and that has been psychologically very important for me.
10. If there are disadvantages of olaparib over current treatments on the NHS please describe these. For example, are there any risks with olaparib? If you are concerned about any potential side effects you have heard about, please describe them and explain why	Obviously taking adjuvant olaparib has involved an extra year of treatment for me. But as described above, the impact this has had on me and my day to day life is minimal compared to chemo and is also vastly outweighed by significant reduction in the risk of recurrence and improved survival.
11. Are there any groups of patients who might benefit more from olaparib or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	Patients that have difficulty swallowing may have trouble taking olaparib. Patients that have issues with their memory may have difficulty remembering to take it twice a day, although there are obviously ways around this.
12. Are there any potential equality issues that should be taken into account when considering HER2-, BRCA+ early breast cancer and olaparib? Please	Women with triple negative breast cancer that have BRCA mutations may be eligible for olaparib. Black women and younger women are more likely to develop triple negative breast cancer.

explain if you think any groups of people with this condition are particularly disadvantaged Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	No.

Part 2: Technical engagement questions for patient experts

Issues arising from technical engagement

The issues raised in the EAG report are listed in table 2. We welcome your comments on the issues, but you do not have to provide a response to every issue, such as the ones that are technical, that is, cost effectiveness-related issues. We have added a comment to the issues where we consider a patient perspective would be most relevant and valuable. If you think an issue that is important to patients has been missed in the EAG report, please let us know in the space provided at the end of this section.

For information: the patient organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAG report, the patient organisation responses will also be considered by the committee.

Table 2 Issues arising from EAG report

Issue 1: immature trial data The median follow-up in the OlympiA trial is 3.5 years, however a limited number of events have occurred, with fewer than 50% of participants having experienced events for each of the effectiveness time-to-event outcomes. Due to this there is uncertainty regarding long term effectiveness and assumptions have been made:	

Patient expert statement

Triple-negative breast cancer (TNBC) population The company assumes a 0% risk of recurrence beyond 5 years. The EAG prefers to use literature on non-zero long-term recurrence in TNBC and assumes a risk of recurrence after 5 years of 5% over the following 10 years. 1. which assumption is most plausible? HR+/HER2- population The company and EAG use different distributions to model recurrence (EAG generalised gamma; company lognormal). These have similar extrapolations up to 20 years but the company's lognormal model assumes the treatment benefit is maintained over a longer period. Due to uncertainty in the long-term estimates, the EAG considers the generalised gamma distribution is the most plausible choice. 2. do the experts have a view on which is most plausible? (please see table 14 of EAG report) Both populations The company and EAG use different distributions to model survival following early metastatic recurrence. The EAG argues that the exponential distribution used by the company is not appropriate when proportional hazards are	

Patient expert statement

violated and prefers the Gompertz distribution as this still gives a plausible difference in survival between arms in the long term.	
Issue 2: Risk of bias for health-related quality of life (HRQoL) data The EAG highlights that there are missing data for HRQoL in the OlympiA trial, caused by low completion rates of questionnaires. This may have resulted in biased EORTC QLQ-C30 estimates which were then mapped to utility scores for the model. The EAG suggests additional analyses to explore the potential impact of missing data on estimates of HRQoL. The company argues that response rates are in line with those expected in clinical trials [redacted] at baseline, dropping to [redacted] at 6 and 12 months, [redacted] at 18 months, and [redacted] at 24 months). 3. what are the experts' views on the quality and completeness of the EORTC QLQ-C30 HRQoL data?	
Issue 3: Health-related quality of life (HRQoL) measures used in the economic model The EORTC QLQ-C30 HRQoL data in the OlympiA trial do not translate directly to utilities. Instead, these data have to be mapped to EQ-5D utilities, which the company performed but used an older mapping algorithm which has	

been shown to provide biased estimates, and applied it to only data cut-off 1 (DCO1). In the absence of a fully externally validated unbiased algorithm being available, the EAG recommends using utility data from the literature and exploring alternative mapping algorithms in sensitivity analyses. The EAG recommends using utility data from Verrill et al 2020, a UK study reporting EQ-5D scores in 299 patients with HER2+ early and metastatic breast cancer. However, using these estimates instead of the company's has a large impact on the cost effectiveness results. The company considers that the estimates from Verrill et al are not suitable because they are derived from a HER2+ population that does not have information on BRCA mutation status. 4. what are the experts' views on the mapped EORTC QLQ-C30 HRQoL data used by the company, and of the suitability for this appraisal of the Verrill 2020 used by the EAG? For information, the utility values used by the company are 0.869 (for progression-free and non-metastatic breast cancer health states) and 0.685 for metastatic breast cancer. The values used by the EAG are 0.732 for the disease-free health state, 0.667 for non-metastatic	

breast cancer, and 0.603 for metastatic breast cancer. 5. the company argues that the 0.732 utility value from Verrill 2020 for the disease-free health state is significantly lower than similar disease-free utility values from recent empirical literature on patient reported HRQoL in early breast cancer. Do the experts have a view on this? The company assumed that the utility value for the non-metastatic recurrence disease state is the same as the disease-free health state. The EAG however set the utility values for non-metastatic recurrence as the mid-point between progression-free and metastatic recurrence. 6. which of these assumptions is most plausible for the non-metastatic recurrence disease state?	
Issue 4: Access to BCRA testing in HR+/HER2- population 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. BCRA testing for all people with TNBC is expected in the near future, but testing is limited	

for people with HR+/HER2- cancer and it is unclear when testing will become routine. The EAG suggest adding the costs of BCRA testing to the HR+/HER2- model. 7. How widespread is BCRA testing in the TNBC and HR+/HER2- groups? 8. Is BCRA testing likely to be used routinely in the HR+/HER2- population?	
Are there any important issues that have been missed in EAG report?	

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Having triple negative early breast cancer, which has a greater risk of recurrence in the years immediately following treatment, but has fewer treatment options to reduce that risk, is daunting.
- Knowing that olaparib significantly reduces the risk of recurrence and improves survival is hugely important psychologically.
- Having an extra year of treatment is vastly outweighed by the benefits of olaparib.
- Treatment with olaparib is much more convenient and a lot less time consuming than chemo.
- The only real issue I have experienced while taking olaparib is fatigue, and this is unlikely to be solely due to olaparib.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see NICE's privacy notice.

NICE National Institute for Health and Care Excellence

Technical engagement response form

Olaparib for adjuvant treatment of high-risk HER2-negative, BRCA-positive early breast cancer after chemotherapy [ID3893]

As a stakeholder you have been invited to comment on the external assessment group (EAG) report for this appraisal.

Your comments and feedback on the key issues below are really valued. The EAG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAG report that are likely to be discussed by the committee. The key issues in the EAG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAG report.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAG report that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

NICE National Institute for Health and Care Excellence

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Deadline for comments by **5pm** on **Tuesday 23 August 2022.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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

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

NICE National Institute for Health and Care Excellence

About you

Table 1 About you

Your name	Jane Deller
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	NHS England Genomics Unit
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**n/a**

NICE National Institute for Health and Care Excellence

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAG report.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Issue 1: Immaturity of trial data	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses
Issue 2: Potential risk of bias in estimates of HRQoL	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses
Issue 3: HRQoL measures used in the economic model	Yes/No	Please provide your response to this key issue, including any new evidence, data or analyses
Issue 4: Access to BCRA testing in HR+/HER2 population	Yes/No	Agree with the EAG that testing for BRCA mutations is not yet routinely available on the NHS for all patients potentially eligible for olaparib in this setting and that the costs of testing should be included in the calculations for cost effectiveness as the activity for germline BRCA testing will increase. The cohort of patients that would be eligible for Olaparib and would currently be eligible for germline BRCA testing would need to meet the following criteria - please note the criteria have changed since the EAG wrote their report – the changes are underlined:

		Living affected individual (proband) with breast or ovarian cancer where the individual +/- family history meets one of the criteria. The proband has: a. Breast cancer (age < 40 years, excluding grade 1 breast cancers), OR b. Bilateral breast cancer (age < 50 years), OR c. Triple negative breast cancer (age < 60 years), OR d. Male breast cancer (any age), OR e. Breast cancer (age <45 years) and a first degree relative with breast cancer (age <45 years), OR f. Pathology-adjusted Manchester score ≥15 or CanRisk score ≥10% g. Ashkenazi Jewish ancestry and breast cancer at any age. A pilot for TNBC using WGS has been implemented but this is not widely available currently but will allow for testing at any age and any point in the patient pathway. Therefore, germline BRCA testing for patients that do not fulfil the current criteria would be additional testing for the NHS to implement and should be considered additional costs. We agree with the EAG that the model for HR+/HER2- patients should include the cost of BRCA testing since olaparib is a BRCA targeting therapy. We would also suggest that the model should include testing TNBC age over 60 years in the immediate term whilst this testing using WGS is currently at a pilot stage only and not available across all England.

