NICE National Institute for Health and Care Excellence

Cost Comparison Appraisal

Olaparib for treating BRCA mutation-positive HER2-negative advanced breast cancer after chemotherapy [ID6336]

Committee Papers

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

COST COMPARISON APPRAISAL

Olaparib for treating BRCA mutation-positive HER2-negative advanced breast cancer after chemotherapy [ID6336]

This is a review of terminated guidance TA762

Contents:

The following documents are made available to stakeholders:

Access the **final scope and final stakeholder list** on the NICE website.

1. **Company submission** from AstraZeneca:
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**

3. **Patient group, professional group, and NHS organisation submission** from:
   a. Breast Cancer Now

4. **External Assessment Report** prepared by ScHARR

5. **External Assessment Group response to factual accuracy check of EAR**

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

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal: cost comparison

Olaparib for treatment of *BRCA* mutation-positive HER2-negative metastatic breast cancer (Review of TA762)

ID3663

Document B

Company evidence submission

June 2024

File name	Version	Contains confidential information	Date
ID6336_Olaparib aBC_Document B_[Redacted]	Final	Yes	3rd June 2024

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Abbreviations

Abbreviation	Definition
AE	Adverse event
AIC	Akaike information criterion
BC	Breast cancer
Bd	Twice daily
BIC	Bayesian information criterion
BICR	Blinded independent central review
BID	Twice daily
BNF	British National Formulary
BoR	Best overall RECIST response
BRCA	Breast cancer susceptibility gene
CDH1	Cadherin-1
CDK4/6	Cyclin-dependent kinase 4 and 6
CHEK2	Checkpoint kinase 2
CI	Confidence interval
CR	Complete response
CRD	Centre for Reviews and Dissemination
CrI	Credible interval
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTSQ	Cancer Therapy Satisfaction Questionnaire
DCO	Data cut-off
DES	Diethylstilbesterol
DNA	Deoxyribonucleic acid
DoR	Duration of response
DSA	Deterministic sensitivity analysis
DSB	Double-stranded break
EAG	External Assessment Group
ECG	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
EFR	Evaluable for response
EMA	European Medicines Agency
eMIT	Electronic market information tool
EORTC	European Organisation for Research and Treatment of Cancer
EORTC QLQ-BR23	Breast cancer specific EORTC Quality of Life Questionnaire
EORTC QLQ-C30	EORTC Core Quality of Life questionnaire
ER+	Oestrogen receptor positive
ESMO	European Society for Medical Oncology
FAS	Full analysis set

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FIGO	International Federation of Gynaecology and Obstetrics
g*BRCA*m	Germline *BRCA1* and *BRCA2* mutations
GI	Gastrointestinal
HER2+/−	Human epidermal growth factor receptor 2 positive/negative
HR	Hazard ratio
HR+/−	Hormone receptor positive/negative
HRD	Homologous recombination deficient
HRQoL	Heath-related quality of life
HRR	Homologous recombination repair
HRT	Hormone replacement therapy
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
IQR	Interquartile range
IRF	Independent radiology facility
ITC	Indirect treatment comparison
ITT	Intention to treat
IV	Intravenous
KM	Kaplan–Meier
mBC	Metastatic breast cancer
mCRPC	Metastatic castration-resistant prostate cancer
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intention-to-treat
MRI	Magnetic resonance imaging
MTP	Multiple testing procedure
N	Number of patients in treatment group
NAD	Nicotinamide adenine dinucleotide
NCCN	National Comprehensive Cancer Network
NG	NICE Guideline
NGTD	National Genomic Test Directory
NHS	National Health Service
NICE	National Institute of Health and Care Excellence
NOS	Not otherwise specified
OS	Overall survival
ORR	Objective response rate
PALB2	Partner and localizer of the *BRCA* gene 2
PARP	Poly (ADP ribose) polymerase
PD	Progressive disease
PD-L1	Programmed cell death ligand 1
PET-CT	Positron emission tomography fused with computed tomography
PF	Progression-free
PFS	Progression-free survival

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PFS2	Time from randomisation to a second progression event or death after a first progression event
PH	Proportional hazards
PIK3CA	Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha
PK	Pharmacokinetics
PR	Partial response
PRISMA	Preferred reporting items for systematic reviews and meta-analysis
PSS	Personal Social Services
PTEN	Phosphatase and tensin homolog
QoL	Quality of life
RANKL	Receptor activator of nuclear factor kappa-B ligand
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria in Solid
RPSFT	Rank preserving structural failure time
SAS	Safety analysis set
SAE	Serious adverse event
s*BRCA*m	Somatic *BRCA* mutations
SD	Standard deviation
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
SOC	Standard of care
TFST	Time to first subsequent treatment
TNBC	Tripple negative breast cancer
TNM	Tumour-node-metastasis
TPC	Treatment of physician's choice
TSST	Time to second subsequent
TTD	Time to treatment discontinuation
TTR	Time to response
USA	United States of America

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

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

- Olaparib is indicated as monotherapy for the treatment of adult patients with germline *BRCA*1/2 mutations, who have human epidermal growth factor receptor 2 negative (HER2−) locally advanced or metastatic breast cancer (mBC). 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 hormone receptor positive (HR+) breast cancer should also have progressed on or after prior endocrine therapy, or be considered unsuitable for endocrine therapy.

This positioning is fully aligned with the population for which talazoparib has received a positive recommendation from the National Institute for Health and Care Excellence (NICE):

- Talazoparib is recommended, within its marketing authorisation, for treating HER2−, locally advanced or mBC with germline *BRCA*1 or *BRCA*2 mutations in adults who have had:[1]
    - an anthracycline or a taxane, or both, unless these treatments are not suitable, and
    - endocrine therapy if they have HR+ breast cancer, unless this is not suitable.

It is proposed that this appraisal of olaparib be considered under the NICE cost comparison appraisal criteria. The NICE manual for health technology evaluations states that a case can be made if a health technology is likely to provide similar or greater health benefits at similar or lower cost than technologies already recommended in published technology appraisal guidance for the same indication. Talazoparib is the most appropriate comparator for olaparib for the following reasons:

- As talazoparib is the first reimbursed targeted treatment for the proposed target population, it is likely to quickly become standard of care for these patients; clinical experts consulted as part of this submission stated that if a patient had a known g*BRCA*m then they would prioritise treatment with a PARP inhibitor (Section B.4.5.1).
- The results of two published indirect treatment comparisons (ITC) between talazoparib and olaparib (Section B.3.8) demonstrate that the two treatments have comparable efficacy and safety (McCrea *et al.* [2021] and Wang *et al.* [2021]).[2, 3] Additionally, given the similarity in mechanism of action between talazoparib and olaparib, clinical experts noted that they would expect the treatments to have similar efficacy and safety (Section B.4.5.1).

The decision problem addressed within this submission is outlined in Table 1.

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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 HER2− locally advanced or mBC with germline *BRCA* 1/2 mutations that has previously been treated with: • an anthracycline and a taxane in the (neo)adjuvant or metastatic setting, unless these treatments would not be suitable. • endocrine therapy in the case of HR+ breast cancer, unless endocrine therapy is not suitable.	As per the NICE final scope	N/A
Intervention	Olaparib monotherapy	As per the NICE final scope	N/A
Comparator(s)	Talazoparib	As per the NICE final scope	N/A
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rate • adverse effects of treatment • health-related quality of life.	As per the NICE final scope	N/A
Economic analysis	• This technology has been selected to be appraised as a cost-comparison. • The time horizon should be sufficient to reflect any differences in costs between the technologies being compared. • Costs will be considered from an NHS and PSS perspective. • The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. • The availability and cost of biosimilar and generic products should be taken into account. • 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 locally advanced or metastatic breast cancer who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test. See section 4.8 of the guidance development manual (available here: https://www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technology-evaluation).	• A cost-comparison analysis has been conducted in Microsoft Excel to estimate the incremental costs of olaparib versus talazoparib • The time horizon for assessing costs was set to 20 years (lifetime), which is sufficiently long to capture the majority of costs associated with the use of olaparib • Costs were considered from an NHS and PSS perspective • Olaparib has a commercial arrangement in place which has been included as part of this analysis	It is proposed that olaparib can be appropriately assessed through the NICE cost-comparison appraisal process due to the similarities in terms of clinical effectiveness between olaparib and talazoparib and as such, a cost-comparison has been submitted.

Abbreviations: *BRCA*: Breast Cancer Gene; HER2: human epidermal growth factor receptor 2; HER2−: HER2-negative; HR+: hormone receptor positive; mBC: metastatic breast cancer; NHS: National Health Service; NICE: National Institute of Health and Care Excellence; PSS: Personal Social Services.

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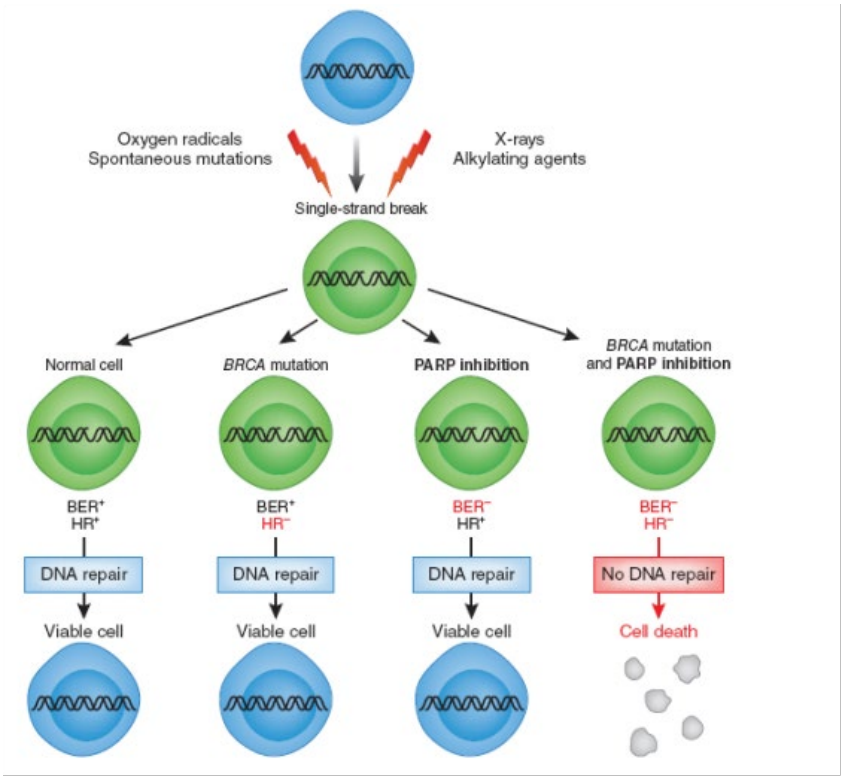
B.1.1 Description of the technology being evaluated

A summary of the mechanism of action, marketing authorisation status, costs and administration requirements associated with olaparib are presented in Table 2.

Table 2: Technology being appraised

UK approved name and brand name	Olaparib (Lynparza®)
Mechanism of action	Olaparib is a selective inhibitor of PARP enzymes that operates by competitively binding to the NAD+ binding sites of PARP1 and PARP2.[4] Members of the PARP protein family, including PARP1, PARP2 and PARP3, have been shown to play a role in DNA repair. They are required for the repair of single-strand breaks in DNA. Olaparib is a potent inhibitor of PARP1, PARP2 and PARP3. Olaparib blocks the repair of single-strand DNA breaks through preventing the dissociation of PARPs from the DNA. The association of PARPs to DNA leads to double-strand breaks in *BRCA*-deficient replicating cells where the replication forks meet. Typically, double-strand breaks are repaired via HRR. However, in *BRCA*-deficient cells, HRR is not properly regulated, leading to inefficient or inaccurate repair of double-strand breaks.[5] This increases genomic instability which can eventually lead to cell death. This means that olaparib can specifically target *gBRCAm* BC cells through exploitation of DNA repair mechanisms of cells. Olaparib is already used as a targeted treatment across multiple tumour types (ovarian, prostate, pancreatic and early breast cancer).[6] **Figure 1: Mechanism of action of PARP inhibitors**  **Abbreviations**: BER: base excision repair; HR: homologous recombination; PARP: poly (ADP-ribose) polymerase. **Source**: Guha (2011).[7]

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Marketing authorisation/CE mark status	EMA marketing authorisation for olaparib in this indication was granted in April 2019.[8]
Indications and any restriction(s) as described in the SmPC	**Indication of interest to this evaluation** Olaparib is indicated as monotherapy for the treatment of adult patients with germline *BRCA*1/2 mutations, who have HER2− locally advanced or mBC. 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. **Other current indications:** 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*1/2mutation and/or genomic instability Breast cancer Olaparib is indicated as: • monotherapy or in combination with endocrine therapy for the adjuvant treatment of adult patients with germline *BRCA*1/2-mutations who have HER2−, high risk early breast cancer previously treated with neoadjuvant or adjuvant chemotherapy • monotherapy for the treatment of adult patients with germline *BRCA*1/2-mutations, who have HER2− locally advanced or mBC. 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 *BRCA*1/2-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 mCRPC and *BRCA*1/2-mutations (germline and/or somatic) who have progressed following prior therapy that included a new hormonal agent • in combination with abiraterone and prednisone or prednisolone for the treatment of adult patients with mCRPC in whom chemotherapy is not

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	clinically indicated **Restrictions** Contraindications include hypersensitivity to the active substance or to any of the excipients or 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.[6]
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)
Additional tests or investigations	*BRCA* testing should be carried out to confirm the presence of g*BRCA*m using a validated testing procedure before olaparib treatment is prescribed. *BRCA* testing is already well established in clinical practice, especially for patients with a high pre-test probability of harbouring a pathogenic mutation.[9] Prior to initiating olaparib treatment, HER2 status will also need to be determined; this is already considered to be standard of care in patients with breast cancer, so no further testing is required.[10]
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, or £4,635.00 per 28-day cycle.
Patient access scheme (if applicable)	A confidential commercial access agreement is in place for olaparib that provides a discount of [redacted] per 14-day pack).

Abbreviations: *BRCA*: breast cancer susceptibility gene; DNA: deoxyribonucleic acid; DSB: double-stranded break; EMA: European Medicines Agency; FIGO: International Federation of Gynaecology and Obstetrics; HER2: human epidermal growth factor 2; HR+: HR-positive; HER2−: HER2-negative; HRD: homologous recombination deficient; HRR: homologous recombination repair; mBC: metastatic breast cancer; mCRPC: metastatic castration-resistant prostate cancer; NAD: nicotinamide adenine dinucleotide; NG: NICE Guideline; NHS: National Health Service; PARP: poly (ADP-ribose) polymerase; SmPC: Summary of Product Characteristics; TNBC: triple negative breast cancer.

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B.1.2 Health condition and position of the technology in the treatment pathway

Disease overview

- Breast cancer (BC) is the most common cancer diagnosed in the UK, accounting for 15% of new cancer cases.[11]
- mBC occurs when cancer spreads to other distant tissues. mBC is an incurable disease characterised by rapid progression and poor survival.[12]
- Prognosis in BC is influenced by HER2 and hormone receptor status.[13] There are two types of HER2− BC:
    - HR+/HER2− BC, which can be treated with endocrine-based therapy.
    - Triple negative breast cancer (TNBC), a particularly aggressive form of the disease.[14]
- *BRCA*1 and 2 are breast cancer susceptibility genes that encode proteins responsible for DNA repair (double-strand breaks). Mutations in *BRCA1* and *BRCA2* lead to deficiency in homologous recombination repair (HRR), the pathway for repair of double-strand breaks.[15] Germline *BRCA1* and *BRCA2* mutations (g*BRCA*m) increase the risk of developing BC and ovarian cancer.
- Approximately 10% of patients with HER2− BC also have g*BRCA*m.[16]
- Patients with g*BRCA*m 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.[17]

Disease burden

- Patients with advanced or mBC experience lower health-related quality of life (HRQoL) than the general population,[18-20] related not only to symptomatic burden and treatment-related toxicities, but also the emotional impact of disease.[21] HRQoL declines further in patients with more metastatic sites and on later lines of therapy.[20, 22]
- Patients with g*BRCA*m may experience a greater burden of BC, including diagnosis at an earlier age, which impacts their HRQoL.[20, 22] A UK-based study of patients with g*BRCA*m showed that social wellbeing is significantly reduced for younger women with BC.[23]
- mBC also has a large economic burden on the UK healthcare system, due to treatment visits, hospital stays as well as the need for additional treatment and targeted therapies.[24]

Treatment pathway

- The aim of treatment for locally advanced or mBC is to extend the length of life, while delaying a deterioration of patients' quality of life.
- For HR+/HER2− locally advanced or mBC with *BRCA* mutations, the established first-line treatments are cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors with endocrine therapy.
- For patients who progress on first-line treatment but remain sensitive to endocrine therapy, second-line treatment options include alpelisib with fulvestrant (for PIK3CA-mutated disease) and everolimus with exemestane (for HR+ disease). For patients who are not (or no longer) responsive to endocrine therapy at second or later lines, treatment options are limited to single-agent chemotherapies such as anthracyclines, taxanes, capecitabine, vinorelbine and eribulin.
- For patients with metastatic TNBC with *BRCA* mutations, first-line therapies include immunotherapy plus chemotherapy when the cancer is programmed cell death ligand 1 (PD-L1) positive. Single-agent chemotherapies such as anthracyclines, taxanes, capecitabine, vinorelbine and eribulin are considered in PD-L1 negative patients or in those who progress on first-line PD-L1-targeted therapies.
- More recently, talazoparib was recommended by NICE for patients with HER2− locally advanced or mBC who also have g*BRCA*1/2m in adults who have had an anthracycline or a taxane, or both, unless these treatments are not suitable, and endocrine therapy if they have HR+/HER2− breast cancer, unless this is not suitable.[1]

Proposed positioning of olaparib

- Olaparib is an orally administered poly(ADP-ribose) polymerase (PARP) inhibitor, and was the first genetically targeted treatment for *BRCA*m BC. The proposed indication for olaparib in this submission is for patients with g*BRCA*m HER2− locally advanced or mBC and the relevant comparator is talazoparib.

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B.1.2.1 Disease overview

BC is the most prevalent cancer across the globe, accounting for 7.8 million cancer cases worldwide by the end of 2020.[25] Approximately 685,000 women died from BC in 2020, making it the most common cause of death amongst women.[25] In the UK, it is estimated 55,500 women and 370 men are diagnosed with BC each year and it is the 4th most common type of cancer in the UK.[11] Between 2016 and 2017, it was estimated 11,499 people died from BC in the UK, accounting for approximately 7% of all cancer deaths (2017–2019).[11]

Several risk factors have been associated with the development of BC, including genetic predisposition (family history), lifestyle and environmental factors, medical history, menstrual history and previous medical interventions (Table 3).[13] A key factor is family history and the inheritance of genetic mutations that increase the risk of developing BC. Several mutations in the following genes have been linked to BC: *BRCA1/2, PIK3CA, TP53, PTEN, PALB2, CHEK2 and CDH1.*[26] *BRCA* (breast cancer susceptibility gene) mutations are some of the most prevalent (approximately 10% in HER2– mBC patients) and testing for these mutations is important for identifying patients with a high pre-test probability of harbouring a pathogenic mutation as well as supporting early diagnosis, guiding interventions to reduce cancer risk and informing treatment decisions related to targeted therapy.[16, 27] g*BRCA*m are discussed in further detail below.

Table 3: Risk factors for the development of breast cancer

Category	Risk factors leading to increased risk of BC
Family history	• Patients that have close blood relatives with BC; alterations (mutation and/or amplification) in the following genes can be associated with an increased risk of BC: *BRCA1/2*, *PIK3CA*, *TP53*, *PTEN*, *PALB2*, *CHEK2* and *CDH1*
Race and ethnicity	• Caucasian women are slightly more likely to develop BC than black 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 BC, 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 environment factors	• Excessive alcohol consumption, obesity, and lack of physical exercise

Abbreviations: BC: breast cancer; *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 *et al*. (2018)[26]

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B.1.2.1.1 Disease staging and types of BC

BC is a heterogenous disease that varies in both the clinical presentation and the molecular mechanisms that underpin the disease. A variety of treatments are therefore required to treat individual subtypes of BC due to different sensitivities to anticancer treatments.[28] There are numerous methods used to classify BC to provide a more distinct diagnosis and to guide treatment pathways. All patients should be assigned a clinical stage of disease at diagnosis and a pathological stage of disease, before proceeding with treatment.[29] In addition to disease stage, treatment is informed by the biomarker (hormone and HER2 receptor) status and genetic status of the cancer. The stages and types of BC are described in further detail in the below sections.

Clinical staging

The tumour-node-metastasis (TNM) cancer staging system is used to assign a clinical stage of disease to patients with BC.[29, 30] Clinical staging describes the severity of an individual's cancer based on the extent of the primary tumour (T), the extent of spread to the lymph nodes (N), and the presence of metastasis (M).[29, 31] Once the T, N and M have been determined, they are combined and an overall stage of 0–IV is assigned (Table 4).[31]

Table 4: TNM stage grouping

Stage	Description
0	Non-invasive breast cancer – carcinoma *in situ*
I	Localised breast cancer (tumour size ≤2 cm)
II	Early, locally advanced breast cancer
III	Late, locally advanced breast cancer
IV	Advanced/mBC

Abbreviations: mBC: metastatic breast cancer; TNM: tumour-node-metastasis.
Source: AJCC TNM Classification of Tumours (8th Edition), 2017.[32]

mBC is an advanced form of BC that occurs when BC spreads to other parts of the body.[33] More specifically, mBC has the following characteristics which are used for diagnosis: the cancer can be any size; the lymph nodes may or may not contain cancer cells; and the cancer will have metastasised to other parts of the body such as lungs, bones, liver and brain.[33] This is distinct from locally advanced BC in which the cancer has spread to surrounding area, such as the lymph nodes, skin or chest muscle, but not to more distant parts of the body.[33] However, locally advanced and metastatic BC are often collectively referred to as advanced BC (which is the population of interest to this evaluation) and both patient populations are treated in the same way in clinical practice.[34, 35]

mBC is currently considered incurable and treatment will often focus on prolonging the life of patients. mBC can rapidly progress and whilst treatable, prognosis is generally poorer for patients with mBC than for patients with locally advanced BC, with 5-year survival rates of 27% and 72%, respectively.[36]

A study by Palmieri *et al.* estimated that prevalence of mBC in England between April 2020 and March 2021 was 57,215 patients.[37] The same study also compared the estimated prevalence of mBC between 2016 and 2020 and reported an increase in prevalence of mBC over time in England which is comparable to trends observed in USA and Australia.[37]

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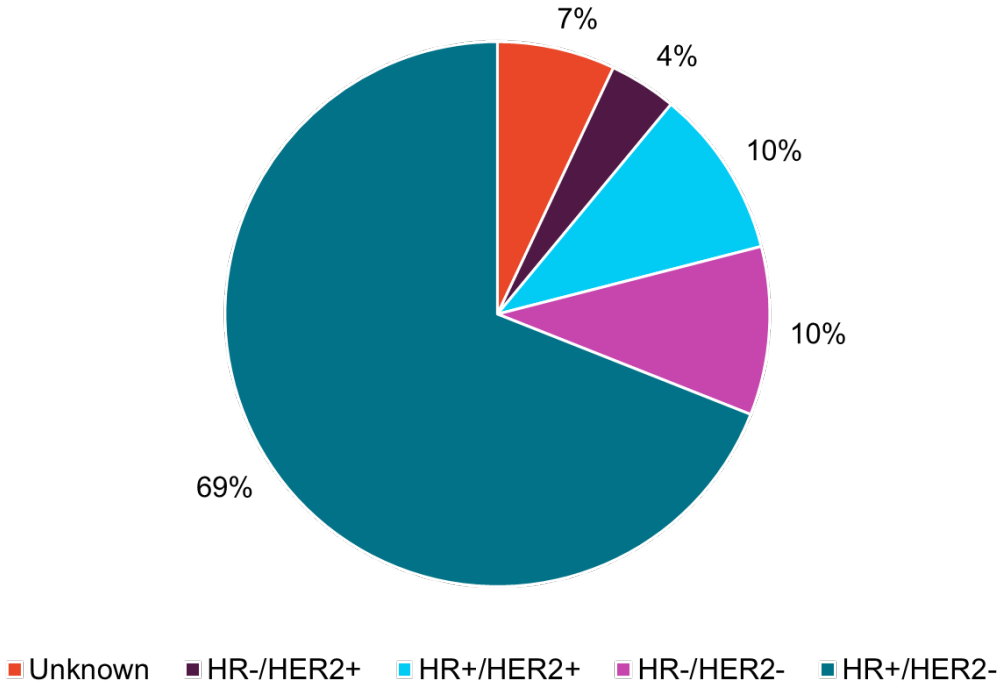
Hormone and HER2 receptor status

Hormonal (oestrogen [ER] and progesterone [PR]) and growth (HER2) receptors define four basic breast tumour molecular subtypes, listed below in order of prevalence (subgroups of interest to this evaluation are highlighted in bold):

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

HER2− BC is more common than HER2+ BC.[38] HER2− BC is subclassified further into HR+/HER2− and TNBC (i.e. both HER2− and HR−). In England, it is estimated that 69% of BC are classified as HR+/HER2− and 10% are TNBC (2016−2020 estimates) (Figure 2).[39] Patients with TNBC and HER2+ disease BC were also 6.4- to 20.0-fold more likely to present with high-grade disease.[40] TNBC has particularly low estimates of 5-year survival, particularly for those with distant metastases according to the SEER Combined Summary Stage (12.8%) (Figure 3).

Figure 2: Percent of female BC cases by cancer subtype



Abbreviations: BC: breast cancer; HER2: human epidermal growth factor 2; HR: hormone receptor.
Source: NCI SEER 22: Cancer Stat Facts (2016 – 2020) [39]

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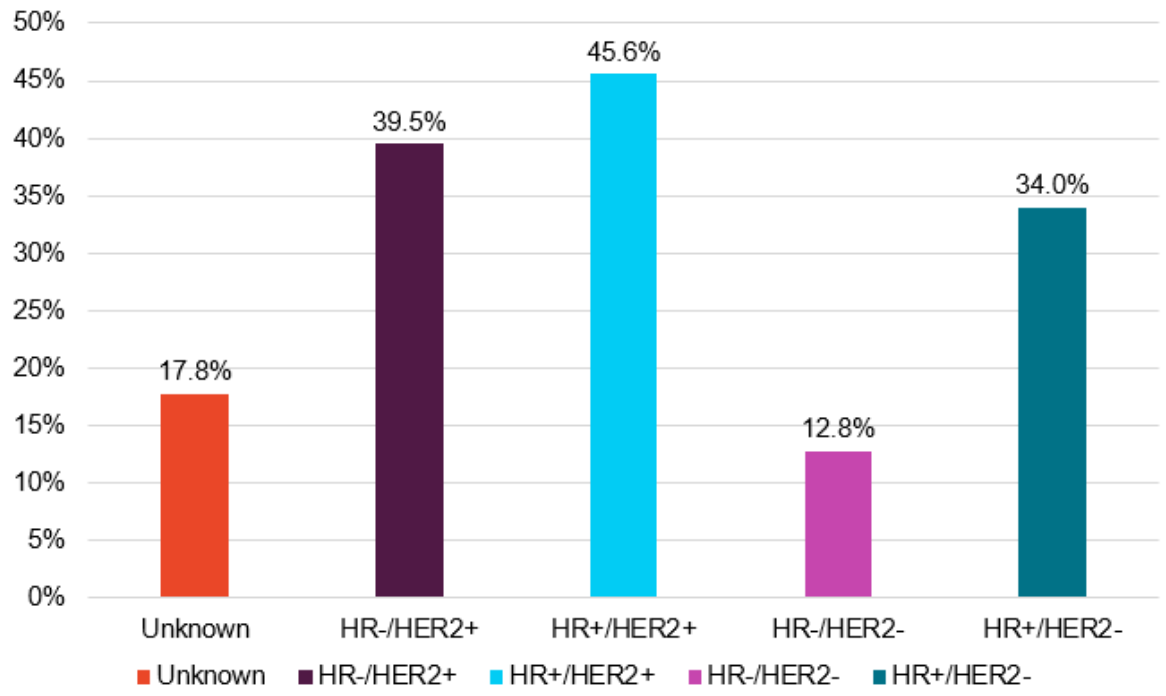
Figure 3: 5-year relative survival percent, female BC (with distant metastases) cases by cancer subtype



Abbreviations: BC: breast cancer; HER2: human epidermal growth factor 2; HR: hormone receptor.
Source: NCI SEER 22: Cancer Stat Facts (2016 – 2020)[39]

BRCA mutations

BRCA1 and *BRCA2* are BC susceptibility genes that encode proteins responsible for DNA repair (double-strand breaks). Mutations in *BRCA1* and *BRCA2* lead to deficiency in HRR, the pathway for repair of double-strand breaks.[15] These mutations can either be 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.[26, 41]
- **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.[41]

The majority of *BRCA*m are sporadic and only approximately 25% are g*BRCA*m, but both increase the risk of developing BC. By the age of 80, approximately 72% of women with the g*BRCA1*m and 69% with the g*BRCA2*m will be diagnosed with BC.[16] The presence of a g*BRCA*m not only increases the risk of developing BC and/or ovarian cancer, but has also been linked to more severe disease outcomes and diagnosis at a younger age. For patients with *BRCA1*m, the median age of diagnosis is 40 years, whilst the median age for diagnosis is 43 years for patients with *BRCA2*m.[42] In comparison, 8 out of 10 BC cases occur in women over 50 years of age.[43] Similarly, a study estimated the outcomes for patients with g*BRCA*m and mBC was performed using a database comprised of patient data (collected 2008–2016) from France and observed that g*BRCA*m carriers were generally younger and presented with more aggressive forms of cancer.[44]

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There are several risk factors associated with the g*BRCA*m subtype including family history of BC or ovarian cancer, young age for onset of disease, multiple primary cancers, ethnicity (e.g. founder mutations in Ashkenazi Jewish populations), male BC and specific cancer subtypes.[17] *BRCA1m* are most frequently associated with TNBC subtypes (present in 9–18% of patients).[16, 45, 46] Meanwhile, *BRCA2m* are more likely to be reported in HR+/HER2− BC.

Importantly, breast cancers with *BRCA*m are more susceptible to PARP inhibitors.[47]

B.1.2.1.2 Diagnosis of BC and g*BRCA*m testing

The majority of BC cases are diagnosed at early stage of disease, however, a diagnosis of locally advanced or mBC (stage III or IV) is provided at initial diagnosis in ~15% of patients.[36] In the UK, BC screens are performed as a part of the National Health Service (NHS) BC screening programme, with women aged between 50 and <71 invited to take part. In 2020, the screening programme resulted in the detection of 17,771 cases of BC.[48] People who are considered to be at greater risk of BC due to the inheritance of the g*BRCA*m are also offered magnetic resonance imaging (MRI) screens from 30 years of age.