NICE National Institute for Health and Care Excellence

Additional issues

All: Please use the table below to respond to additional issues in the EAG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (for example, at the clarification stage).

Table 3 Additional issues from the EAG report

Issue from the EAG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Insert additional issue	Please indicate the section(s) of the EAG report that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue 2: Insert additional issue	Please indicate the section(s) of the EAG report that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

NICE National Institute for Health and Care Excellence

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the EAG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Insert key issue number and title as described in the EAG report	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the EAG report	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER.
Insert key issue number and title as described in the EAG report	…	…	[INSERT / DELETE ROWS AS REQUIRED]
Company's base case following technical engagement (or revised base case)	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide company revised base-case ICER

Sensitivity analyses around revised base case
[PLEASE DESCRIBE HERE]

NICE National Institute for Health and Care Excellence

Technical engagement response form

Olaparib for adjuvant treatment of high-risk HER2-negative, BRCA-positive early breast cancer after chemotherapy [ID3893]

As a stakeholder you have been invited to comment on the external assessment group (EAG) report for this appraisal.

Your comments and feedback on the key issues below are really valued. The EAG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAG report that are likely to be discussed by the committee. The key issues in the EAG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAG report.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAG report that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under [redacted], all information submitted under [redacted] and all information submitted under [redacted] in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the (sections 3.1.23 to 3.1.29) for more information.

Deadline for comments by **5pm** on **Tuesday 23 August 2022.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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

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

Technical engagement response form

Olaparib for adjuvant treatment of high-risk HER2-negative, BRCA-positive early breast cancer after chemotherapy [ID3893]

1 About you

Table 1: About you

Your name	
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	AstraZeneca UK – stakeholder
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**Nothing to disclose**

2 Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAG report.

Table 2: Key issues

Key Issue	Does this response contain new evidence, data or analyses?	Response	EAG response
Issue 1: Immaturity of trial data	No	Although it is acknowledged that the clinical data from OlympiA are somewhat immature, this is an inherent challenge when studying adjuvant treatments for use in early stages of disease, often when there is no known residual disease after surgery. This limitation has been acknowledged and accepted in prior appraisals (e.g., TA810,[1] where the lack of statistically significant OS benefit was acknowledged to relate to the treatment setting). In such early-stage trials, it can take decades to reach the median for certain time-to-event efficacy outcomes, particularly OS. Generally, such clinical trials do not continue follow-up indefinitely, given the associated costs, and the burden which this would impose on participating patients, so median values may never be reached. Despite olaparib being an adjuvant therapy in an early disease setting, and unlike many other trials in the eBC setting (including the MonarchE trial which informed TA810)[1], **the OlympiA trial has already demonstrated a statistically significant OS benefit; this is a remarkable result in this setting**. At DCO2 of the OlympiA trial, the ITT iDFS data were 18.6% mature (341 events/1,836 patients).[2] This is higher than the maturity of the iDFS data which were used to inform TA810 (at the AFU1 analysis, iDFS data were 10.0% mature (565 events/5,637 patients).[1] Given these considerations, the OlympiA data should be considered sufficiently mature to inform decision-making, particularly in the TNBC subgroup.	The fact that Olaparib data is less immature than data on different appraisal (TA810) does not invalidate the fact that Olaparib data are not immature. The ITT data are only 18.6% mature (341 events/1,836 patients) while TNBC are 18.7% mature (282 events/1509 patients). This objective immaturity of the data is supported by the clinical expert feedback from Stuart McIntosh, who stated "…early breast cancer (even high-risk early breast cancer, as in the OlympiA participants) has a relatively good prognosis, with

		We acknowledge the EAG's concern regarding the higher uncertainty in the HR+/HER2- subgroup, given the smaller number of patients recruited, as well as the shorter follow-up in this group. This resulted in fewer iDFS events in the HR+/HER2- group and meant that the use of ITT data as a proxy for the HR+/HER2- subgroup in the economic model was the most appropriate approach. Although we have validated the related assumptions with clinical experts to minimise uncertainty as much as possible, we agree with the EAG assessment that a degree of unresolvable uncertainty remains. Longer follow-up from the OlympiA trial is anticipated to resolve this uncertainty in the coming years, with DCO3 expected [redacted]. AstraZeneca suggest that the HR+/HER2- subgroup could be [redacted] to resolve this specific uncertainty.	around 60-70% 5 year survival overall" This would indicate 30-40% events are expected over 5 years, so fewer than <20% events is immature, despite generally good prognosis in the patient group.
Issue 2: Potential risk of bias in estimates of HRQoL	Yes	Although we acknowledge the EAG's concern of potential bias in the OlympiA trial HRQoL estimates and the uncertainty regarding the choice of mapping algorithm that is applied, we firmly believe that the OlympiA trial provides the set of utility values that are most relevant to the current decision problem. We believe that the key issue that should ultimately be addressed is which **HRQoL data source most appropriately reflects the utility** experienced by patients in the OlympiA indication, specifically those who are and remain progression-free. For this reason, we have structured and combined our response to Key Issues 2 and 3 as follows: 1. Demonstrating the relevance and appropriateness of the OlympiA HRQoL data 2. A critique of the EAG's preferred HSUVs from Verrill et al. (2020) 3. A discussion of the face validity of the EAG's preferred HSUVs and ultimately what value best reflects the HRQoL of patients who are progression-free in this eBC indication The EAG's main concern around the OlympiA HRQoL data is that potentially non-random missing data resulting from low completion rates of the HRQoL questionnaires	The EAG stands by their reasoning to choose estimates for real EQ-5D utilities from BC patients in other studies over mapping algorithms of trial disease-specific HRQoL scores in Olympia. We will further explain our reasoning below and structure our response following the company's points: 1. Relevance and appropriateness of the OlympiA HRQoL data. We stand by our response to the FAC in terms of the potential risk of bias in estimates of HRQoL. Just

		could have impacted, and thereby biased, the trial's HRQoL estimates. Although we do not contend that there is missing data, we would like to point out that: • A certain level of missing data in HRQoL questionnaires is present in all clinical trials and **does not directly infer that the data itself is biased**. As presented in our response to the factual accuracy check, the HRQoL response rate in OlympiA was in line with that expected in clinical trials in this setting, with response rates of [redacted] at baseline, dropping to only [redacted] at 24 months[3] (please refer to Appendix A [Table A1] for an overview of the OlympiA HRQoL questionnaire response rates over time). • More importantly, as demonstrated in Appendix A (Table A2), the EORTC QLQ-C30 scores in OlympiA remain [redacted]. If the majority of missing observations were not random and attrition bias was therefore present, there would be an expectation that the average utility score would increase over time as the remaining sample would consist of healthier patients. Therefore, even if there was some level of attrition bias as a result of more severe patients not completing the questionnaires, evidence suggests that the **magnitude of this potential bias on the HRQoL estimates is negligible**. In addition to the concern around biased HRQoL estimates, the EAG also argue that it is not appropriate to consider any algorithm to map the OlympiA EORTC QLQ-C30 data to HSUVs, stating that none of the available algorithms are unbiased and fully externally validated. However, by making this conclusion and thus recommending an external study (Verrill et al., 2020)[4] as the main HRQoL reference for the economic model, the EAG discards the most robust and applicable source of HSU data for the patient population relevant to this appraisal. Although the SLR described in Section B.3.4.3 of Document B identified 5 studies which reported on HSUVs in eBC (including Verrill et al., 2020)[4], none of the studies are representative of the specific population considered within the current decision problem,	because missing data is a common issue, it does not invalidate the potential for risk of bias from missing HRQoL data. We disagree with the suggestion that similarity in estimates over time suggests that the magnitude of this potential bias on HRQoL estimates is negligible. It is equally possible that had everyone completed HRQoL there would have been a change in HRQoL over time. The issue is that what impact the missing data had on QoL estimates and it is not possible to accurately predict the direction of this bias. The EAG agrees that the patient population of the OlympiA trial would have been the most appropriate one to represent the population of interest and includes more patients than other studies with direct EQ-5D utilities. However, the company has opted not to collect direct EQ-5D data (a very short, generic HRQoL questionnaire) allowing for utilities to be derived directly for the Olympia trial population. Instead it