Patients typically present with symptoms including a lump in the breast, change in size/ shape of the breast, dimpling in the skin and changes in nipple structure and discharge.[49] For mBC, general symptoms can include nausea, feeling tired and loss of appetite/weight loss. Symptoms will also depend on the location to which the cancer has spread and initial investigations for mBC are dependent on the patient's symptoms (e.g., bone and back pain, issues concerning urination, feeling confused or feeling thirsty are all indicators that cancer has spread to the bones).[49-51] The extent of the metastatic disease is then subclassified into stages using additional imaging. Imaging techniques include ultrasound, bone scintigraphy, computed tomography (CT), MRI and positron emission tomography fused with computed tomography (PET-CT).[50] Additional common sites of metastatic disease such as lung, liver and bone may be explored.

Further testing is then carried out to identify the subtype of BC according to hormone receptor and HER2 status, frequently using immunohistochemistry tests.[52] Moreover, g*BRCA*m testing is routinely offered to patients with a high pre-test probability of harbouring a pathogenic mutation. The National Test Directory (NGTD) has defined specific eligibility criteria for routine familial g*BRCA*m testing (test code: R208) 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 I but the two criteria most applicable to this appraisal are:[9]

- g*BRCA*m testing offered to women aged <60 years with TNBC
- g*BRCA*m testing offered to women aged <40 years for other breast cancer types (including HR+/HER2− patients)

Beyond familial g*BRCA*m testing for patients with a high pre-test probability of harbouring a pathogenic mutation, the NGTD also defines specific criteria for g*BRCA*m testing to determine eligibility for NICE-approved PARP inhibitor treatment in early breast cancer (test code: R444.1; for those patients who don't meet the standard criteria for g*BRCA*m testing described above). The full NGTD eligibility criteria for NICE-approved PARP inhibitor treatment in early breast cancer are also presented in Appendix I.

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Accordingly, clinical experts consulted during the talazoparib appraisal (TA952) noted that there had been an increased uptake in *BRCA* testing following the NICE recommendation of *BRCA*-targeted olaparib treatment in early breast cancer in 2022.[1] While *BRCA* testing is routinely available for people with TNBC, it was noted during the appraisal that the cost of testing should be included for some patients with HR+/HER2− locally advanced or mBC. Olaparib reimbursement in the locally advanced or mBC setting is not expected to lead to an increase in gBRCA testing volumes.

Detection of g*BRCA*m informs the management plan for both the patient and their family. For the patient themselves, it may inform the choice of surgical approach and pharmacological treatment regimen in early breast cancer. 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.[53]

B.1.2.1.3 Humanistic burden

The recurrence of BC and subsequent progression to mBC has been shown to negatively impact the quality of life of patients. This is evidenced by a real-world study performed in the Netherlands that showed patients (N=2,684) who had recurring BC or mBC reported a lower HRQoL) than patients who were disease-free.[54] HRQoL decreased with disease severity, whereby patients with mBC reported poorer HRQoL than those with recurring disease. Patients with mBC report physical effects including pain, disrupted body image and daily life limitations. In addition, many patients report the impact of mBC on family roles and interpersonal relationships, as well as psychological effects.[55]

Moreover, patients with g*BRCA*m may experience a greater burden of BC which impacts their HRQoL. Patients with g*BRCA*m are typically diagnosed at an earlier age with BC which can impact career development and family life.[44] A UK-based study of patients with g*BRCA*m showed that social wellbeing is significantly reduced for younger women with BC.[23] In addition, being a g*BRCA*m carrier comes with added complexity in terms of diagnosis and clinical pathology.[24,56] Patients who consent to undergo g*BRCA*m genetic testing have to communicate results to family members and may face anxiety about whether they have passed the mutation on to their children.[57, 58] They may also present with severe metastases which impact HRQoL.[57]

B.1.2.1.4 Economic burden

Overall, mBC has a large economic burden on the UK and international healthcare systems.[59] In 2024, the total cost of breast cancer in the UK is estimated to be £2.6–2.8 billion.[60] This burden is likely due to treatment visits and hospital stays as well as the need for additional treatment and targeted therapies.[24] Between 2020 and 2021 in England, 974,320 hospital spells were reported as being related to mBC with the number of hospital spells has also been shown to increase over a five year period (2016–2017: 393,180; 2020–2021: 974,320).[37] The number of treatment visits is especially high amongst patients with HER2− mBC.[61]

mBC not only has a significant economic impact on the healthcare system, but also affects work productivity (due to the large symptomatic burden of the disease) and personal finances of patients. This work impairment is especially prevalent in patients with *BRCA* mutations with 20% more patients with HER2− *BRCA*m BC reporting an impaired ability to work compared to patients

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with HER2− BC without *BRCA* mutations. The effect of g*BRCA*m is also considered to have a greater economic burden on patients due to the younger age of onset of disease by carriers.[62]

B.1.2.2 Treatment pathway

The aim of treatment for locally advanced or mBC is to extend the length of life, while delaying deterioration of HRQoL. The initial treatment guidelines set out by NICE for patients with HER2− early BC are the same for patients regardless if patients are g*BRCA*m carriers.[10, 50] However patients with early BC who have g*BRCA*m disease that has a high risk of recurrence after surgery and chemotherapy are now eligible for treatment with adjuvant olaparib (TA886).[63] Treatment in the metastatic setting is specific to each patient and depends on the treatments received in early BC, as well as hormone receptor status (Figure 4).

Clinical guidelines for the management of advanced BC are available from NICE (CG81, last updated in 2017) and for mBC from the European Society for Medical Oncology (ESMO, 2021).[50, 64] For HR+/HER2− locally advanced or mBC with g*BRCA*m, the established first-line treatments are CDK4/6 inhibitors with endocrine therapy, as recommended in NICE technology appraisal guidance (TA495, TA496, TA563).[64-67] Endocrine monotherapy may be considered in first line in a small group of patients with comorbidities or a performance status that prevents the use of CDK4/6 inhibitor combinations.[50, 64] For patients whose disease is imminently life-threatening or requires early relief of symptoms because of significant visceral organ involvement, chemotherapy may be considered as first-line treatment.[50, 64]

For patients who progress on first-line treatment but remain sensitive to endocrine therapy, typical second-line treatment options include alpelisib with fulvestrant (for PIK3CA-mutated disease; TA816) and everolimus with exemestane (for HR+ disease; TA421).[64, 68, 69] Meanwhile, for patients who are not (or no longer) responsive to endocrine therapy at second or later line, treatment options are limited to single-agent chemotherapies such as anthracyclines, taxanes, capecitabine, vinorelbine and eribulin (TA423, after at least two prior chemotherapy regimens).[70] Clinical experts consulted within the talazoparib appraisal (TA952) noted that platinum-based chemotherapy is not often used as a second-line treatment and that use of alpelisib with fulvestrant and everolimus with exemestane was also limited due to the related toxicities.[1]

For patients with TNBC, first-line therapies include immunotherapy plus chemotherapy when the cancer is PD-L1 positive. Single-agent chemotherapies such as anthracyclines, taxanes, capecitabine, vinorelbine and eribulin are considered in PD-L1 negative patients or in those who progress on first-line PD-L1-targeted therapies. Subsequent treatment is limited to sequential courses of chemotherapy. For people with metastatic TNBC, genetic testing is recommended for patients whose age is less than 60 years.[71]

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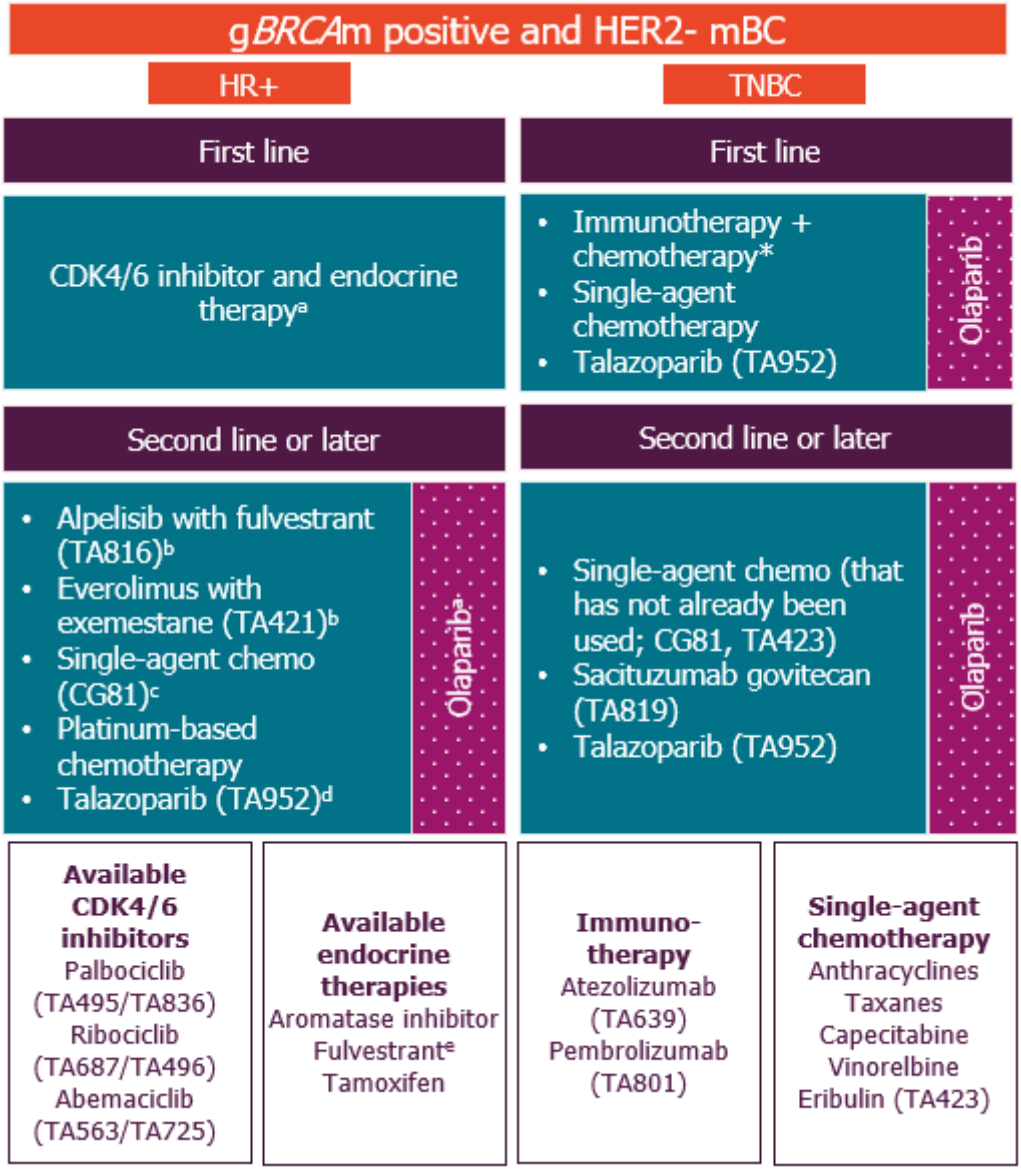
Figure 4: Current treatment pathway



[a] Endocrine monotherapy may be considered in first line in a small group of patients with comorbidities or a performance status that prevents the use of CDK4/6 inhibitor combinations. For patients whose disease is imminently life-threatening or requires early relief of symptoms because of significant visceral organ involvement, chemotherapy may be considered as first-line treatment; [b]Therapies typically used at second-line in patients who progress following first-line therapy but remain sensitive to endocrine therapy; [c]Single-agent chemotherapy is an option for patients who are not (or are no longer) responsive to endocrine therapy at second or later line; [d]For patients with HR+ disease, talazoparib is recommended only in patients with mBC who have had prior endocrine therapy (i.e. second line or later), unless this is not suitable. Olaparib is positioned in the same population for which talazoparib received a recommendation. [e]Fulvestrant monotherapy is not recommended by NICE.
Abbreviations: CDK: cyclin-dependent kinase; g*BRCA*m: germline breast cancer susceptibility gene mutation; HR: hormone receptor; mBC: metastatic breast cancer; TNBC: triple negative breast cancer.
Source: TA816[68]; TA421[69]; TA423[70]; CG81[50]; TA819[72]; TA495[65]; TA836[73]; TA687[74]; TA496[66]; TA563[67]; TA725[75]; TA639[76]; TA801[77].

More recently, talazoparib (TA952) has been approved for treating patients with HER2− locally advanced or mBC with g*BRCA*m.[1] In line with the licence for talazoparib, such patients will have previously been treated with an anthracycline or a taxane, or both, unless these treatments are not suitable, and should have been treated with endocrine therapy if they have HR+ BC, unless this is not suitable. Talazoparib is positioned for treating g*BRCA*m and HR+/HER2− locally

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advanced or mBC as a second-line treatment, whilst it is positioned for the treatment of TNBC with g*BRCA*m in both first and second-line settings.

B.1.2.3 Unmet need with current treatment

Although there have been recent advances in targeted treatments for locally advanced or mBC, such as the recommendation of talazoparib, there is still a large unmet need for specific subtypes of BC, including for patients with HER2− locally advanced or mBC.[1] As a large proportion of BC are HER2−, treatment is mostly limited to chemotherapy with toxic side effects once hormonal therapy has been deemed no longer suitable.[78] Targeted therapies (such as everolimus with exemestane and alpelisib with fulvestrant) are available for patients who are sensitive to endocrine therapy.[68, 69] Greater challenges are faced by patients who are not responsive to endocrine therapy and thus for whom endocrine therapies are not viable treatment options, and in particular those with TNBC due to the aggressive nature of these tumours and their metastatic potential.[14] Once progression to metastatic disease has occurred in patients with TNBC, patients have short OS.[14] There are limited therapeutic options, and talazoparib is currently the only treatment available in the NHS specifically for patients with HER2− BC with g*BRCA*m in the locally advanced and mBC setting.

As discussed, the lack of cure and the focus on extending patient life and prolonging remission takes a toll on patient HRQoL. Chemotherapy treatment can help to reduce symptoms, but the toxic effects of treatment decreases HRQoL.[55] This gets progressively worse with more severe prognosis of disease due to more metastatic sites and third-line therapies.[64, 79] Additionally, current chemotherapy treatments for people with locally advanced or mBC are often administered intravenously, requiring regular hospital visits and impacting patients' ability to lead normal lives.[18,21]

There is therefore an unmet need for additional targeted therapies for patients with g*BRCA*m HER2− locally advanced or mBC. Orally administered treatments would be preferable to reduce the impact that more invasive treatments such as eribulin, vinorelbine and capecitabine have on HRQoL. This unmet need is reflected in recommendations from recently updated guidelines for use of a PARP inhibitor (the National Comprehensive Cancer Network [NCCN] guidelines and ESMO mBC guidelines recommend olaparib and talazoparib for patients with *BRCA*-associated HER2− locally advanced or mBC tumours.[64, 79]

Although the recent recommendation of talazoparib in this setting goes some way to address these unmet needs, clinicians would benefit from additional therapeutic options to treat patients with g*BRCA*m HER2− locally advanced or mBC. As outlined in Section B.3.8, ITCs have shown that the efficacy and overarching safety profile of olaparib and talazoparib are comparable. However, these analyses have shown that the risk of specific AEs differs slightly, with olaparib having an increased risk of the gastrointestinal (GI) events of nausea and vomiting, but a lower risk of alopecia and anaemia versus talazoparib. Seven clinical experts consulted by AstraZeneca have validated this finding, with four of the experts stating that olaparib and talazoparib have overall similar safety profiles, with three stating that they valued the slightly different safety profile of olaparib, especially in terms of haematological events (Section B.4.5.1). Clinical experts also stated that they were familiar with prescribing olaparib due to use in the early BC setting. A positive NICE recommendation for olaparib in gBRCAm HER2− locally advanced or mBC would therefore provide clinicians with an additional treatment option with comparable efficacy but with a different balance in the side effect profile. This would enable

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clinicians to select the best available PARPi for a given patient, considering their individual circumstances, comorbidities, contraindications, and preferences.

B.1.2.4 Olaparib for the treatment of HER2− g*BRCA*m mBC

Positioning of olaparib in the treatment pathway

Olaparib is an orally administered treatment that is proposed to be used as a monotherapy for the treatment of adult patients with germline *BRCA*1/2 mutations, who have HER2− locally advanced or mBC. 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. This is consistent with the population for which talazoparib has received a recommendation (TA952).[1] Talazoparib is likely to become standard of care for patients with HER2− locally advanced or mBC with g*BRCA*m, given feedback from clinical experts that PARP inhibitors would be prioritised for patients with known g*BRCA*m (Section B.4.5.1). As such, talazoparib represents the most relevant comparator for olaparib.

B.1.3 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 Key drivers of the cost effectiveness of the comparator(s)

B.2.1 Clinical outcomes and measures

As described in Section B.1, olaparib is anticipated to represent an alternative treatment option to talazoparib, which has received a positive recommendation for reimbursement by NICE in TA952.[1] Within the appraisal, talazoparib was compared to treatment of physician's choice (TPC; capecitabine, eribulin or vinorelbine) for HER2− locally advanced or mBC with germline *BRCA*1/2-mutations.

The following section provides an overview of the key clinical outcomes and measures considered in the cost-effectiveness evaluation submitted as part of TA952. As stated in Section B.1.1, for this submission, a cost-comparison analysis has been conducted between olaparib and talazoparib which assumes comparable efficacy and safety between the two treatments; therefore, clinical outcomes discussed in this section are not considered in the cost-comparison model for this submission (presented in Section B.4).

Two key outcomes of efficacy were considered within the talazoparib appraisal, progression-free survival (PFS) and OS. The committee concluded that talazoparib was associated with delayed disease progression. The OS data were considered uncertain due to immaturity of the data and because EMBRACA was not powered to detect statistical differences in OS; the committee ultimately concluded that there was no evidence of a survival benefit with talazoparib.

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Health state utility values for the progression-free (PF) health state were derived from HRQoL data collected within the EMBRACA trial and mapped to EQ-5D-3L. The utility values in the PF health state were treatment-specific, which the External Assessment Group (EAG) considered to be uncertain due to the open-label nature of the EMBRACA trial. The committee acknowledged the uncertainty but accepted the values as appropriate given there may be other factors that could affect how a person feels when having talazoparib or the comparator treatment. These values were a key driver of the cost-effectiveness results. Utility values for the progressive disease health state were derived from the literature.

Further detail on clinical outcomes and measures used in the talazoparib evaluation are presented in Table 5. As highlighted above, some of these outcomes are only relevant to a cost-effectiveness analysis and are therefore not relevant to this appraisal.

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Table 5:Clinical outcomes and measures appraised in the NICE TA952 (talazoparib)

Outcomes	Endpoint definition	Used in cost-effectiveness model?	Impact on ICER?	Committee preferred assumption	Uncertainties
Progression-free survival (PFS)	Radiographic PFS defined as the time from randomisation until the date of radiologic progressive disease per modified RECIST 1.1, as determined by central IRF assessment, or death due to any cause, whichever occurred first.	**Yes**, with parametric survival curves fitted to the KM data to extrapolate beyond the trial duration.	PFS benefit was a key driver of cost-effectiveness, with different extrapolation approaches explored in scenarios resulting in a varied impact on the ICER (range: £30,545 – £39,151).	The committee concluded that talazoparib was associated with delayed disease progression, and did not discuss the company's approach to modelling of PFS.	N/A – The EAG considered the modelling of PFS to be acceptable.
Overall survival (OS)	OS defined as the time from randomisation to death due to any cause.	**Yes**, with parametric survival curves fitted to the KM data for the talazoparib arm to extrapolate beyond the trial duration. A hazard ratio adjusted for subsequent use of PARP inhibitors using a RPSFT model was used to estimate OS in the TPC arm.	The different extrapolation approaches had a minimal effect on the ICER (range: £33,262 – £35,158).	The committee noted that because the PH function was violated, the hazard ratio for OS was not an appropriate measure of talazoparib treatment effect. Modelling separate curves to talazoparib and TPC was considered acceptable with lognormal curve used to model OS in the talazoparib arm, and a Weibull curve in the TPC arm. However, it was noted that the separately fitted curves implicitly included a survival benefit for talazoparib. The committee ultimately concluded that there was no evidence of a survival benefit with talazoparib and that it was most appropriate to consider modelling with no survival benefit for talazoparib (i.e. OS for TPC was informed by the talazoparib curve).	The data collected within the trial was not sufficient to inform the total time horizon of the model due to immaturity of the data. Therefore, extrapolation of survival data from EMBRACA was required to inform long-term outcomes. Subgroup analyses of OS by hormone receptor status and by previous line of treatments were detailed within the appraisal but were considered uncertain by the committee and thus not appropriate to inform decision-making, as the EMBRACA trial was not powered to detect difference between talazoparib and TPC in these subgroups.

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Objective response rate (ORR)	ORR defined as the proportion of patients with a complete or partial response as defined by the modified RECIST 1.1 in the ITT with measurable disease population by investigator.	**Yes**, within the PF state, a certain proportion of patients (i.e., "responders") responded to the treatment and achieved objective responses (CR or PR), with the remaining patients in SD. A constant ratio of responders to non-responders was assumed. Frequencies of healthcare resource use differed by response status, but the same utility value was applied.	When response rate was not considered within the economic analysis (investigated within a scenario analysis), the ICER was higher compared to the base case.	The EAG explained that no evidence supporting differential resource use depending on response type was provided. It also noted that there was no precedent in using this approach in previous appraisals for advanced breast cancer. The committee concluded that resource use that does not differ by response type was appropriate for decision making.	N/A – committee-preferred assumptions excluded the impact of response status.
Time to treatment discontinuation (TTD)	N/R	**Yes**, the company used EMBRACA trial median TTD data to estimate treatment costs for patients treated with talazoparib and TPC.	The modelling of time to treatment discontinuation was a key driver of the cost-effectiveness results, with the EAG's scenario increasing the ICER from £33,016 to £50,938.	The committee preferred the use of the KM curves directly from the EMBRACA trial to estimate TTD for talazoparib and TPC.	4.4% of people in the talazoparib arm were still on-treatment at the end of 5 years in the EMBRACA trial and therefore the use of KM directly may underestimate the true cost of treatment with talazoparib.
Adverse events	The incidence of adverse events, including serious adverse events, change in clinical laboratory tests (serum chemistry and haematology), change in vital signs and concomitant medication use.	**Yes**, the ten most frequently occurring treatment-related Grade 3–4 serious AEs were included in the economic model.	Adverse events were not reported to be a key driver of cost-effectiveness.	N/A – Topic not discussed by committee, no preferences identified.	N/A – Topic not discussed by committee.
HRQoL	Patient-reported outcomes were assessed as an exploratory efficacy endpoint using the EORTC QLQ-C30 and EORTC QLQ-BR23 scales at baseline, Day 1 of each cycle, and at the end of treatment.	**Yes**, EORTC QLQ-C30 data collected within the trial were mapped to EQ-5D-3L based on an algorithm described in Longworth 2014.[80] The results were used to inform utilities for the PF health state (CR/PR and SD).	The utility values for the PF health state were a key driver of cost-effectiveness.	As the EMBRACA trial was an open-label trial, the potential for bias in response by treatment arm exists. The EAG considered that it was inappropriate to use PF health state utilities that differ depending on treatment in the company	The committee acknowledged that the treatment-specific PF utility values from EMBRACA were considered uncertain because of its open-label design, which is prone to bias.

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		Utility values were estimated separately for talazoparib and TPC in the PF health state. The utility estimate for progressive disease was derived from the literature, calculated as the midpoint between values reported in Huang et al. 2020 and Lambert-Obry et al. 2018.[81, 82]		base case. The committee concluded that the EMBRACA utilities were acceptable, given there may be other factors that could affect how a person feels when having talazoparib or the comparator treatment, for example the need for red blood transfusions or hospital visits. The EAG explained that the Huang et al. 2020 was only an abstract with unclear population information, and thus the committee preferred the use of the value from Lambert-Obry et al. 2018.[81]	

Abbreviations: AE: adverse event; CR: complete response; EAG: External Assessment Group; EORTC QLQ-BR23: breast cancer specific European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – BR 23; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30; HRQoL: health-related quality of life; ICER: incremental cost-effectiveness ratio; IRF: independent radiology facility; KM: Kaplan–Meier; ORR: objective response rate; OS: overall survival; TPC: treatment of physician's choice; PF: progression-free; PFS: progression-free survival; PH: proportional hazards; PR: partial response; RPSFT: Rank preserving structural failure time; SD: stable disease; TTD: time to treatment discontinuation.
Source: NICE TA952.[1]

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B.2.2 Resource use assumptions

Resource use and cost elements included in the talazoparib evaluation (TA952) that are most relevant to the current evaluation were:

- **Drug acquisition costs** for talazoparib and TPC; capecitabine, eribulin and vinorelbine) were included within the cost-effectiveness analysis. Unit costs were derived from standard sources including the British National Formulary (BNF) and Drugs and pharmaceutical electronic market information tool (eMIT).
- **Drug administration costs** were applied to intravenous (IV) drugs, which differed by the time of administration (initial versus subsequent regimen) and the duration of each infusion. Orally administered medications did not incur ongoing administration costs; however, in the model, a specific administration cost was applied for talazoparib at treatment initiation.
- **Red blood cell transfusions for patients with anaemia** were considered in the model. The company used a rate of 8.3% as published in Mahtani *et al.* (2022) because the rate of transfusions in the EMBRACA trial (38.1%) was too high and did not reflect anticipated UK clinical practice.[83]
    - The EAG considered that the EMBRACA rates should be used because there was uncertainty in the correlation between the rate of red blood cell transfusion, dose modifications, and the efficacy of talazoparib. The committee concluded that a rate of 23.1%, a midpoint of the EMBRACA (38.1%) and Mahtani (8.3%) values was appropriate for decision making. The committee agreed that the NHS transfusion rate for talazoparib will be lower than the rate in EMBRACA, with clinical experts noting that in practice they would manage anaemia with dose reduction first instead of red blood cell transfusion, because transfusion is associated with risks. The committee noted that there is uncertainty in how this lower transfusion rate would impact the rate of dose reductions and thus the treatment effect of talazoparib and patients' quality of life seen in the trial.
- **Subsequent treatment costs** were applied to everyone in the progressed disease health state, assuming that both treatment arms incurred the same subsequent treatment costs based on the combined TPC costs.
    - The EAG disagreed with this approach as they considered that not everyone would choose to have a subsequent treatment and it was unlikely that subsequent treatments would continue until death. The EAG considered that it would be more appropriate to model subsequent treatments as a one-off cost applied at the time of progression. Therefore, the EAG applied a micro-costing option using EMBRACA per arm subsequent treatment data, adjusted to remove PARP inhibitors and reweighted such that patients only receive one treatment at a time (EMBRACA reports the proportions of patients receiving subsequent treatments at any point post-progression, which sum to greater than 100%). The committee concluded that this approach was acceptable for decision making.
- **Health state costs** were considered within the model, including the costs associated with PF (complete response [CR]/partial response [PR] and stable disease [SD]) and progressive disease (including oncology consultant visits, CT scans, red blood cell transfusions and platelet transfusions) health states**.** The frequency of resource use was based on UK clinical opinion due to lack of data.

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    - In the original submission, the company assumed that resource use in the PF health state differed depending on whether people had a response (CR/PR) or SD. However, the EAG disagreed with this assumption and the company subsequently changed its approach such that resource use did not differ by response type.

- **Terminal care costs** representing the management, monitoring and resource use for patients in the months prior to death and were applied to patients who enter the death state as a one-off cost. A weighted terminal care cost was calculated using the approach used in TA639 with unit costs sourced from PSSRU.[76]
- **Adverse event costs** covering the cost of treating common grade 3 and 4 adverse events (AEs) were included with costs per AE sourced from 2020/21 National Cost Collection data. In the original submission, the company modelled the cost of treating neutropenia using an NHS outpatient appointment cost and the cost of treatment with an immunostimulant (filgrastim) in the PF health state.
    - The EAG used the cost of a 14-day single course of filgrastim for treating an episode of neutropenia because filgrastim posology is a daily dose for no more than 14 days. In its revised analyses at consultation, the company submitted an updated base case and used the cost of a 14-day course of filgrastim for treating an episode of neutropenia, which was accepted by the committee.
- ***BRCA* testing costs** were considered appropriate by the committee for a proportion of patients (19%) as it noted that although *BRCA* testing is routine for people with TNBC, some people with HR+/ HER2− BC were not currently eligible.

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B.3 Clinical effectiveness

Summary of clinical effectiveness of olaparib: OlympiAD

- OlympiAD was a high quality, multicentre, Phase III, open-label randomised controlled trial (RCT) that assessed the efficacy and safety of olaparib monotherapy in comparison with chemotherapy TPC for the treatment of patients with g*BRCA*m HER2–negative mBC
    - In the OlympiAD 302 patients were randomised into the two treatment arms (2:1 olaparib [n=205], TPC [n=97]), stratified according to previous use of chemotherapy for metastatic disease (yes vs no), hormone receptor status (HR+/HER2− vs TNBC) and previous use of platinum-based therapy (yes vs no)
    - Treatment was continued until disease progression or unacceptable toxic effects occurred
    - Patient baseline characteristics and demographics were well-matched between arms
- OlympiAD demonstrates that olaparib monotherapy significantly improved the outcomes of patients with g*BRCA*m HER2-negative mBC. At the primary analysis for PFS (data cut-off [DCO] 9th December 2016):
    - Patients in the olaparib group had a statistically significant and clinically meaningful improvement in PFS compared to the TPC group (median PFS: 7.0 months versus 4.2 months, respectively; hazard ratio [HR] for disease progression or death: 0.58 [95% CI: 0.43–0.80; P<0.001] as assessed by blinded independent central review [BICR])
    - A statistically and clinically meaningful benefit in objective response rate (ORR) was also observed for patients treated with olaparib (59.9%) compared to TPC (28.8%)
- Analysis of OS and the safety of olaparib was also performed at a secondary DCO: 25th September 2017:
    - OlympiAD was not powered to assess differences in OS between treatment groups, and whilst OS numerically favoured olaparib, there was no statistically significant demonstration of improvement for olaparib compared to TPC (median OS: 19.3 months vs 17.1 months; HR: 0.90; 95% CI: 0.66–1.23; P=0.513).
    - Safety analysis demonstrated olaparib is well tolerated, with the rate of grade 3 or higher AEs being lower (38.0%) for olaparib than TPC (49.5%)
    - AEs were generally of low grade and there was a low rate of discontinuation amongst the olaparib group (4.9%)
    - The risk of anaemia also did not increase with olaparib treatment

Summary of indirect evidence

- In the absence of head-to-head evidence comparing the efficacy of olaparib and talazoparib in this treatment setting, an anchored ITC compared two studies: OlympiAD and EMBRACA
- The EMBRACA trial analysed the efficacy and safety of talazoparib compared to TPC for patients with locally advanced BC and/or mBC with g*BRCA*m and ECOG performance status ≤2
- A Bayesian fixed-effects ITC of data was performed using PFS assessed by BICR as the outcome of interest. A safety data comparison was also performed
- No difference in PFS assessed by BICR was found between olaparib and talazoparib from the ITC analysis (HR: 1.09; 95% Credible Interval [CrI]: 0.72–1.65).
- The ITC also found no notable difference in the overall risk of any-grade AEs between olaparib and talazoparib treatment, although the CrIs were wide (OR 1.07, CrIs: 0.13, 9.15). There were slight differences in the types of AEs that were of higher risk in talazoparib or olaparib-treated patients, indicating a differential AE profile between the two treatments.
- The results of the ITC show that olaparib was associated with comparable efficacy and safety in compared with talazoparib. Based on this, a cost-comparison approach was considered suitable for this submission

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B.3.1 Identification and selection of relevant studies

A systematic literature review (SLR) was conducted to identify published RCT data for the management of patients with HER2– locally advanced or mBC and g*BRCA*m. Initial searches of electronic databases were performed in May 2019. Hand searching of conference proceedings, health technology assessment agencies and reference lists were also performed. Searches were updated in November 2023. Overall, the searches identified a total of 84 relevant publications, reporting on 13 clinical trials. The SLR identified only one clinical trial, the OlympiAD trial, that provides clinical evidence for olaparib monotherapy for the treatment of HER2− g*BRCA*m mBC.[84, 85]

See Appendix F for full details of the process and methods used to identify and select the clinical evidence relevant to the treatment being evaluated.