		as all studies lacked information on *BRCA* mutation or risk of recurrence status. The **OlympiA trial therefore represents the most robust and applicable source of HRQoL data for patients with g*BRCA*m, high-risk eBC**. Furthermore, the HRQoL data collected in OlympiA can be considered more robust than the HSU evidence from Verrill et al. (2020) for several reasons (further critique given under Point 2, below): • The OlympiA trial includes a large pool of patients, with the PRO analysis set comprising n=1,751 patients (out of 1,836 patients in total).[3] A total of [redacted] questionnaires ([redacted] in the olaparib and placebo arms, respectively) were completed over the first 2 years of follow-up.[5] This is a significantly larger and more relevant cohort than in the study by Verrill et al. (2020), which only recruited 108 patients in Group 2 (patients with HER2+ eBC who had completed treatment and were in remission).[4] • One of the key strengths of the OlympiA trial is that it captures the HRQoL of patients across multiple time points (completed at baseline before randomisation and every six months for a period of two years),[3] whereas the report by Verrill et al. (2020) is based on a cross-sectional study.[4] As such, it does not allow for an assessment and consideration of the temporal relationship between disease/treatment stage and impact on HRQoL, which is something that the HRQoL data from OlympiA does reflect. Furthermore, we have provided additional sensitivity analyses to address the EAG's critique of potential bias in the mapping algorithms through the application of different algorithms, including those from Longworth et al. (2014),[6] Crott and Briggs (2010)[7] and Gray et al. (2021);[8] the latter having been newly submitted as part of this response (Appendix C [Table C1]). We have also provided an additional UK analysis of the OlympiA EORTC QLU-C10D (see UK value set) which, although not aligned with NICE's preferred measure of HRQoL, presents another set of sensitivity analysis around the mapping algorithms.	opted for using the disease-specific and much longer EORTC-QLQ C30 questionnaire, more burdensome, prone to missing data, and does not allow for utilities to be derived. The company opted to rely on mapping algorithms to obtain utilities. **The methods to obtain mapping algorithms are ever-evolving**; there are a multitude of algorithms allowing for flexibility to choose between them. These algorithms were developed on BC populations that are HER+ or mostly HER+, not the HER- population of interest. **The older algorithms have already been shown to produce biased estimates. The newer ones have not been used and tested enough for robust results.** These biases cannot fully be estimated, and results from sensitivity analyses are not informative. The company has failed to take advantage of the temporal changes in HRQoL measurements by using all scores across the period for mapping. For group 2 in Verrill

As demonstrated in Table 2-1, the mapped utility scores for the PF health state from the three different algorithms and the EORTC QLU-C10D analysis fall significantly and meaningfully above (+~0.07) the utility scores from Verrill et al. (2020). These results also show that the **choice of algorithm is not a key driver of the mapped utility estimates from OlympiA** as there is a reasonable amount of consistency between the different values.

Table 2-1: Summary of the company and EAG's HSUVs for the PF state

Source	HSUV (PF state)
Crott & Briggs (2010) mapping algorithm[7]	0.869
Gray et al. (2021) mapping algorithm[8]	0.815
OlympiA EORTC QLU-C10D analysis	[redacted]
Longworth et al. (2014) mapping algorithm[6]	0.802
Verrill et al. (2020)[4]	0.732

Abbreviations: DCO: data cut-off; EORTC: European Organisation for Research and Treatment of Cancer; HSUV: health state utility value; PF: progression-free.

We appreciate that the EAG has provided additional rationale and justification for choosing the HSUVs from Verrill et al. (2020) in their base-case economic analysis as part of their response to the factual accuracy check. However, we would like to stress that the **respective HSUV of 0.732 for the PF state lacks face validity** and the study is subject to significant limitations. We further elaborate on the face validity argument under Point 3 (below), but first would like to make the following comments about the study by Verrill et al. (2020):

- The study by Verrill et al. (2020) is **not representative of a younger *BRCA* population** due to its older mean age of 57.7 years in Group 2 (vs. 43.3 years in OlympiA).[3, 4] Feedback from KEEs has indicated that the demographics of the patient population in OlympiA better align with the patient group clinicians anticipate would receive olaparib in clinical practice. Caution should therefore be taken when interpreting the health utilities from Verrill et al. (2020).

2020 (informing the iDFS state), the median time since patients completed their adjuvant therapy was 27.5 months (IQR=30.8 months), similar to the last follow-up of OlympiA trial patients.

In table 2-1, the company is comparing direct utilities from the EQ-5D (Verrill's 2020) to utilities from mapping algorithms. These cannot be compared. Verrill's is using a completely different tool, the NICE recommended EQ-5D questionnaire, to obtain utilities directly. The mapping algorithm estimates presented are either proven to be biased and wrong, or not validated yet. They must therefore be discarded as valid comparators.

2. Critique of Verrill's estimates.

Of all the studies and mapping algorithms that the EAG has considered, we stand firm by our decision that Verrill's estimates are the most appropriate to portray the

		• A second important critique of Verrill et al. (2020) is that the study was cross-sectional with patients recruited based on their physician's referral. Specifically, almost half of the patients in Group 2 (48.1%) were unemployed and their questionnaires were collected on average ~4 years after their initial diagnosis, which **indicates a potential selection bias**. Patients with a 'normal' HRQoL are likely to have returned to work at this point if they remain progression-free, have an improved quality of life, and are therefore unlikely to have completed the questionnaire in the study. The measured health utility of 0.732 from Verrill et al. (2020) for Group 2 is therefore likely to be negatively biased, and thus not applicable and relevant to the general demographics of the OlympiA patient population. Overall, the bias inherent in the HRQoL scoring from Verrill et al. (2020) cannot be easily elucidated or explored within the economic model. The differing age, selection bias from recruitment and the lack of g*BRCA*m and TNBC patients in the study are likely to impart **bias in the utility results and limit its generalisability to OlympiA patients.** As discussed in the Technical Engagement call, we believe that the discussion should not primarily centre around the potential bias of the HRQoL data from OlympiA or the appropriateness of the mapping algorithms, but ultimately **which HSUVs best reflect the HRQoL of UK patients with g*BRCA*m, high-risk eBC**. Importantly, we believe that assigning a **utility value of 0.732** to a young patient group who have early-stage, treatable BC and are in remission **lacks face validity** for several reasons: • First, the UK general population utility for women aged 43.3 years (mean age in OlympiA) is 0.877. Considering that patients in the PF state are in remission, with a significant proportion of patients expected to achieve long-term remission, these patients are not expected to experience any significant continuing BC-related symptoms or AEs from treatment, especially given the strong safety	true HRQoL of the Olaparib's population. We disagree with the company on several aspects of their critique of our choice: Firstly, face validity should not be judged by comparing estimates from mapping algorithms of disease-specific scores to direct EQ-5D utilities. Second, group 2 in Verrill's 2020 informing iDFS in the EAGs base case was 55 years at the time of entering the study, (compared 43 years entering OlympiA), not 57.7. We have adjusted the age difference on Verrill's utilities from 55 years to 43, in our sensitivity analysis scenarios, and present these new utilities and ICER results. Third, **it is false that 48% of patients in the Verrill's study were unemployed**. 51% of patients in were employed, 36% were retired, 4.6% were unable to work and 8.3% did not state or had an unknow employment status. Fourth, Verrill's patient group responded to questionnaires