B.3.2 List of relevant clinical effectiveness evidence

OlympiAD was the only trial identified by the SLR that provides clinical evidence on the efficacy and safety of olaparib as a treatment in the patient population of relevance for this submission. A summary of the OlympiAD trial is presented in Table 6.

Table 6: Clinical effectiveness evidence

Study	OlympiAD trial (NCT02000622)[84, 85]
Study design	Phase III, multicentre, randomised, open-label trial
Population	Patients with HER2-negative mBC and germline *BRCA* mutation. Patients had previously received no more than two chemotherapy regimens for metastatic disease. Patients with HR+ who had received at least one prior endocrine therapy unless contraindicated.
Intervention(s)	Olaparib (300 mg twice daily)
Comparator(s)	SOC chemotherapy with a single-agent of the physician's choice (TPC) (selected from three pre-specified chemotherapy regimens: capecitabine, eribulin, or vinorelbine in 21-day cycles)
Indicate if study supports application for marketing authorisation (yes/no)	Yes
Reported outcomes specified in the decision problem	• Progression-free survival (PFS) • Overall survival (OS) • Response rate (ORR) • Adverse events (AEs) • Health-related quality of life scores (HRQoL)
All other reported outcomes	• Treatment satisfaction score • Time from randomisation to a second progression event or death after a first progression event (PFS2)

Abbreviations: AE: adverse events; *BRCA*: breast cancer susceptibility gene; HER2: human epidermal growth factor receptor type 2; HR+: HR-positive; HRQoL: health-related quality of life; mBC: metastatic breast cancer; ORR: objective response rate; OS overall survival; PFS: progression-free survival; SOC: standard of care; TPC: treatment of physician's choice.
Source: Robson *et al.* (2017),[84] Robson *et al.* (2019)[85]

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B.3.3 Summary of methodology of the relevant clinical effectiveness evidence

B.3.3.1 Trial design

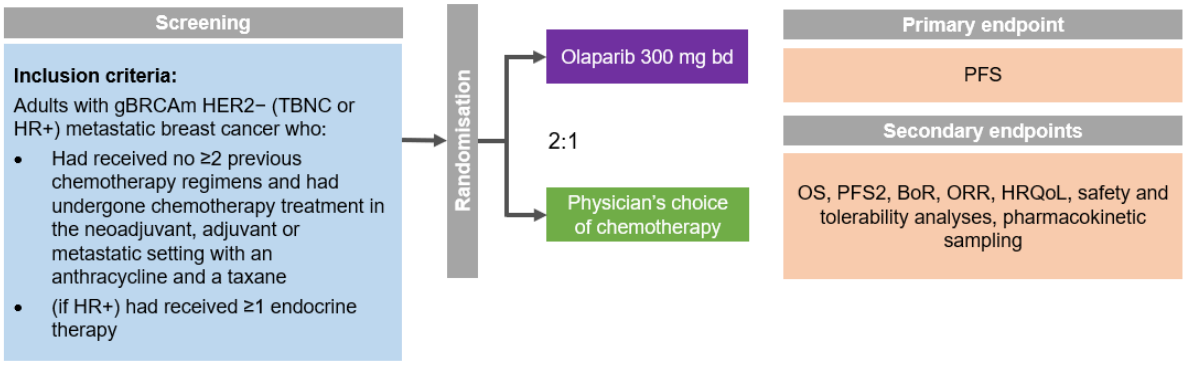
The OlympiAD trial was an international, Phase III, multicentre, open-label, RCT that assessed the efficacy and safety of olaparib in comparison with TPC chemotherapy for patients with g*BRCA*m HER2− mBC. The overall trial methodology is summarised in Table 7 and Figure 5.[84, 85]

Patients were randomly assigned to receive olaparib (300 mg twice daily) or TPC in a 2:1 ratio. Randomisation was stratified according to previous use of chemotherapy for metastatic disease (yes vs no), hormone receptor status (HR+/HER2− vs TNBC) and previous use of platinum-based therapy (yes vs no). This information was obtained locally at the time of trial registration with the use of an interactive voice or Web response system.

The OlympiAD trial was open-label and therefore not blinded, due to different methods and timing of chemotherapy administration and toxicity profiles for patients receiving olaparib and TPC. Given that performing a blinded study was not possible, rigorous methodology was employed to ensure that the assessment of the primary endpoint was robust by performing blinded independent central review (BICR) of all patient scans prior to primary PFS analysis.

The primary endpoint of the OlympiAD trial was PFS, which was assessed at the primary DCO (9th December 2016), alongside secondary endpoints objective response rare (ORR), time to second progression event (PFS2), time to first subsequent treatment (TFST), time to second subsequent (TSST), OS and safety. The median follow-up was 14.5 months for the olaparib group and 14.1 months for the TPC group. Updated OS and safety analyses were performed at the secondary DCO (25th September 2017), which had a median follow-up was 25.3 and 26.3 months for the olaparib and TPC groups, respectively.

Figure 5: Flow chart of study design



Abbreviations: g*BRCA*m: germline breast cancer susceptibility gene mutated; HER2: human epidermal growth factor receptor 2; HR: hormone receptor; PRO: patient reported outcomes; RECIST: Response Evaluation Criteria in Solid Tumors version 1.1; TNBC: triple negative breast cancer.
Source: AstraZeneca Data on File (OlympiAD CSR).[86]

B.3.3.2 Trial methodology

The OlympiAD trial methodology is summarised in Table 7 and outcome measures and definitions are summarised in Table 9.

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Table 7: Summary of trial methodology

Trial name	OlympiAD (NCT02000622)[84, 85]
Location	OlympiAD was conducted across 19 countries worldwide including: Bulgaria, China, Czech Republic, France, Hungary, Italy, Japan, Korea, Mexico, Peru, Poland, Romania, Russia, Spain, Switzerland, Taiwan, Turkey, United Kingdom and United States
Trial design	The OlympiAD trial was a high-quality, international, Phase III, multicentre, open-label, controlled trial that assessed the efficacy and safety of olaparib in comparison with SOC chemotherapy for patients with g*BRCA*m HER2− mBC
Eligibility criteria for participants	Patients were deemed eligible for inclusion in the OlympiAD trial if they were: • ≥18 years of age • Had HER2− mBC • Both HR+/HER2− and TNBC patients were permitted • Had confirmed deleterious or suspected deleterious g*BRCA*m • Patients were required to have received no more than two previous chemotherapy regimens for metastatic disease and had received chemotherapy treatment in the neoadjuvant, adjuvant or metastatic setting with an anthracycline (unless it was contraindicated) and a taxane • At least one endocrine therapy was administered to patients with HR+/HER2− mBC unless contraindicated • Previous neoadjuvant or adjuvant platinum treatment was allowed if ≥12 months had passed since it was last given. If no evidence of disease progression had occurred during treatment, platinum treatment was also permitted for patients with metastatic disease • Patients were required to have normal baseline organ and bone marrow function, as well measurable disease. Measurable disease was defined as at least one lesion suitable for baseline and subsequent assessment for disease according to modified RECIST, version 1.1 Full inclusion and exclusion criteria are presented in Appendix I
Intervention	Olaparib administered orally at a dose of 300 mg twice daily
Comparator	Three pre-specified standard chemotherapies (repeated every 21 days) were prescribed according to TPC: • Capecitabine administered orally at a dose of 2,500 mg per square meter of body-surface area daily (divided into two doses) for 14 days • Eribulin mesylate administered intravenously at a dose of 1.4 mg per square meter on day 1 and day 8 • Vinorelbine administered intravenously at a dose of 30 mg per square meter of body surface area on day 1 and day 8
Method of study drug administration	Olaparib was administered orally
Permitted and disallowed concomitant medication	Investigators were able to prescribe any medications or treatments that were considered necessary for the patients as long as it was not considered to interfere with the study. There were detailed exceptions that were not permitted and all concomitant medications were recorded in detail. Any unplanned diagnostic, therapeutic or surgical procedure also performed during the study period, including blood transfusions, were also recorded. Concomitant medications included the following: • Contraception • Anti-hormonal agents: tamoxifen, anastrozole or letrozole • Anti-emetics/ anti-diarrhoeals (after reporting an AE) • Anti-coagulant therapy

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	• Bisphosphonates or RANKL inhibitor started at least 5 days prior to randomisation • Subsequent therapy for cancer after continuation (details were collected) Disallowed medications include the following: • Other anti-cancer agents • Live virus and bacteria vaccines • CYP3A inhibitors: ketoconazole, itraconazole, ritonavir, indinavir, saquinavir, telithromycin, clarithromycin and nelfinavir • CYP3A inducers: phenytoin, rifampicin, rifapentine, rifabutin, carbamazepine, phenobarbitone, nevirapine, modafinil and St John's Wort
Primary outcome(s)	The primary endpoint of the OlympiAD trial was PFS (defined in Table 8)
Secondary endpoints	Secondary and safety outcomes of the OlympiAD trial included: • OS • PFS2 • BoR • ORR • HRQoL • Safety and tolerability analyses • Pharmacokinetic sampling Secondary endpoints are defined in Table 8
Exploratory endpoints (relevant to the submission)	Exploratory outcome variables include:[86] • The impact of olaparib on symptoms and global health status/HRQoL • The health economic impact of treatment and the disease on hospital-related resource use • Treatment satisfaction measured by CTSQ
Pre-planned subgroup analyses	Subgroup analyses of the key OlympiAD endpoints were performed to assess consistency of outcomes, including PFS. The following subgroups were of primary interest, based on predicted prognostic factors and baseline stratification: • Previous chemotherapy for mBC • Hormone receptor status (HR+/HER2− or TNBC) • Previous platinum-based therapy for breast cancer • Measurable disease • Progressive disease at the time of randomisation • *BRCA* mutation type • Age (<65 years or ≥65 years) • Region (Asia, Europe and North and South America) • Race (White or Other)
Duration of study and follow-up	• Data from the primary DCO (9th December 2016) represent a median duration of follow-up of 14.5 months and 14.1 months in the olaparib and TPC groups, respectively[84] • Data from the secondary DCO (25th September 2017) represent a median duration of overall follow-up of 25.3 and 26.3 months in the olaparib and TPC group, respectively[85]

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Abbreviations: AE: adverse event; BoR: best overall RECIST response; BICR: blinded independent central review; *BRCA*: breast cancer susceptibility gene; CTSQ: Cancer Therapy Satisfaction Questionnaire; ECG: echocardiogram; DCO: data cut-off; EORTC: European Organisation for Research and Treatment of Cancer; EORTC QLQ-C30: EORTC Core Quality of Life questionnaire; HR+: HR-positive; HER2: human epidermal growth factor receptor type 2; HER2−: HER2-negative; g*BRCA*m: germline *BRCA* mutation; HR: hormone-receptor; HRQoL: health-related quality of life score; mBC: metastatic breast cancer; ORR: objective response rate; OS overall survival; PFS: progression-free survival; PFS2: Time from randomization to a second progression event or death after a first progression event (PFS2); RANKL: Receptor activator of nuclear factor kappa-B ligand; RECIST: Response Evaluation Criteria in Solid; SAE: serious adverse event; TNBC: triple negative breast cancer; TPC: treatment of physician's choice.
Source: Robson *et al.* (2017)[84], Robson *et al.* (2019)[85], AstraZeneca Data on File (OlympiAD CSR)[86]

Table 8: Outcome measures and definitions

Outcome	Definition
PFS	Time from randomisation until the date of objective radiological disease progression according to modified RECIST 1.1 or death (by any cause). RECIST 1.1 criteria included:[87] • CR: disappearance of all target lesions, pathological lymph nodes must have reduction in short axis to <10mm • PR: At least 30% decrease in sum of diameters of target lesions, using baseline sum of diameters as reference • PD: At least a 20% increase in the sum of diameters of target lesions, where smallest sum on study is used as reference. The sum must also demonstrate an absolute increase of 5mm • SD: Neither sufficient increase or decrease to qualify for PR or PD, using smallest sum on study for reference PFS was assessed by a BICR by two main reviewers and adjudication by a third reviewer in the event of disagreement
OS	Time from the date of randomisation until death due to any cause
PFS2	Time from the date of randomisation to the earliest of the progression event subsequent to that used for the primary PFS or death
BoR	Calculated based on the overall visit responses from each RECIST assessment
ORR	Defined as the number of patients who have a CR or PR determined using RECIST 1.1 criteria (see above) divided by the number of patients with measurable disease
DoR	Defined as the time from the first documentation of CR/PR until the date of progression, or the last evaluable RECIST assessment for patients that did not progress or progressed after two or more missed visits
HRQoL	Adjusted mean change from baseline in global QoL score from the 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 patient
Safety and tolerability	Analyses including AEs, SAEs, discontinuation of investigational product due to AE(s), deaths, laboratory data, vital signs and ECGs

Abbreviations: AE: adverse event; BoR: best overall RECIST response; BICR: blinded independent central review; *BRCA*: breast cancer susceptibility gene; CR: complete response; DoR: duration of response; ECG: echocardiogram; EORTC: European Organisation for Research and Treatment of Cancer; EORTC QLQ-C30: EORTC Core Quality of Life questionnaire; HER2: human epidermal growth factor receptor type 2; g*BRCAm*: germline *BRCA* mutation; HR: hormone-receptor; HRQoL: health-related quality of life score; ORR: objective response rate; OS overall survival; PD: progressive disease; PFS: progression-free survival; PFS2: Time from randomization to a second progression event or death after a first progression event (PFS2); PR: partial response; RECIST: Response Evaluation Criteria in Solid; SAE: serious adverse event; SD: stable disease.
Source: Robson *et al.* (2017)[84], Robson *et al.* (2019)[85], AstraZeneca Data on File (OlympiAD CSR)[86], Schwartz *et al.* (2016)[87]

B.3.3.3 Baseline Characteristics

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Key baseline characteristics were well-balanced across olaparib and TPC groups (Table 9). Patients were well-matched in terms of age, sex, ethnicity, Eastern Cooperative Oncology Group (ECOG) performance status, hormone receptor status, *BRCA* mutation type, metastatic sites and location and prior treatment (chemotherapy and platinum-based therapy). The patient characteristics and demographics from the OlympiAD trial are also comparable with those reported in the EMBRACA trial, further detail on this is provided in Section B.3.8.[88]