		profile of olaparib. Therefore, there is **no clear rationale as to why the utility value assigned to these patients should be significantly lower than the values of the age-matched UK general population**. • This argument can be further supported by comparing the different mapped OlympiA PF HSUVs and the HSUV from Verrill et al. (2020) with utility values from previous NICE appraisals in the early and metastatic BC settings and relevant empirical literature, as presented in Table 2-2. It is clear from this overview that **there is no precedent of either accepting or concluding such a low utility value** for eBC patients who are in (long-term) remission. Specifically, in all previous NICE appraisals in eBC, including two appraisals (TA632 and TA424)[9, 10] which covered a 'high-risk' patient population (with the latter also focusing on locally advanced disease), values significantly above Verrill et al. (2020) were continuously accepted as the appropriate HSUV for the DF health state. • Furthermore, although we acknowledge that the patient groups and decision problem of the two mBC NICE appraisals differ slightly from those currently under consideration, we disagree with the EAG that these do not provide a relevant reference for this appraisal. Instead, considering that patients with newly diagnosed mBC are shown to have a utility value of ~0.73, it is **highly unrealistic to assume that such a utility value would also apply to patients with early-stage disease**, specifically those individuals who remain progression-free for a long period of time. • This finding was also confirmed during interviews with UK clinical oncologists, who unanimously commented that the HRQoL of eBC patients will become similar to the age-matched general population over time. It is therefore highly reasonable to assume that the **'true' HSUV for (long-term) disease-free patients with high-risk, g*BRCA*m early disease ranges between 0.8–0.877**.	around 2 years after completing neo-adjuvant therapy, as did patients in the OlympiA trial. It is unclear how this fact has more potential for bias than OlympiA's HRQoL estimates. 3. Appropriate utilities to use in the model The EAG agrees that Verrill's study population is 55 years old for the DF state, and not 43 years old as in OlympiA, and therefore agree to increase the utility estimates proportionally for age in a sensitivity analysis. However, we also note that the HER- population in Olaparib should have received a decrement in utility, compared to the HER+ population in Verrill's study. We do not know by how much the HER- patients would have decreased their utility and it is possible that this decrement is larger than the increase due to age. In sensitivity analyses, we now present additional results adjusting for the age difference in Verrill's estimates. We would like to

Table 2-2: An overview of different sources and appraisals on utility values for patients with eBC who are disease-free

Health state	Utility values	Source	Population specifics
General population *Never had BC*	0.877	Ara & Brazier (2010)[11]	Mean value, UK population norms for women aged 43.3 years
iDFS in eBC *Patient treated for eBC and currently disease-free*	0.872	Criscitiello et al (2021)[12]	HR+/HER2- eBC, either receiving adjuvant treatment or under post-adjuvant surveillance, UK cohort
	0.802–0.869	OlympiA	Based on 3 different mapping algorithms
	0.837	NICE TA612 (November 2019): Neratinib (ExteNET)[13]	Extended adjuvant treatment of HR+/HER2+ eBC after adjuvant trastuzumab-based treatment <1 year ago
	0.822[a]	NICE TA569 (March 2019): Pertuzumab + IV trastuzumab +ChT (APHINITY)[14]	Adjuvant treatment of HER2+ eBC with lymph node-positive disease

stress that these **new sensitivity analysis results are ultimately the best-case scenario**, and that the true utility value would be lower (albeit unknown) pushing the ICERs close to our base case results.

We stand by our response in the FAC that utility values from previous NICE appraisals are not valid as a comparison for the Olaparib study. They model a different population and a different indication and cannot be used to provide evidence of face validity for the company's preferred utility values.

In table 2-2 the company is comparing other utility estimates with the population norm of 0.877 for females aged 43.3 years. We feel that these comparisons are not valid and critique each of them in turn.

Criscitiello et al is a company sponsored study based on n=1,110 patients of which only 63 are from the UK. The utility estimates are a weighted average of the tariffs from

			0.788[a]	NICE TA632 (June 2020): Trastuzumab emtansine (KATHERINE)[9]	Adjuvant treatment of HER2+ eBC with residual invasive disease after neoadjuvant treatment	numerous other countries, and not using UK validated societal preference values. These estimates are therefore against the NICE reference case and cannot be used for comparison. The mapping algorithms for the OlympiA trial EORTC scores are derived from HER+ populations and not valid as comparators for the reasons described above. Previous NICE TAs are appraising HER+ breast cancers, for which clinical experts have advised the estimates may be higher. They are also appraising other technologies and using other models in different research questions, not relevant for comparison. Lidgren 2007 is a comparable study to Verrill's and these estimates are close to Verrill's. Lidgren is however an older study and in a Swedish BC population. Lindgren's estimates also removed all negative values of utilities, overestimating the results. Verrill is a much more recent study and in the UK population. Verrill's
			0.779[b]	NICE TA424 (December 2016): Pertuzumab + IV trastuzumab +ChT (NeoSphere, TRYPHAENA)[10]	Neoadjuvant treatment of HER2+ locally advanced, inflammatory or eBC at high risk of recurrence	
			0.779	Lidgren et al (2007)[15]	Patients with BC, in the second and following years after primary BC/recurrence, Swedish study	
			0.732	Verrill et al (2020)[4]	HER2+ eBC patients who completed treatment and were in remission, UK study	
		PFS in mBC *Patient treated for mBC and currently progression-free*	0.72–0.77	NICE TA495 (December 2017): Palbociclib + aromatase inhibitor (PALOMA-1 & 2)[16]	HR+/HER2- locally advanced or metastatic BC as initial endocrine-based treatment	
			0.726	NICE TA639 (July 2020): Atezolizumab with nab-paclitaxel (IMpassion130)[17]	Unresectable, locally advanced or metastatic TNBC with PD-L1 ≥1% and no prior ChT for mBC	
		Footnotes: [a]In some cases, slightly different utility values were used for patients on and off treatment – in these cases, the off-treatment values are presented here to represent the long-term; [b]This appraisal uses				

different values for the first year and beyond the first year. The value presented here is for beyond the first year.
Abbreviations: BC: breast cancer; ChT; chemotherapy; DCO: data cut-off; eBC: early breast cancer; HER2: human epidermal growth factor 2; HR: hormone receptor; iDFS: invasive disease-free survival; IV: intravenous; mBC: metastatic breast cancer; NICE: National Institute for Health and Care Excellence; PFS: progression-free survival; TA: technology appraisal; TNBC: triple negative breast cancer; UK: United Kingdom.

Therefore, we firmly believe that the **utility values applied in the company's base-case analysis represent a set of estimates that better reflect the HRQoL** of patients for the specific indication addressed in this appraisal. However, we also accept that there is uncertainty regarding the most appropriate choice of mapping algorithm to utilise, and that the approach adopted in the company's base-case analysis resulted in the highest possible utility value for the DF state. Therefore, to mitigate against this uncertainty, we have selected the HSUV for the DF state from the Gray et al. (2021) mapping algorithm[8] (0.815) in an additional scenario analysis, which represents a significant reduction in the utility value that is applied in this health state. It should however be noted that this utility estimate is likely still highly conservative considering the feedback from KEEs that the HRQoL of eBC patients who remain disease-free will eventually become similar to the age-matched general population over time. Furthermore, KEEs also commented that TNBC patients who are and remain DF are generally in better health than those with HR+/HER2- disease, simply because they do not receive long-term endocrine therapy which may impact their HRQoL. The DF HSUV for these patients should therefore realistically be higher as well. For this reason, we have provided another scenario analysis choosing a midpoint HSUV for the DF state of 0.842 ([0.869-0.815]/2) to reflect this feedback and to further support the committee's decision-making. The cost-effectiveness results from both scenario analyses are presented in Table 2-3.

Table 2-3: Additional DF HSUV scenario analysis results (discounted)

	HSUV DF state	ICER TNBC	ICER HR+/HER2-

estimates are therefore superior to Lidgren's.

Estimates from PFS in mBC from previous NICE TAs are based on older estimates appraising a different technology. They are not too dissimilar to our estimates (0.67 in base case, 0.70 in sensitivity analysis).

The EAG stands by our base-case assumptions. Verrill's estimates may be overvalued due to the BC type being HER+ and not HER- as for the Olaparib population, which favours the Olaparib arm in this appraisal. They may be undervalued due to the average older population. We have therefore estimated an average impact of the age increment in the utility value and re-estimated the ICERs accordingly in sensitivity analyses.

Our new utility estimates in sensitivity analysis are:

		Base-case (Crott & Briggs, 2010)	0.869	£35,855	£41,879	iDFS: 0.7695, up from 0.732 previously; Non-mBC: 0.7017, up from 0.6675 mBC: 0.6339, up from 0.603. Our sensitivity analyses ICERs changed from **£46,549** (base case) **to £44,272 for TNBC** and **from £64,773** (base case) **to £61,603 for HR+/HER-.** We note that these **scenarios are optimistic**, as the utility estimates do not account for the decrease in HRQoL experienced by the HER- population, compared with the HER+ population in Verrill's estimates. Additional scenarios using the above utilities but excluding BRCA testing costs for HR+/HER2-, and using Gray et al. 2021 mapping and midpoint approach for DF, are also presented in **Table 1** of the "TE EAG Additional scenario results" document.
		Scenario analysis 1 (Gray et al., 2021)	0.815	£38,324	£44,780	
		Scenario analysis 2 (midpoint approach)	0.842	£36,910	£43,127	
		Footnotes: Please note that in both scenario analyses we have kept the HSUV for the metastatic states as 0.685 taken from Lidgren et al. (2007)[15] and the HSUV for the locoregional health state as the midpoint between the DF and metastatic HSUVs (0.75 and 0.7635 for scenario analysis 1 and 2 respectively). **Abbreviations:** DF: disease-free; HER2: human epidermal growth factor receptor 2; HR: hormone receptor; HSUV: health state utility value; ICER: incremental cost-effectiveness ratio; TNBC: triple negative breast cancer.				
Issue 3: HRQoL	Yes	Please see our response to Key Issue 2 above.				NA

<table>
<tr><td>measures used in the economic model</td><td></td><td></td><td></td></tr>
<tr><td>Issue 4: Access to BCRA testing in HR+/HER 2 population</td><td>Yes</td><td>Overarching comment on BRCA testing:
The EAG highlight that BRCA testing is currently limited to only a proportion of the HR+/HER2- population, based on the current testing eligibility criteria laid out in the National Genomic Test Directory (NGTD). However, we contend that the vast majority of HR+/HER2- patients who are potentially eligible for olaparib in this indication, would already be identified if current testing criteria were uniformly implemented in clinical practice, particularly given the expansion of these criteria which occurred in April 2022. This is because the OlympiA trial exclusively recruited patients at high risk of recurrence, and many of the prognostic factors associated with an increased risk of recurrence overlap with those associated with an increased risk of testing positive for a BRCA mutation.

To illustrate this point, an analysis of current NGTD BRCA testing criteria, compared to the demographic data of the HR+/HER2- subgroup in the OlympiA trial is provided in Table 2-4.

Table 2-4: Comparison of NGTD BRCA testing criteria with OlympiA HR+/HER2- subgroup
<table>
<tr><th>NGTD criteria[18]</th><th>Relevant demographic data from the of the Olymp trial[19]</th></tr>
<tr><td>Breast cancer (age <40 years, excluding grade 1 breast cancers)</td><td>Median age was [redacted] years, and [redacted] of patients were under the age of 40.</td></tr>
</table></td><td>We thank the company for providing additional data.

Without knowing about overlap between categories (e.g., how many of the men were also age<40), we do not consider it possible to say what proportion of those eligible for olaparib would also be eligible for BRCA testing.

We also sought further input from our clinical advisers. Although they agreed that OlympiA would likely represent the HR+/HER2- target population, they were quite conservative about the proportion who would be eligible for BRCA testing under NGTD criteria. They indicated that <10-20% of the NGTD population would harbour a BRCA1 or 2 mutation and then there would be a significant proportion of these that would not have significantly high enough risk</td></tr>
</table>

		Bilateral breast cancer (age <50 years)	[redacted] of patients who received neoadjuvant chemotherapy had bilateral disease, as well as [redacted] of those who received adjuvant chemotherapy.	clinicopathologic factors to be eligible. Clinical expert adviser Stuart McIntosh stated that BRCA testing is only routinely available for TNBC, as per the current version of the Genomic Test Directory (v 4.0 May 2022). He indicated that BRCA testing will increase in the HR+/HER2- population but agreed that it was not currently done for all patients with HR+/HER2- breast cancer. Given uncertainty around eligibility and the proportion eligible, we therefore consider our base case of including BRCA testing for this population in the model to be appropriate. We have provided a scenario with no BRCA testing under HR+/HER2- (ICER £57,443/QALY) and different proportions would give ICERs between the base case ICER (£64,773/QALY) and this scenario.
		Male breast cancer (any age)	[redacted] of patients were male.	
		Breast cancer (age <45 years) and a first degree relative with breast cancer (age <45 years)	Although family history was not analysed specifically in the HR+/HER2- subgroup, this was reported in the full analysis set. A high proportion of patients had a 1st degree relative with breast cancer diagnosed under the age of 50 ([redacted] and [redacted] had an affected female relative in the olaparib and placebo arms, respectively).	
		Pathology-adjusted Manchester score ≥15 or CanRisk score ≥10%	This is unknown as Manchester score and CanRisk score were not specifically recorded. However, these scales are strongly influenced by factors such as family history, and tumour pathology (e.g., grade 3 disease in the Manchester score).[20, 21] • Grade: [redacted] of patients who received neoadjuvant chemotherapy, and [redacted] of those who received adjuvant chemotherapy had histological grade 3 disease. • Family history: a significant proportion of patients have a positive family history of either breast and / or ovarian cancer (see Appendix B, Table B4 for details).	
		Ashkenazi Jewish ancestry and breast cancer at any age	[redacted] of patients had Ashkenazi Jewish ancestry.	
		Footnotes: Full demographic data are presented in Appendix B. **Abbreviations**: BRCA: breast cancer susceptibility gene; HER2: human epidermal growth factor 2; HR: hormone receptor; NGTD: National Genomic Test Directory.		

		Therefore, if the existing NGTD criteria were uniformly implemented in clinical practice, a substantial majority of the relevant HR+/HER2- patients would already be identified. However, AstraZeneca understand that in current clinical practice many such patients may not be tested despite meeting the NGTD eligibility criteria, as clinicians feel that there is limited clinical value in knowing the *BRCA* status of such patients when there are currently no targeted treatments available. However, it is anticipated that testing rates would increase after the launch of olaparib in this indication, as we anticipate a move towards a test-to-treat mindset in the clinical community. Furthermore, broader genetic testing is expected in the coming years given the evolving NHS policy landscape and wider NHS objectives, including a move towards improved outcomes through personalised medicine,[22, 23] and an ambition to be the world's most advanced genomic healthcare ecosystem via the Genome UK strategy.[24] Section 4.4.15 of the NICE methods guide states that consideration should be given for situations where there is an established plan to change practice or service delivery in the NHS, and where introducing the new technology will lead to identifiable benefits that are not captured in health technology evaluations.[25] Both such considerations apply to *BRCA* testing, particularly considering the wider familial benefits of identifying *BRCA* mutations, and the potential to optimise surgical approach for affected patients, which are not captured in our economic evaluation. **Response to EAG proposed model updates:** Given the above, and reiterating the fact that *BRCA* testing provides additional benefits to a patient beyond just determining eligibility for *BRCA* targeted therapy (e.g., impacting choice of surgical approach, as well as informing familial testing and risk-reducing strategies), AstraZeneca maintain that it is inappropriate to include the cost of *BRCA* testing in the base case for the HR+/HER2- subgroup. As such, testing costs are included in scenario analyses only.	

3 Additional issues

All: Please use the table below to respond to additional issues in the EAG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (for example, at the clarification stage).