Table 9: Baseline characteristics of patients in the OlympiAD study

Characteristic	Olaparib (n=205)	TPC (n=97)
Age, years		
Median	44	45
Range	22–76	24–68
Male sex	5 (2.4)	2 (2.1)
Race or ethnic group[a]		
White	134 (65.4)	63 (64.9)
Asian	66 (32.2)	28 (28.9)
Other	5 (2.4)	6 (6.2)
ECOG performance status[b]		
0	148 (72.2)	62 (63.9)
1	57 (27.8)	35 (36.1)
***BRCA*m type**[c]		
*BRCA*1	117 (57.1)	51 (52.6)
*BRCA*2	84 (41.0)	46 (47.4)
*BRCA*1 and *BRCA*2	4 (2.0)	0
HR status[d]		
HR+/HER2−	103 (50.2)	49 (50.5)
TNBC	102 (49.8)	48 (49.5)
New mBC	26 (12.7)	12 (12.4)
Previous chemotherapy for metastatic mBC	146 (71.2)	69 (71.1)
Previous platinum-based therapy for breast cancer	60 (29.3)	26 (26.8)
≥2 metastatic sites	159 (77.6)	72 (74.2)
Location of the metastasis		
Bone only	16 (7.8)	6 (6.2)
Other[e]	189 (92.2)	91 (93.8)
Measurable disease	167 (81.5)	66 (68.0)

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Data are n (%) unless otherwise specified. [a]Race or ethnic group was self-reported. The other category includes black (five patients), American Indian or Alaska Native (four), unknown (one) and declined to specify (one). [b]ECOG performance status scores range from 0 to 5, with 0 indicating no symptoms, 1 indicating mild symptoms, and higher numbers indicating increasing degrees of disability. [c]In the majority of patients, *BRCA* mutation type was confirmed by central testing with BRACAnalysis® patients in the olaparib group and two patients in the physician's choice chemotherapy group had their mutation type confirmed by local testing only. Percentages may not sum to 100 because of rounding. [d]Hormone receptor positive disease is oestrogen receptor positive, progesterone receptor positive or both. Triple negative disease is human epidermal growth factor receptor type 2 negative, oestrogen receptor negative and progesterone receptor negative. [e]Data for the other category include patients who did not have metastases in the bone, as well as patients who may have had metastases in the bone along with metastases in other location.
Abbreviations: *BRCA*m: breast cancer susceptibility gene mutation; ECOG: European Cooperative Oncology; HR: hormone receptor; HR+: HR-positive; mBC: metastatic breast cancer; TNBC: triple negative breast cancer; TPC: treatment of physician's choice.
Source: Robson *et al.* (2017)[84]

B.3.3.4 Participant flow

A total of 302 patients underwent randomisation, with 97 patients assigned to the TPC group and 205 patients allocated to the olaparib group. At the time of the primary DCO (9th December 2016), 36 (17.6%) patients in the olaparib arm and 3 (3.3%) patients in the TPC arm were still receiving study treatment. Moreover, as of the secondary DCO (25th September 2017), 26 patients were still receiving olaparib but no patients were still being treated with TPC. The median follow-up for OS was 26.3 months for patients receiving TPC and 25.3 months for patients in the olaparib group.

A total of 257 (86.8%) of patients discontinued treatment, including 169 patients (82.4%) and 88 patients (96.7%) in the olaparib and TPC treatment groups respectively. The majority of patients who discontinued treatment in both the olaparib group and TPC did so due to objective disease progression (olaparib: 72.7%, TPC: 74.7%), and a minor proportion discontinued due to AEs (olaparib: 4.9%, TPC: 6.6%), patient decision (olaparib: 3.4%, TPC: 9.9%), or other reason (olaparib: 1.5%, TPC: 5.5%). Further details on the patient disposition are presented in Appendix F.

B.3.3.5 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

Efficacy and safety analyses were performed in accordance with a detailed Statistical Analysis Plan.[86] The definitions used for the study populations in the trials are presented in Table 10. A summary of the key endpoints and their associated DCO are presented in Table 11. A summary of the statistical analysis methods used in the trials are presented in Table 12.

Statistical analyses were performed in two stages. At the primary DCO (9th December 2016), the primary endpoint, PFS, was assessed in addition to secondary endpoints PFS, ORR, PFS2, TFST, TSST, OS (interim) and safety (Table 11). At the secondary DCO (25th September 2017), the final analyses of OS (64% data maturity) and safety data were performed. PFS data were not explored in the secondary DCO as per the statistical analysis plan, as data were 77% mature at the primary DCO.

Table 10: Trial populations used for the analysis of outcomes in OlympiAD

Analysis Set	Definition	Outcomes analysed
Full analysis set: ITT (n=302)	The primary efficacy analysis included all randomised patients and compared the treatment groups on the basis of	Efficacy and HRQoL

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	randomised treatment, regardless of the treatment actually received. All efficacy and HRQoL data were analysed using the Full Analysis Set on an intention-to-treat (ITT) basis and takes into account patients who were randomised but did not go on to receive treatment.	
Safety analysis set (n=296)	All patients who received at least one treatment dose; patients who received at least one dose of olaparib were assigned to the olaparib arm for safety analysis.	Safety
Evaluable for response (EFR) analysis set (n=233)	Subset of ITT patients who have measurable disease at baseline as per the RECIST 1.1 criteria as defined by the BICR data and the investigator assessment data.	Efficacy

Abbreviations: BICR: blinded independent central review; EFR: evaluable for response; HRQoL: health-related quality of life; ITT: intention to treat; PK: pharmacokinetics; RECIST: Response Evaluation Criteria in Solid Tumours.
Source: Robson *et al.* (2017)[84]

Table 11: Data cut-off dates for efficacy and safety analyses presented

Endpoint	Analysis performed at data cut-off	
	Primary DCO (9th December 2016)	**Secondary DCO (25th September 2017)**
PFS[a]	Yes	No
ORR	Yes	No
PFS2	Yes	No
TFST, TSST[b]	Yes	No
OS	Yes (interim)	Yes (final)
Safety	Yes	Yes

[a]BICR; Investigator Assessed. [b]including subsequent therapy.
Abbreviations: BICR: blinded independent central review; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; TFST: time to first subsequent treatment; TSST: time to second subsequent treatment.
Source: Robson *et al.* (2017)[84]

Table 12: Statistical methods for the primary analysis

Hypothetical objective	The study was designed to test the hypothesis that olaparib tablets 300 mg BID have superior efficacy and acceptable tolerability compared to TPC in patients with g*BRCA*m mBC who have previously been treated with anthracycline (unless contraindicated) and a taxane
Statistical analysis	• The primary statistical analysis of the efficacy of olaparib included all randomised patients and compared the treatment groups on the basis of randomised treatment, regardless of the treatment actually received (ITT). When assessing safety and tolerability, summaries were produced based on the Safety Analysis Set. This included all patients who received at least one dose of randomised treatment (olaparib or chemotherapy). The safety data were summarised descriptively and were not formally analysed **Primary endpoint: PFS** • PFS was analysed using a log rank test stratified by the trial stratification factors. The HR together with its 95% confidence interval (CI) and p-value was presented (a HR less than 1 will favour olaparib). This analysis was performed when approximately 230 progression events had occurred. The

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	primary analysis was based on a BICR of disease progression by RECIST 1.1; however, a sensitivity analysis was performed using the investigator-recorded assessment. The Kaplan–Meier method was used to generate time-to-event curves, from which medians and PFS event rates at 12 months were calculated • Subgroup analyses were conducted to assess consistency of treatment effect across potential or expected prognostic factors. An analysis was not to be performed if there were too few events available for a meaningful analysis of a particular subgroup (i.e., if there are less than 20 events in a subgroup) **Key secondary endpoints** • An initial OS and PFS2 analysis was performed at the same time as the primary analysis of PFS and used the same methodology and model as PFS. • A further analysis of OS and PFS2 was performed when the OS data were approximately 60% mature (~190 events) and a multiplicity adjustment was made to account for the different analyses • Supportive analyses of time to subsequent therapy or death, and time to second subsequent therapy or death were provided, using the same methodology as specified for the primary analyses of PFS; however no multiplicity adjustment was applied as these are viewed as supportive endpoints • Objective tumour response rates (based on central review) were summarised for the two treatment arms. In addition, the investigator reported response rates was also summarised
Sample size, power calculation	• It was planned that approximately 310 patients were recruited and randomised (2:1) into the study to achieve 230 events (data maturity is approximately 75%). If the true HR was 0.64, the study would have 90% power to show statistical significance in PFS at the two-sided 5% significance level • It is anticipated that the study accrual period will be approximately 2.6 years and that 230 progression events will be observed approximately 3 years after the first patient is randomised in the study
Data management, patient withdrawals	• Patients were free to withdraw from the study without prejudice to further treatment (withdrawal of consent). Such patients were always asked about the reason(s) and the presence of any adverse events. If possible, they were seen and assessed by an investigator. Withdrawn patients will not be replaced • If a patient withdrew consent (i.e., no further assessment or collection of their data) they were specifically asked if they were also withdrawing consent to the use of any of their samples (tumour and blood) taken during the trial • Data obtained prior to withdrawal of consent was maintained in the clinical database and used in the study reporting • The status of ongoing, withdrawn (from the study) and 'lost to follow up' patients at the time of an OS analysis were obtained by the site personnel by checking the patients notes, hospital records, contacting the patients general practitioner and checking publicly available death registries. In the event that the patient had actively withdrawn consent to collection of further data the vital status of the patient could be obtained by site personnel from publicly available resources where it was possible to do so under applicable local laws
Multiplicity	• A multiple testing procedure (MTP) was employed across the primary endpoint (PFS) and key secondary endpoints (PFS2 and OS), to strongly control the type I error at 2.5% (1-sided) • Time to second progression was only to be tested if statistical significance was shown for PFS • OS was only to be tested if statistical significance was shown for PFS2 • The Lan and DeMets approach that approximates the O'Brien and Fleming

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	spending function was to be employed to preserve the overall 1-sided type I error rate of 2.5%[89]

Abbreviations: BICR: blinded independent central review; CI: confidence interval gBRCAm: germline breast cancer susceptibility gene mutation; HR: hazard ratio; ITT: intention-to-treat; KM: Kaplan-Meier; mBC: metastatic breast cancer; OS: overall survival; PFS: progression-free survival.
Source: Robson et al. (2017)[84]

B.3.4 Critical appraisal of the relevant clinical effectiveness evidence

Full details of the SLR, including methods and results of the quality assessment can be found in Appendix F. A summary of the quality assessments conducted based on the University of York's Centre for Reviews and Dissemination (CRD) checklist for RCTs for OlympiAD trial is presented in Table 13.

Table 13: Assessment of quality and risk of bias in the OlympiAD trial

Criteria	Response	Notes
Was randomisation carried out appropriately?	Yes	-
Was the concealment of treatment allocated adequate?	Yes	-
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	-
Were the care providers, participants, and outcomes assessors blind to treatment allocation?	No	This was an open-label trial due to different methods and timing of chemotherapy administration and toxicity profiles for patients receiving olaparib and TPC. Rigorous methodology was employed to ensure that the assessment of the primary endpoint was robust by performing BICR of all patient scans prior to primary PFS analysis
Were there any unexpected imbalanced in dropouts between groups?	No	-
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	-
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Efficacy analysis was ITT and safety analysis were mITT. No methods were used to account for missing data.

Abbreviations: BICR: blinded independent central review; ITT: intention-to-treat; mITT: modified intention-to-treat; PFS: progression-free survival; TPC: treatment of physician's choice.

B.3.5 Clinical effectiveness results of the relevant studies

OlympiAD met its primary objective, demonstrating superior efficacy in terms of PFS for patients receiving olaparib when compared to patients receiving TPC in g*BRCA*m mBC. Statistical and clinically meaningful benefits of olaparib were also demonstrated amongst the secondary efficacy endpoints, as shown Table 14.

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Table 14: Summary of OlympiAD efficacy endpoints

Outcome Measure	Olaparib (n=205)	TPC (n=97)
PFS (primary DCO: 9th December 2016)		
Number of events, n (%)	163 (79.5)	71 (73.2)
Median PFS	7.03	4.17
HR (95% CI)	0.58 (0.43–0.80)	
Log-rank test: p-valued	0.0009	
OS (secondary DCO: 25th September 2017)		
Number of events, n (%)	130 (63.4)	62 (63.9)
Median OS	19.25	17.12
HR (95% CI)	0.90 (0.66–1.23)	
Log-rank test: p-valued	0.513	
PFS2 (primary DCO: 9th December 2016)		
Number of events, n (%)	104 (50.7)	53 (54.6)
Median PFS2	13.17	9.26
HR (95% CI)	0.57 (0.40–0.83)	
Log-rank test: p-valued	0.0033	
ORR (primary DCO: 9th December 2016)		
Number of events, n (%)	100 (59.9)	19 (28.8)
95% CI for HR	52.03–67.38	18.30–41.25
TFST (primary DCO: 9th December 2016)		
Number of events, n (%)	154 (75.1)	85 (87.6)
HR (95% CI)	0.34 (0.24–0.47)	
Log-rank test: p-valued	<0.0001	
TSST (primary DCO: 9th December 2016)		
Number of events, n (%)	122 (59.5)	69 (71.1)
HR (95% CI)	0.53 (0.38–0.74)	
Log-rank test: p-valued	0.0002	

Abbreviations: CI: confidence interval; DCO: data cut-off; HR: hazard ratio; ORR: objective response rate; OS overall survival; PFS: progression-free survival; PFS2: Time from randomization to a second progression event or death after a first progression event (PFS2); TFST: time to first subsequent cancer therapy; TPC: treatment of physician's choice; TSST: time to second subsequent cancer therapy.
Source: Robson *et al.* (2017),[84] Robson *et al.* (2019),[85] AstraZeneca Data on File (OlympiAD CSR)[86]

B.3.5.1 Primary endpoint: PFS

The risk of disease progression or death was 42% lower and the median PFS was 2.8 months longer with olaparib than with TPC (median PFS: 7.0 months vs. 4.2 months; HR: 0.58; 95% confidence interval [CI]: 0.43–0.80; P<0.001). Given the association between disease progression and poor HRQoL, prolonging PFS can alleviate mBC disease burden for patients and their families.[90] Achieving improvement in PFS represents a key treatment aim, potentially offering patients relief from cancer-related symptoms and treatment-related toxicities as well as the ability to pursue personal goals.[78]

PFS, the primary endpoint, was assessed after 77.5% (234 of 302) patients demonstrated disease progression or had died at the primary DCO (9th December 2016) across both treatment arms. Results were consistent between assessment based on BICR (median PFS: 7.0 months

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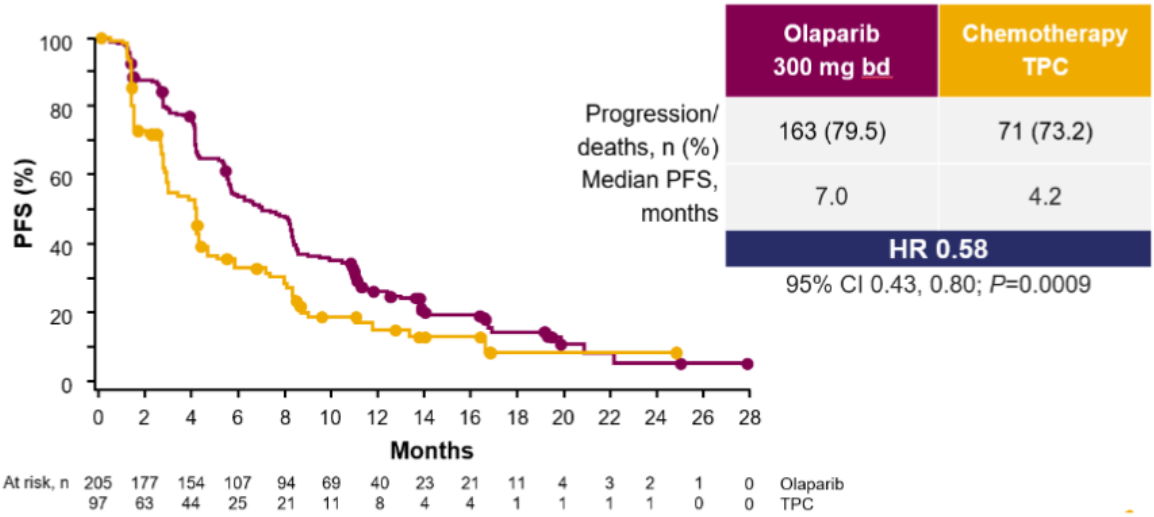
vs. 4.2 months; HR: 0.58; 95% CI: 0.43–0.80; P<0.001) and investigator assessment (median PFS: 7.8 months vs 3.8 months; HR: 0.50; 95% CI: 0.36–0.68; P<0.001).