Table 3: Additional issues from the EAG report

Issue from the EAG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response	EAG response
Additional issue 1: The EAG's suggestion to use an alternative distribution for recurrence in the HR+/HER2- subgroup analysis	Sections 1.4 (The Clinical and Cost-Effectiveness Evidence: Summary of the EAG's Key Issues) and 4.2.6 (Treatment Effectiveness and Extrapolation)	No	In Section 4.2.6 of the EAG report, the suggestion is made to apply the generalised gamma instead of the lognormal distribution to extrapolate DFS for patients in the HR+/HER2- analysis; this is on the basis that the generalised gamma indirectly incorporates a conservative waning of the treatment effect at 5.4 years (vs 14.5 years with the lognormal function). However, we would like to argue that: 1. Although we acknowledge that both distributions have very similar AIC/BIC and long-term extrapolations, the lognormal was consistently selected as the preferred parametric model by UK KEEs considering it generates slightly more pessimistic 10- and 20-year iDFS estimates ([redacted] and [redacted]) vs the generalised gamma ([redacted] and [redacted]), which was argued to better reflect the continuing long-term	Thank you for further considering the uncertainty around the recurrence distribution in the HR+/HER2- population. Regarding point 1, we note that the percentages quoted do not match Table 29 of Doc B placebo or Olaparib, nor do they match the percentages in EAG Report Table 14. EAG Report Table 14 was generated using the economic model and thus incorporating the assumptions that hazard on Olaparib is never higher

			risk of recurrence and thus survival outcomes of patients with HR+/HER2- disease. 2. Furthermore, there is no precedent from other eBC NICE appraisals (TA632, TA612, TA810)[1, 9, 13] or historical trial data in eBC to assume a treatment waning effect of <7.5 years. For example, the 10-year follow-up data from the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial in HR+ eBC patients showed a continuing level of treatment effect beyond 8 years.[26] Although we acknowledge the differing mechanism of action of endocrine therapy or the technologies in the appraisals above vs PARP inhibitors, the lasting treatment effect which has been observed and accepted in these appraisals indicates the existence of a lasting treatment effect in eBC that is not derived from one specific mechanism of action and is independent of the specific treatment received. For these reasons, we disagree with the EAG's suggestion to select the generalised gamma distribution for the iDFS extrapolations; however, to address the inherent uncertainty about long-term treatment effects, we have provided two additional scenario analyses with the base-case lognormal distribution, applying a treatment waning effect at 7.5 and 10 years (Table 3-1).	than hazard on placebo. Using these, the iDFS for placebo were lower at 10 and 20 years for lognormal ([redacted] and [redacted]) than on generalised gamma ([redacted] and [redacted]). Conversely, iDFS for Olaparib is lowest at 10 and 20 years for generalised gamma ([redacted] and [redacted]) rather than lognormal ([redacted] and [redacted]). This is therefore mixed and not a reason to choose lognormal or generalised gamma. We instead maintain that generalised gamma is the most conservative option as it gives smallest difference in long-term iDFS used in the model (EAG Report Table 14), and because of the earlier treatment effect waning at 5.4 years rather than 14.5 years. Our response to point 2 is that ATAC is an endocrine therapy, Trastuzumab

Table 3-1: Treatment waning scenario analysis results (discounted, HR+/HER2- analysis)

Scenario	ICER HR+/HER2-
Base-case analysis: TP1/2 distribution: lognormal	£41,879
TP1/2 distribution: lognormal with a 7.5 years waning of the treatment effect of olaparib	£42,211
TP1/2 distribution: lognormal with a 10 years waning of the treatment effect of olaparib	£43,075

Abbreviations: HR: hormone receptor; HER2: human epidermal growth factor receptor 2; ICER: incremental cost-effectiveness ratio; TP: transition probability.

emtansine a monoclonal antibody (TA632), Neratinib a tyrosine kinase inhibitor (TA612), and abemaciclib a CDK inhibitor selective for CDK4 and CDK6 (TA810); they therefore do not give evidence on the long-term efficacy of the PARP inhibitor Olaparib. We confirmed this assessment with our clinical advisors.

We could not reproduce the scenario analyses provided by the company and the results lack face validity. In the base case, if using a lognormal curve, the placebo and Olaparib curves cross at 14.5 years, after which the hazards are assumed to be the same. Setting hazards to be equal at 7.5 years and 10 years should give higher ICERs, and the 7.5 year scenario should have the greatest ICER. This is the opposite

				of what the company found, and thus lacks face validity. We instead ran a scenario using a lognormal instead of generalised gamma for HR+/HER2- in our EAG base case. In the two scenarios, we set the hazards for Olaparib and placebo to be equal from 10 and 7.5 years. We repeated these for the company base case. Results are presented in the table below. **Table 2 Treatment waning scenario analysis results (discounted, HR+/HER2- analysis)**

Model for recurrence (TP1/TP2 for both Olaparib and placebo)	ICER HR+/HER2-

				EAG Base case	£64,773
				EAG with lognormal (waning at 14.5 years)	£58,204
				EAG with lognormal for recurrence (waning at 10 years)	£58,654
				EAG with lognormal (waning at 7.5 years)	£59,848
				Company Base case (lognormal, waning at 14.5 years)	£41,879
				Company with lognormal (waning at 10 years)	£42,195
				Company with lognormal (waning at 7.5 years)	£43,030

Additional issue 2: Innovation	Section 7 – Severity and Innovation.	No	The EAG report states that the company is "not making a case for severity or innovation". Although we have not requested formal consideration within our cost-effectiveness model relating to severity or innovation, we would nonetheless consider olaparib to be innovative in the eBC setting, considering both a broader clinical definition of innovation, as well as the narrow definition of innovation referred to in Section 2.2.24 of the NICE process and methods manual,[25] which focusses on the potential for health-related benefits which are unlikely to be captured in the economic model. Olaparib represents the first personalised treatment option for HR+/HER2- eBC patients with a *BRCA* mutation, targeting the underlying genetic driver of their disease to deliver a statistically significant and clinically meaningful OS benefit.[2] This is a remarkable outcome in this treatment setting. Furthermore, there are wider benefits of introducing olaparib in the eBC setting which are not captured in our economic model. Specifically, a move towards more personalised treatment of eBC patients, and a greater focus on the genetic drivers of disease may drive more consistent application of the NGTD *BRCA*	

			testing criteria, and thus more frequent identification of such mutations. Family members of affected patients will benefit from early identification via cascade testing, potential risk-reducing interventions, and genetic counselling, all of which may ultimately reduce the incidence of breast, ovarian, and prostate cancers in affected families.	
Additional issue 3: Considering the application of a 1.5% discount rate	Section 4.2.5 – Perspective, Time Horizon, and Discounting	No	The EAG conclude in their report that a discount rate of 3.5% is most appropriate for olaparib in the OlympiA indication, citing immaturity of the clinical trial results. We acknowledge that this conclusion may be true for the HR+/HER2- subgroup; however, we argue that the TNBC population clearly supports application of the lower 1.5% discount based on the criteria outlined in the Methods Guide. Therefore although we maintain the 3.5% value in our base-case, we defend the relevance of a scenario analysis using the 1.5% rate for the TNBC population, as presented in Table 3-3. In the NICE process and methods manual (Section 4.5),[25] non-reference-case discounting at a 1.5% rate may be considered by the committee if all three of the following criteria are met: • Criteria 1: The technology is for people who would otherwise die or have a very severely impaired life. • Criteria 2: It is likely to restore them to full or near-full health.	As we commented in Section 4.2.5 of our report, the clinical trial data are too immature to justify the use of 1.5% discounting. The ITT data are only 18.6% mature (341 events/1,836 patients) while TNBC are 18.7% mature (282 events/1509 patients). This is insufficient to be confident that Olaparib will restore patients to full health (Criteria 2) or that its benefits will be sustained over a very long period (Criteria 3). The second of these (Criteria 3) is particularly difficult to justify.

			• Criteria 3: The benefits are likely to be sustained over a very long period. Criteria 1 is true for a significant proportion of the high-risk g*BRCA*m TNBC patients in the OlympiA trial who, without olaparib therapy, would experience a distant recurrence and progress to metastatic disease. The 5-year survival rate of women with mBC in England (at diagnosis) is only 26.2%.[27] Criteria 2 is also true for such patients; patients who do not experience a recurrence would be expected to eventually regain a similar functional status and HRQoL as they had before their breast cancer diagnosis. This is particularly true when considering the long-term picture for such patients, once they have fully recovered from surgery, completed all endocrine therapy, and mentally recovered from the shock and anxiety associated with a breast cancer diagnosis. Criteria 3 is also true for many patients. Clinical experts have stated that the risk of recurrence progressively falls as patients remain disease-free for longer, and that this effect is particularly pronounced in TNBC patients.[28, 29] Therefore avoiding recurrence in the years immediately following treatment of their primary breast cancer is expected to result in long-term cure for some patients. Finally, we would like to highlight that during the NICE methods review process, it was concluded that the	

<table>
<tr>
<td></td>
<td></td>
<td></td>
<td>evidence suggests there is a case to change the reference-case discount rate to 1.5%, but that this was not implemented. Given this conclusion, we feel that it is appropriate to consider the 1.5% discount rate as a non-reference case analysis for this appraisal for the TNBC subgroup; the results of such an analysis are presented in Table 3-3.