At 12 months, 25.9% of the patients in the olaparib group and 15.0% of the patients in the TPC group were free of progression or death, assessed by BICR (Figure 6).

Figure 6: Kaplan–Meier curve for PFS based on blinded-independent central review: OlympiAD study (primary DCO: 9th December 2016)



Patients who had not progressed or died at the time of analysis, or who progressed or died after 2 or more missed visits, were censored at the latest evaluable RECIST assessment, or day 1 if the patient had no evaluable visits or no baseline assessment (unless they died within 2 visits of baseline).
Abbreviations: bd: twice daily; PFS: progression-free survival; HR: hazard ratio; TPC; treatment of physician's choice.
Source: Robson *et al.* (2017)[84]

B.3.5.2 OS

At the primary DCO (9th December 2016), a total of 94 patients (45.9%) in the olaparib group and 46 patients (47.4%) in the TPC group had died. OS did not differ significantly between groups (HR: 0.90; 95% CI: 0.63–1.29; P=0.57).[84]

At the time of the secondary DCO (25th September 2017), the OS data were 64% mature and 192 patients had died. Patients who were treated with olaparib achieved a numerically higher median OS of 19.3 months versus 17.1 months in the TPC group results (HR: 0.90; 95% CI: 0.66–1.23; P=0.513), however this was not statistically significant (Figure 7). The median follow-up in censored patients was 25.3 for the olaparib group and 26.3 months for the TPC group. Additionally, numerically, a greater proportion of patients in the olaparib group were alive at 6, 12 and 18 months than patients in TPC (Figure 7): OS was 93.1% versus 85.8%, 72.7% versus 69.2% and 54.1% versus 48.0%, for olaparib versus TPC at 6, 12 and 18 months, respectively.

Although no significant difference in OS was observed between olaparib treatment and TPC, OS numerically favoured olaparib consistently at both the primary and secondary DCO. It is important to note that the OlympiAD trial was not powered to assess differences in OS between treatment groups. Analysis of OS is also likely to be confounded by subsequent treatment, and more patients in the TPC group than in the olaparib group received treatment with PARP inhibitors, platinum-based therapy, and cytotoxic chemotherapy following disease progression (Table 15). This observation was also noted in the EMBRACA trial where an analysis found that

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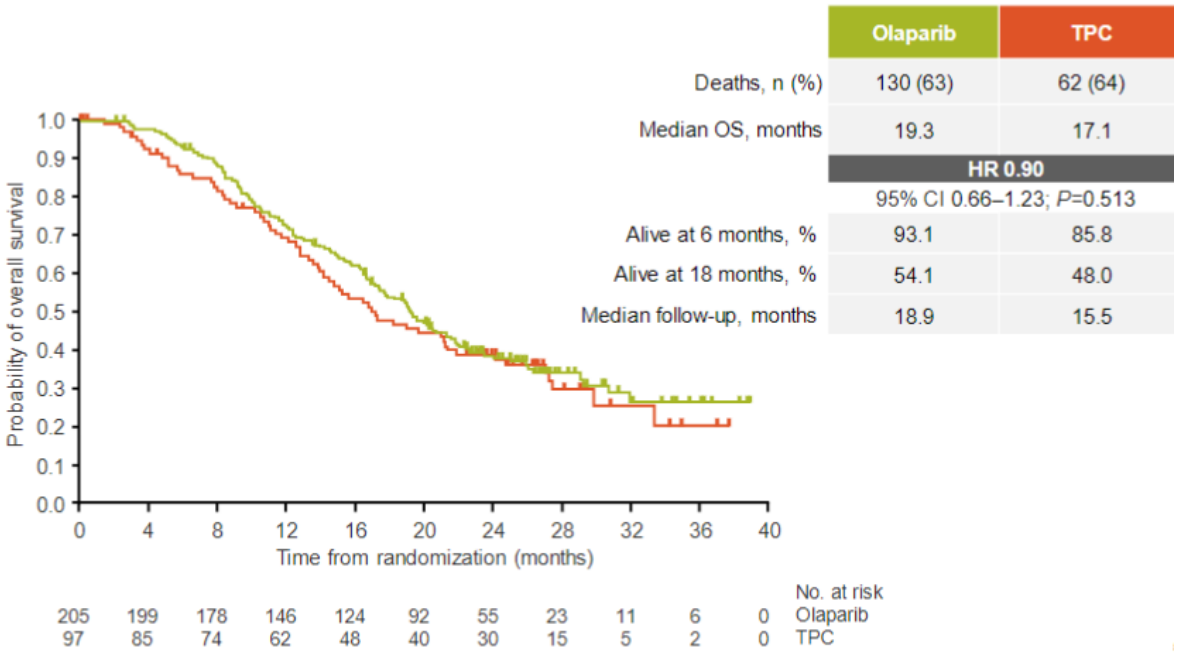
the primary OS analysis was impacted by subsequent use PARP inhibitor and/or platinum therapies (Section B.3.8).[91] Improvements in PFS may suggest a potential for improving OS in patients with mBC, especially for new treatments used in the 2nd-line setting and beyond.[92, 93] The observed PFS benefit with olaparib (See Section B.3.5.1) therefore suggests there is a potential for improving OS.

Figure 7: Kaplan–Meier curve for OS in the olaparib and TPC groups: OlympiAD study (secondary DCO: 25th September 2017)



Patients not known to have died at the time of analysis were censored at the latest recorded date on which the patient was known to be alive.
Abbreviations: CI: confidence interval: OS: overall survival; HR: hazard ratio; TPC; treatment of physician's choice.
Source: Robson *et al.* (2019)[85]

Table 15: Summary of all subsequent cancer therapies among patients who were no longer receiving study treatment at the time of the secondary DCO (25th September 2017)[a,b]

Subsequent treatment, n (%)	Olaparib 300 mg (n=179)	Standard chemotherapy (n=97)
No subsequent cancer therapy	32 (17.9)	18 (18.6)
PARP inhibitor	2 (1.1)	8 (8.2)
Platinum chemotherapy	77 (43.0)	44 (45.4)
Other cytotoxic chemotherapy	125 (69.8)	70 (72.2)
Hormonal therapy	33 (18.4)	24 (24.7)
Targeted/biologics	30 (16.8)	19 (19.6)
Other	8 (4.5)	2 (2.1)

[a]26 olaparib patients in the olaparib arm were continuing to receive study treatment; no patients in the TPC arm continued study treatment; [b]A patient may have received ≥1 type of subsequent cancer therapy.
Abbreviations: PARP: poly (ADP ribose) polymerase; TPC: treatment of physician's choice.
Source: Robson *et al.* (2019)[85]

B.3.5.3 PFS2: Time to second progression

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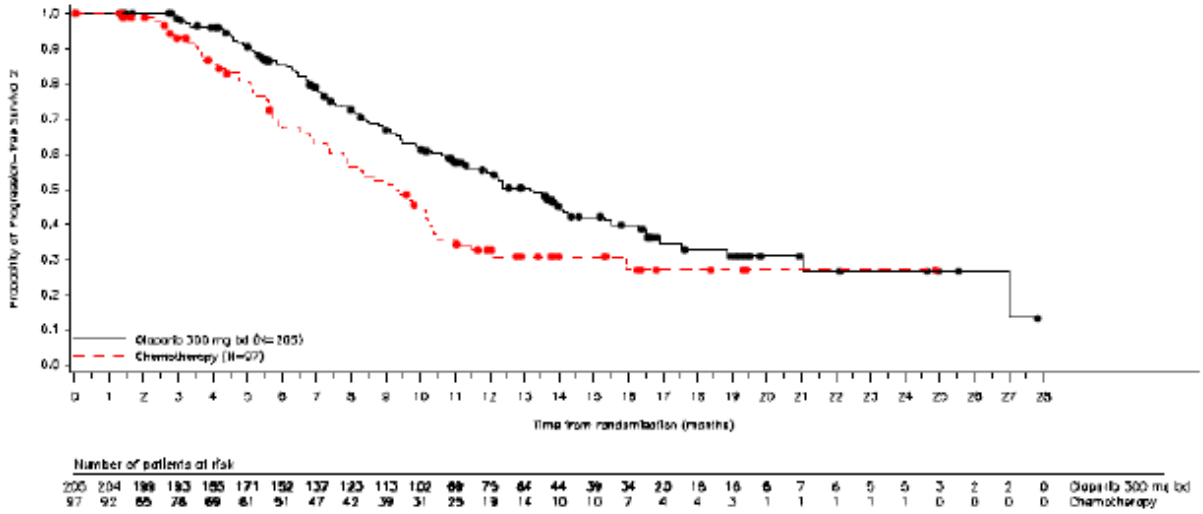
PFS2 allows assessment of whether the PFS benefit of being treated with olaparib persists after initial progression, and thus whether initial olaparib treatment has any impact on response to subsequent therapy. At the time of primary DCO (9th December 2016), 50.7% of patients had secondary progression events or died (PFS2) in the olaparib group, whilst 54.6% of patients in the TPC group had secondary progression events (based on investigator assessment). Olaparib significantly increased the time to second progression (PFS2) by 3.9 months vs TPC (13.2 months vs 9.3 months (HR: 0.57; 95% CI: 0.40–0.83; P=0.003), demonstrating a continued and consistent benefit beyond first progression (Figure 8). In previous studies in solid tumours, PFS2 has been shown to strongly correlate with OS, supporting the use of PFS2 to measure long-term clinical benefit when it is challenging to assess OS, such as in the presence of confounding by subsequent treatments.[94, 95] These results support the clear benefit of treatment with olaparib compared to TPC that was demonstrated in the results of the primary endpoint, PFS.

Figure 8: Kaplan–Meier estimate of time from randomisation to second progression or death (investigator assessed): OlympiAD study (DCO: 9th December 2016)



Patients who had not had a second disease progression or died at the time of analysis, or who had second progression or died after 2 or more missed visits, were censored at the latest evaluable assessments where they were last time known to be alive and without a second disease progression
Abbreviations: CI: confidence interval: PFS: progression-free survival; HR: hazard ratio; TPC; treatment of physician's choice.
Source: AstraZeneca Data on File (OlympiAD CSR)[86]

B.3.5.4 Objective response rate

ORR in the olaparib arm was doubled (59.9%; 95% CI: 52.0–67.4) versus the TPC arm (28.8%; 95% CI: 18.3–41.3), including a higher percentage of patients demonstrating CR (9.0% vs 1.5%) (Table 16). These data are consistent with results from patients who were assessed by the investigator, with a higher percentage of patients in the olaparib arm achieving (57.6%) the objective response in comparison to the TPC patients (22.2%). This is an important result for patients with symptomatic or rapidly progressing disease (Section B.1.2).

At the primary DCO (9th December 2016), the olaparib group had a median DOR of 6.4 months (IQR: 2.8–9.7) and 7.1 months (IQR: 3.2–12.2) in the TPC group. The median DOR was longer in the olaparib group than in the TPC at the secondary DCO (25th September 2017), with median DOR of 6.9 months (IQR: 2.8–10.1) and 4.5 months (IQR: 2.7–8.5) respectively, demonstrating the durability of response to olaparib. Time to response (TTR) is an important consideration for

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symptomatic or rapidly progressing patients. A similar TTR was observed in both arms: 47 days in the olaparib arm and 45 days in the TPC arm, at the primary DCO.

Table 16: Objective response rate (ORR) based on independent central review (evaluable for response analysis set) (DCO: 9th December 2016)

	Olaparib 300 mg	TPC
Response evaluable population, n	167	66
ORR, n(%)	100 (59.9)	19 (28.8)
Complete response, n (%)	15 (9.0)	1 (1.5)
Partial response, n (%)	85 (50.9)	18 (27.3)
Median duration of response, months (95% CI)	6.4 (2.8-9.7)	7.1 (3.2-12.2)
Median time to onset of response, days	47.0	45.0

Abbreviations: CI, confidence interval; N, number of patients in treatment group; ORR: objective response rate; TPC: treatment of physician's choice.
Source: Robson *et al.* (2017).[84]

B.3.5.5 Time to subsequent therapies

There was a statistically significant delay in the TFST in the olaparib patient group when compared to the TPC group (HR: 0.34; 95% CI: 0.24–0.47; P<0.0001, median: 9.4 months vs 4.2 months) at the primary DCO (9th December 2016). This effect was maintained to the secondary DCO (25th September 2017), demonstrating a longer delay in the olaparib patient group than the TPC group (HR: 0.32; 95% CI: 0.23–0.44; P<0.001; median 9.4 months vs 4.2 months) (Figure 9).

TSST was significantly prolonged for olaparib (median: 14.3 months) when compared to TPC (median: 10.5 months) at the primary DCO (9th December 2016). This was also consistent with results at the secondary DCO (25th September 2017) (HR: 0.51; 95% CI: 0.38–0.70; P<0.001; median 14.5 months vs 10.5 months, respectively).