Table 3-3: Discount rate scenario analysis
<table>
<tr><th>Scenario</th><th>ICER TNBC</th></tr>
<tr><td>Base-case: discount rate 3.5%</td><td>£35,855</td></tr>
<tr><td>Scenario analysis: discount rate 1.5%</td><td>£25,287</td></tr>
</table>
Abbreviations: HER2: human epidermal growth factor receptor 2; HR: hormone receptor; ICER: incremental cost-effectiveness ratio; TNBC: triple negative breast cancer.</td>
<td></td>
</tr>
</table>

4 Summary of changes to the company's cost-effectiveness estimate(s)

: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Technical engagement response form

Table 4: Changes to the company's cost-effectiveness estimate

Key issue(s) in the EAG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
N/A – no changes made to base case	N/A – no changes made to base case	N/A – no changes made to base case	N/A – no changes made to base case

Sensitivity analyses around revised base case

N/A – no changes made to base case

5 References

1. NICE. TA810: Abemaciclib with endocrine therapy for adjuvant treatment of hormone receptor-positive, HER2-negative, node-positive early breast cancer at high risk of recurrence. 2022. Available from: (accessed 16/08/2022).
2. AstraZeneca Data on File. OlympiA Efficacy Analysis (DCO2). 2022.
3. AstraZeneca Data on File. OlympiA Clinical Study Report. 2021.
4. Verrill M, Wardley AM, Retzler J, et al. Health-related quality of life and work productivity in UK patients with HER2-positive breast cancer: a cross-sectional study evaluating the relationships between disease and treatment stage. Health Qual Life Outcomes 2020;18:353.
5. AstraZeneca Data on File. OlympiA PRO Analysis (DCO2). 2022.
6. Longworth L, Yang Y, Young T, et al. Use of generic and condition-specific measures of health-related quality of life in NICE decision-making: a systematic review, statistical modelling and survey. Health Technol Assess 2014;18:1-224.
7. Crott R, Briggs A. Mapping the QLQ-C30 quality of life cancer questionnaire to EQ-5D patient preferences. Eur J Health Econ 2010;11:427-34.
8. Gray LA, Hernandez Alava M, Wailoo AJ. Mapping the EORTC QLQ-C30 to EQ-5D-3L in patients with breast cancer. BMC cancer 2021;21:1-10.
9. NICE. TA632: Trastuzumab emtansine for adjuvant treatment of HER2-positive early breast cancer [ID1516]. Committee Papers. 2020. Available at: (accessed 31/05/2022).
10. NICE. TA424: Pertuzumab for the neoadjuvant treatment of HER2-positive breast cancer [ID767]. Committee Papers. 2016. Available at: (accessed 31/05/2022).
11. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. Value Health 2010;13:509-18.
12. Criscitiello C, Spurden D, Piercy J, et al. Health-Related Quality of Life Among Patients With HR+/HER2- Early Breast Cancer. Clin Ther 2021;43:1228-1244.e4.
13. NICE. TA612: Neratinib for extended adjuvant treatment of hormone receptor-positive, HER2-positive early stage breast cancer after adjuvant trastuzumab [ID981]. Committee Papers. 2019. Available at: (accessed 31/05/2022).
14. NICE. TA569: Pertuzumab for adjuvant treatment of HER2-positive early breast cancer [ID1192]. Committee Papers. 2018. Available at: (accessed 31/05/2022).
15. Lidgren M, Wilking N, Jönsson B, et al. Health related quality of life in different states of breast cancer. Quality of life research 2007;16:1073-1081.
16. NICE. TA495: Palbociclib with an aromatase inhibitor for previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer. 2017. Available at: (accessed 16/08/2022).
17. NICE. TA639: Atezolizumab with nab-paclitaxel for untreated PD-L1-positive, locally advanced or metastatic, triple-negative breast cancer. 2020. Available at: (accessed 09/02/2022).
18. NHS England. National Genomic Test Directory. Available at: (accessed 06/01/2022), 2021.
19. AstraZeneca Data on File. OlympiA Clinical Study Report (Supplementary Materials 1). 2021.
20. Evans DG, Harkness EF, Plaskocinska I, et al. Pathology update to the Manchester Scoring System based on testing in over 4000 families. Journal of Medical Genetics 2017;54:674-681.

21. CanRisk Knowledgebase. When calculating mutation carrier probabilities, which input data/parameters most strongly influence the resulting probabilities? Available at: . Accessed: 16/08/2022. 2021.
22. NHS. The NHS Long Term Plan. 2019.
23. NHS. Improving Outcomes Through Personalised Medicine. Available at: (accessed 06/03/2022). 2016.
24. UK Government. Genome UK: The Future of Healthcare. Available at: (accessed 12/01/2022). 2020.
25. NICE. PMG36. NICE health technology evaluations: the manual. 2022. Available at: (accessed 12/04/2022).
26. Cuzick, J., et al. (2010). "Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 10-year analysis of the ATAC trial." **11**(12): 1135-1141.
27. Cancer Research UK. Breast cancer survival statistics. Available from: (accessed 12/03/2022), 2021.
28. AstraZeneca Data on File. Early breast cancer clinical interviews March 2022 (Data on File Number: GB-35540). 2022.
29. AstraZeneca Data on File. Early breast cancer clinical interviews December 2021 (Data on File Number: GB-35535). 2022.

6 Appendices

Appendix A OlympiA HRQoL questionnaires longitudinal response rates

Tables A1 and A2 present an overview of the OlympiA HRQoL questionnaire response rates and OlympiA EORTC-QLC-C30 scores overtime, respectively.

Table A1: Status of HRQoL questionnaires received by treatment group and visit (PRO analysis set)

	Olaparib 300 mg bd (N=876)			Placebo (N=875)		
	Forms expected, n[a]	Forms received	Expected forms received, %	Forms expected, n[a]	Forms received, n	Expected forms received, %
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: DCO2: 12 July 2021. [a]Form is expected for all visits for all patients who complete baseline questionnaire and initiate study medication. Once patients experience a disease recurrence or a second primary cancer they are not expected to continue with the PRO assessments.
Abbreviations: bd: twice daily; DCO: data cut-off; HRQoL: health-related quality of life; PRO: patient-reported outcome.
Source: AstraZeneca Data on File (OlympiA DCO2: PRO Analyses).[5]

Table A2: Summary of EORTC QLQ-C30 scores in OlympiA (PRO analysis set; DCO2)

	Olaparib (N=876)			Placebo (N=875)		
	n	Mean (SD)	Median	n	Mean (SD)	Median
Patients with prior neoadjuvant treatment (olaparib: n=440; placebo: n=435)						
EORTC QLQ-C30 Global Health Status QoL						
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Olaparib (N=876)			Placebo (N=875)		
	n	Mean (SD)	Median	n	Mean (SD)	Median
Change from Baseline to 6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from Baseline to 12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from Baseline to 18 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from Baseline to 24 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EORTC QLQ-C30 Nausea and Vomiting Symptom Scale						
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from Baseline to 6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from Baseline to 12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from Baseline to 18 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from Baseline to 24 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EORTC QLQ-C30 Diarrhoea Symptom Scale						
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from Baseline to 6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from Baseline to 12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from Baseline to 18 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from Baseline to 24 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients with prior adjuvant treatment (olaparib: n=436; placebo: n=440)						
EORTC QLQ-C30 Global Health Status QoL						
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Olaparib (N=876)			Placebo (N=875)		
	n	Mean (SD)	Median	n	Mean (SD)	Median
Change from Baseline to 6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from Baseline to 12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from Baseline to 18 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from Baseline to 24 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EORTC QLQ-C30 Nausea and Vomiting Symptom Scale						
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from Baseline to 6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from Baseline to 12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from Baseline to 18 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from Baseline to 24 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EORTC QLQ-C30 Diarrhoea Symptom Scale						
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from Baseline to 6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from Baseline to 12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from Baseline to 18 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change from Baseline to 24 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: DCO2: 12 July 2021. All EORTC QLQ-C30 scales range in score from 0 to 100. Higher score indicates better QoL/functioning or worse symptom severity.
Abbreviations: DCO: data cut-off; EORTC QLQ-30: European Organisation for Research and Treatment of Cancer quality of life questionnaire; PRO: patient reported outcome; SD: standard deviation; QoL: quality of life.
Source: AstraZeneca Data on File (OlympiA DCO2: PRO Analyses).[5]

Appendix B Demographic and baseline patient characteristics for the OlympiA HR+/HER2- subgroup

Tables B1, B2, B3 and B4 present demographic and baseline patient characteristics for the OlympiA HR+/HER2- subgroup (DCO1; 27 March 2020), and are limited to those characteristics which are considered relevant to the EAG Key Issue 4 relating to eligibility for BRCA testing.

Table B1: Demographic characteristics for HR+/HER2- patients (DCO1; full analysis set)

	Olaparib 300 mg bd (N=168)	Placebo (N=157)	Overall (N=325)
Age (years)[a]			
Mean	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Min	[redacted]	[redacted]	[redacted]
Max	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]
Age groups			
<30 years	[redacted]	[redacted]	[redacted]
30-39 years	[redacted]	[redacted]	[redacted]
40-49 years	[redacted]	[redacted]	[redacted]
50-59 years	[redacted]	[redacted]	[redacted]
60-69 years	[redacted]	[redacted]	[redacted]
≥70 years	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]

Sex			
Female	[redacted]	[redacted]	[redacted]
Male	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]
Ashkenazi Jewish descent			
Ashkenazi Jewish	[redacted]	[redacted]	[redacted]
Not Ashkenazi Jewish[b]	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]

Footnotes: DCO1: 27 March 2020. [a]Age is calculated as the patient's age at randomisation; [b]Not Ashkenazi Jewish can mean that the patient is either Jewish but not Ashkenazi Jewish, not Jewish or descent recorded as unknown.
Abbreviations: bd: twice daily; DCO: data cut-off; G: Grade; HER2: human epidermal growth factor 2; HR: hormone receptor; SD: standard deviation.
Source: AstraZeneca Data on File (OlympiA CSR [Supplementary Materials 1]).[19]

Table B2: Pathological characteristics of primary breast cancer at baseline for HR+/HER2- patients who received neoadjuvant chemotherapy (DCO1; full analysis set)

	Olaparib 300 mg bd (N=104)	Placebo (N=92)	Overall (N=196)
Bilateral invasive breast cancer			
No	[redacted]	[redacted]	[redacted]
Yes	[redacted]	[redacted]	[redacted]
Histological grade			
Gx: Cannot be assessed/not done	[redacted]	[redacted]	[redacted]
G1: Well differentiated	[redacted]	[redacted]	[redacted]
G2: Moderately differentiated	[redacted]	[redacted]	[redacted]
G3: Poorly differentiated/undifferentiated	[redacted]	[redacted]	[redacted]

Not done	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]
Nuclear grade			
Gx: Cannot be assessed/not done	[redacted]	[redacted]	[redacted]
G1: Well differentiated	[redacted]	[redacted]	[redacted]
G2: Moderately differentiated	[redacted]	[redacted]	[redacted]
G3: Poorly differentiated/undifferentiated	[redacted]	[redacted]	[redacted]
Not done	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]

Footnotes: DCO1: 27 March 2020.
Abbreviations: bd: twice daily; DCO: data cut-off; G: Grade; HER2: human epidermal growth factor 2; HR: hormone receptor.
Source: AstraZeneca Data on File (OlympiA CSR [Supplementary Materials 1]).[19]

Table B3: Pathological characteristics of primary breast cancer at baseline for HR+/HER2- patients who received adjuvant chemotherapy (DCO1; full analysis set)

	Olaparib 300 mg bd (N=64)	Placebo (N=65)	Overall (N=129)
Bilateral invasive breast cancer			
No	[redacted]	[redacted]	[redacted]
Yes	[redacted]	[redacted]	[redacted]
Histological grade			
Gx: Cannot be assessed/not done	[redacted]	[redacted]	[redacted]
G1: Well differentiated	[redacted]	[redacted]	[redacted]
G2: Moderately differentiated	[redacted]	[redacted]	[redacted]
G3: Poorly differentiated/undifferentiated	[redacted]	[redacted]	[redacted]

Not done	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]
Nuclear grade			
Gx: Cannot be assessed/not done	[redacted]	[redacted]	[redacted]
G1: Well differentiated	[redacted]	[redacted]	[redacted]
G2: Moderately differentiated	[redacted]	[redacted]	[redacted]
G3: Poorly differentiated/undifferentiated	[redacted]	[redacted]	[redacted]
Not done	[redacted]	[redacted]	[redacted]
Missing	[redacted]	[redacted]	[redacted]

Footnotes: DCO1: 27 March 2020.
Abbreviations: Data cut-off; G: Grade; HER2: human epidermal growth factor 2; HR: hormone receptor.
Source: AstraZeneca Data on File (OlympiA CSR [Supplementary Materials 1]).[19]

Table B4: Family history of cancer (DCO1; full analysis set)[a]

Treatment Group	Sex of relative	Age group of relative	Breast		Ovarian		Other	
			1st degree relative	2nd degree relative	1st degree relative	2nd degree relative	1st degree relative	2nd degree relative
Olaparib 300 mg bd (N=921)	Male	≤50 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		>50 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Any	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Female	≤50 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		>50 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Any	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Male	≤50 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Placebo (N=915)		>50 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Any	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Female	≤50 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		>50 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Any	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Footnotes: DCO1: 27 March 2020. [a]A patient can have more than one relative in any age or indication category under a given degree of relatedness. However, the patient will only be counted once in each category. The denominator for the percentages is the number of patients in the full analysis set in each treatment group.
Abbreviations: bd: twice daily; DCO: data cut-off.
Source: AstraZeneca Data on File (OlympiA CSR [Supplementary Materials 1]).[19]

Appendix C OlympiA mapping analysis using the Gray et al. (2021) algorithm

Table C1 presents the summary statistics for the mapped HSU values using the Gray et al. (2021) algorithm by arm and study period based on the OlympiA DCO2 data.

Table C1: Summary statistics for the mapped HSU values using the Gray et al. (2021) algorithm by arm and study period (OlympiA DCO2 data)

Time period	Arm	n	Mean	SD	Median	Min	Max
All visits	Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	All	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline	Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	All	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-recurrence	Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	All	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Post-recurrence	Olaparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	All	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: DCO: data cut-off; HSUV: health state utility; SD: standard deviation.

Table 1 Scenarios with alternative utility assumptions

	HSUV for states	ICER TNBC	ICER HR+/HER2-
EAG Base-case (Verrill et al. 2020)	DF: 0.732 Non-mBC: 0.6675 mBC: 0.603	£46,549	£64,773
EAG Scenario analysis 1 (Verrill et al. 2020 decremented for DF and mBC, mid-point for non-mBC)	DF: 0.7695 Non-mBC: 0.7017 mBC: 0.6339	£44,272	£61,603
EAG Scenario analysis 2 (Verrill et al. 2020 decremented for DF and mBC, mid-point for non-mBC, no BRCA costs)	DF: 0.7695 Non-mBC: 0.7017 mBC: 0.6339	NA	£54,631
EAG Scenario analysis 3 (Gray et al., 2021 for DF, mid-point for non-mBC, Verrill et al. for mBC)	DF: 0.815 Non-mBC: 0.709 mBC: 0.603	£40,995	£56,988
EAG Scenario analysis 4 (midpoint approach for DF, mid-point for non-mBC, Verrill et al. for mBC)	DF: 0.842 Non-mBC: 0.7225 mBC: 0.603	£39,463	£54,844

Table 2 Treatment waning scenario analysis results (discounted, HR+/HER2- analysis)

Model for recurrence (TP1/TP2 for both Olaparib and placebo)	ICER HR+/HER2-
EAG Base case	£64,773
EAG with lognormal (waning at 14.5 years)	£58,203.67
EAG with lognormal for recurrence (waning at 10 years)	£58,654
EAG with lognormal (waning at 7.5 years)	£59,848
Company Base case (lognormal, waning at 14.5 years)	£41,879
Company with lognormal (waning at 10 years)	£42,195
Company with lognormal (waning at 7.5 years)	£43,030