These results suggest that the efficacy of olaparib delays the time to starting the next anti-cancer treatment, offering patients relief from further treatment-related toxicities and prolonging HRQoL. In UK clinical practice, subsequent treatments are likely to include non-targeted treatments such as single-agent chemotherapies, which are associated with toxic effects and decreased HRQoL, as well as requiring regular hospital visits which may impact patients' ability to lead normal lives (Section B.1.2.3).[18,21, 55]

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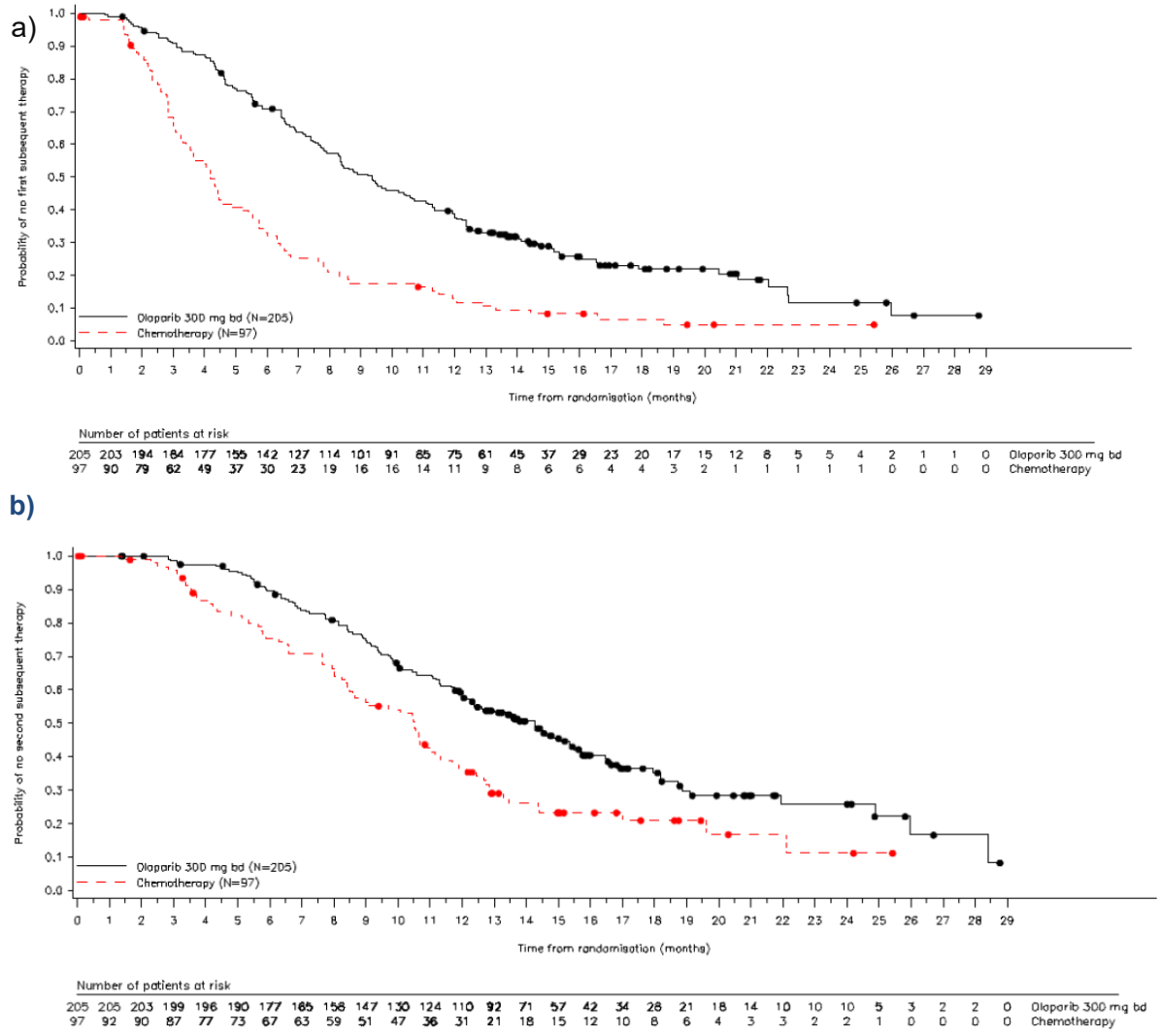
Figure 9: Kaplan–Meier estimate of (a) time to first subsequent treatment or death and (b) time to second subsequent treatment or death (full analysis set): OlympiAD study



Any patient not known to have died at the time of the analysis and not known to have had a further intervention of this type was censored at the last known time to have not received first or second subsequent therapy (for TFST and TSST, respectively), i.e. the last follow-up visit where this was confirmed.
Abbreviations: bd: twice daily; CI: confidence interval; TFST: time to first subsequent treatment; TSST: time to second subsequent treatment.
Source: Robson *et al.* (2017)[84]

B.3.5.6 Patient-reported outcome: health-related quality of life

HRQoL

HRQoL was assessed using EORTC QLQ-C30 at baseline and every 6 weeks until disease progression occurred. EORTC QLQ-C30 is an integrated system for assessing HRQoL in cancer patients participating in international clinical trials, where higher HRQoL response indicates better QoL (range: 0–100). A change by at least 10 points is considered clinically meaningful. Compliance rates for the EORTC QLQ-C30 were high, with 191 patients in the olaparib group and 73 in the TPC group completed the questionnaire at baseline (compliance >95%) and at least one other visit (compliance>75%). Improved or maintained HRQoL is a key treatment goal for patients with mBC and as such, improvements in these endpoints are meaningful for patients.

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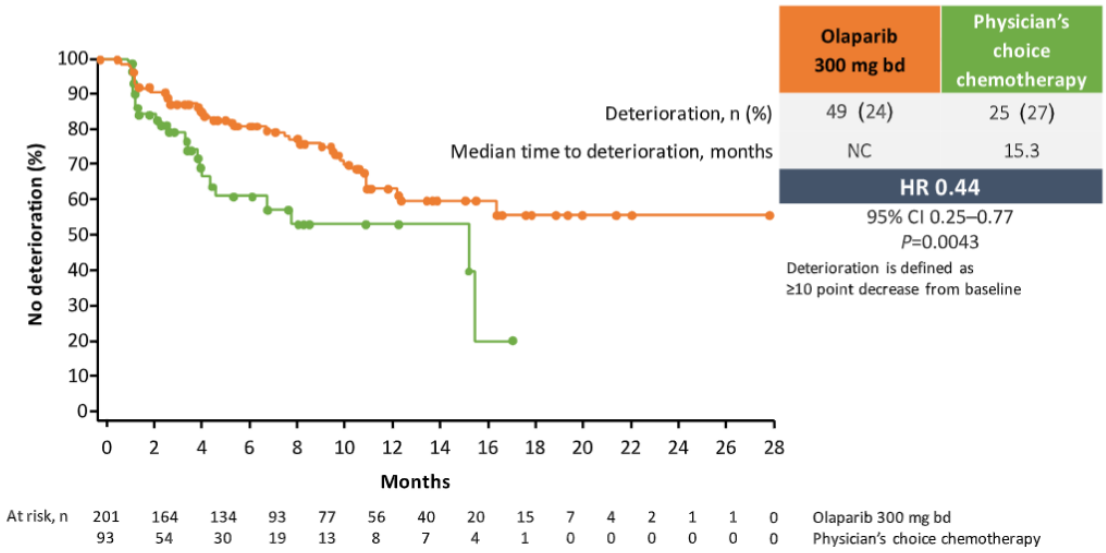
As discussed in Section B.1.2.1.3, progression to mBC has been shown to negatively impact patients' quality of life, with patients reporting physical effects including pain, disrupted body image and daily life limitations. In addition, many patients report the impact of mBC on family roles and interpersonal relationships, as well as psychological effects.[55] Furthermore, whilst existing treatments can help to reduce symptoms, the toxic effects of treatment decreases HRQoL.[55] Maintaining HRQoL is therefore a key treatment aim for patients with mBC.

Olaparib treatment led to statistically significant improvement in HRQoL compared to TPC (3.9±1.2 vs −3.6±2.2, respectively; difference: 7.5; 95% CI: 2.48–12.44; P=0.0035). More than one-third (38.8%) of patients in olaparib arm achieved a clinically meaningful improvement of ≥10 points vs 22.8% in the TPC arm.[96] Patients in the olaparib arm also experienced a prolonged time free from HRQoL deterioration: the proportion of patients (ITT) who were free of deterioration (global HRQoL) was 81.5% in the olaparib arm versus 61.2% in the TPC arm at 6 months, and 64.0% versus 53.5% at 12 months, respectively. The median time to global HRQoL deterioration was not reached in olaparib patients and was 15.3 months for TPC (HR: 0.44; 95% CI: 0.25–0.77; P=0.0043) (Figure 10). However, there may be limitations associated with this analysis due to informative censoring. From baseline, olaparib patients demonstrated the best overall clinically meaningful improvement in HRQoL score from baseline (OR: 2.15; 95% CI: 1.10–4.42). Best overall response rates were observed in the emotional and global functional subscales for olaparib, other subscales were comparable (Figure 11).

Figure 10: Kaplan–Meier plot of time to global HRQoL deterioration. Only patients with a baseline global HRQoL score ≥10 are included (n=201 olaparib, n=93 physician's choice chemotherapy)



Abbreviations: bd: twice daily; CI, confidence interval; HR, hazard ratio; HRQoL, health-related quality of life; NC, not calculable.
Source: Robson M. et al. Poster presented at ESMO Annual Meeting, 8–12 September 2017, Madrid, Spain; primary DCO (9th December 2016).[97]

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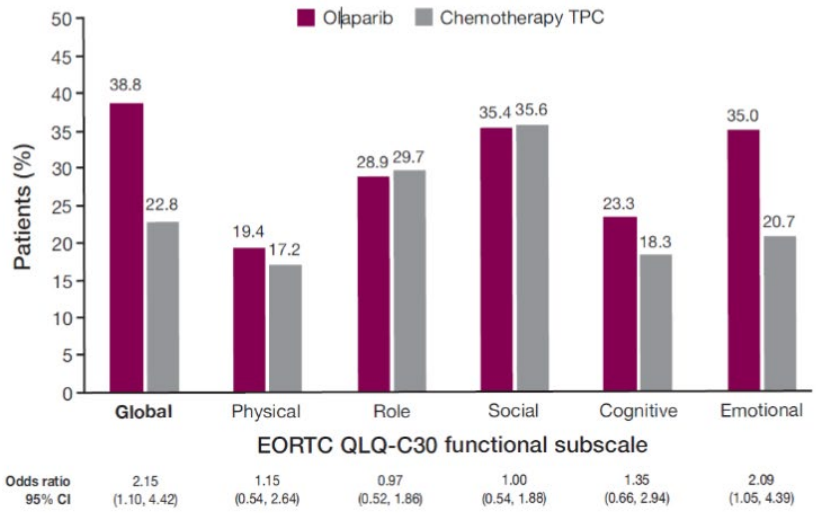
Figure 11: Best overall response rates for EORTC QLQ-C30 functional subscales (global health status/QoL and functional)



Best overall response was defined as a ≥10 point change in baseline in QLQ-C30 Score. Non-responders were defined as having a <10-point change from baseline in QLQ-C30 score. Patients with a best response of 'other' were excluded.
Abbreviations: CI: confidence interval; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core-30; QoL: quality of life; TPC: treatment of physician's choice.
Source: Robson M. et al. Poster presented at ESMO Annual Meeting, 8–12 September 2017, Madrid, Spain; primary DCO (9th December 2016).[97]

Treatment satisfaction

Treatment satisfaction was assessed using CTSQ-16, administered at baseline and then every 6 weeks. Scores ranged from 0 to 100, with higher scores associated with greater treatment satisfaction. Across the majority of visits, mean scores of treatment satisfaction were higher in the olaparib group (range: 71.6–89.3) compared with the TPC group (range 62.5–77.8). Similar results were shown for therapy expectations and feeling less impact of side effects.

B.3.6 Subgroup analysis

Subgroup analyses were explored for the primary endpoint (PFS) to assess the consistency of treatment effect across potential or expected prognostic factors, but were not powered to show differences between olaparib and TPC. The results of these subgroup analyses should therefore be interpreted with caution. The treatment effect in terms of PFS benefit was consistently demonstrated across all pre-specified subgroups (a numerical benefit was seen for olaparib over TPC in all subgroups, and the global interaction test of PFS showed no evidence of treatment effect being different across all pre-specified subgroups p=0.1933). Clinically meaningful reductions in the risk of progression or death in olaparib-treated patients (ranging from 18% to 61%) were observed across all the pre-specified subgroups. These results provide supportive evidence for the benefit of olaparib over TPC.

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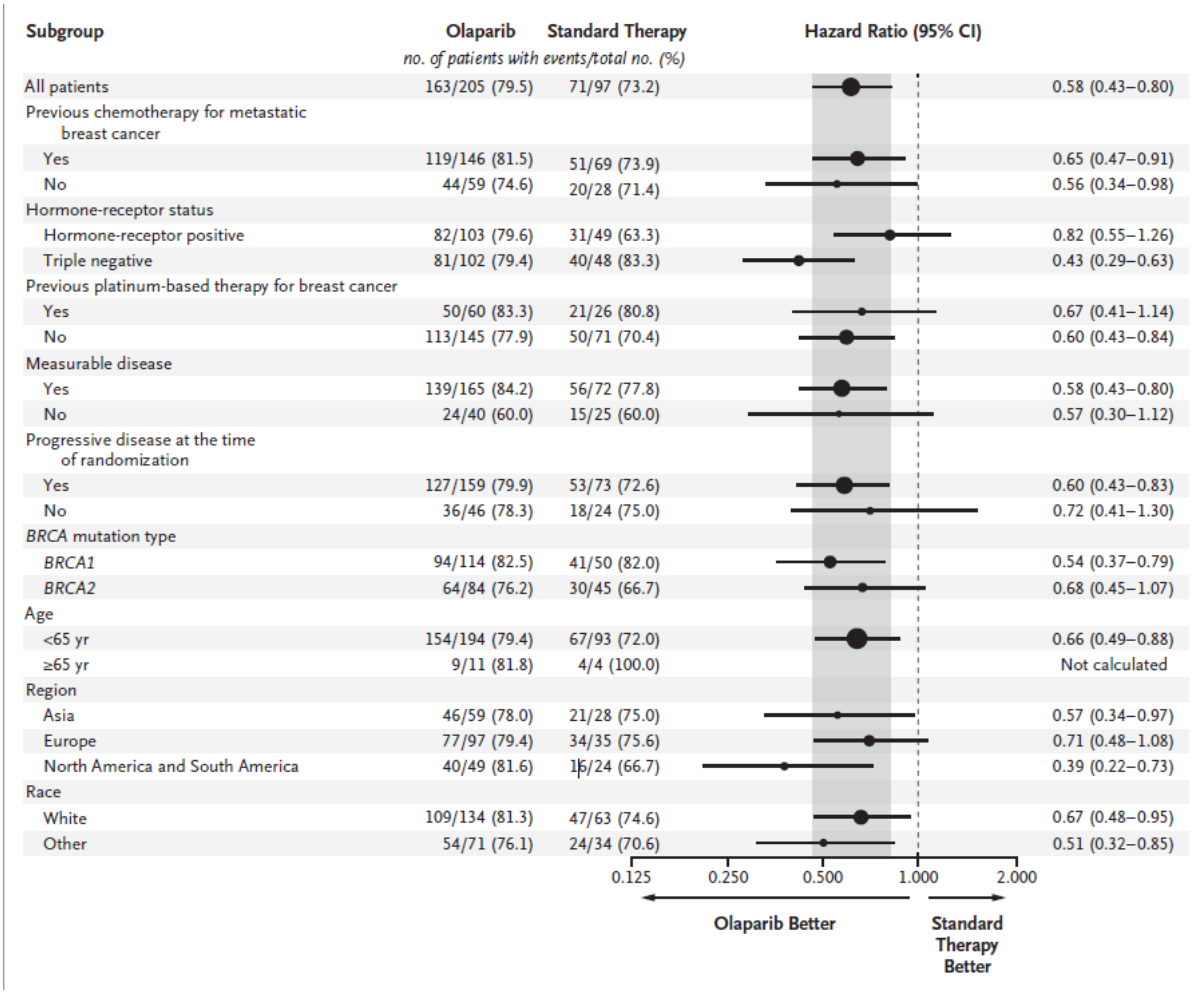
Figure 12: Forest plot for subgroup analyses of PFS (primary DCO: 9th December 2016)



Hormone receptor positive disease is oestrogen receptor positive (ER+), progesterone receptor positive (PgR+) or both. TNBC is HER2 negative, ER negative, and PR negative
Abbreviations: CI: confidence interval; HER2: human epidermal growth factor receptor type 2; PFS: progression-free survival; TNBC: triple negative breast cancer.
Source: Robson *et al.* (2017)[84]

B.3.7 Meta-analysis

As only one trial evaluating the efficacy and safety of olaparib in the relevant patient population and indication was identified, a meta-analysis was not necessary.

B.3.8 Indirect and mixed treatment comparisons

In the absence of head-to-head evidence comparing the efficacy and safety of olaparib versus talazoparib in this treatment setting, an ITC was required. While the SLR described in Section B.3.1 identified meta-analyses and ITCs at the title/abstract review, secondary studies were not included within the eligibility criteria of the SLR and were therefore subsequently excluded. The reference lists of these publications were then searched to ensure all relevant trials were captured within the SLR.

A Bayesian fixed-effects ITC was performed to simulate the comparative efficacy and safety between the two treatments, as reported in McCrea *et al.* (2021).[2] A similar ITC reported by Wang *et al.* (2021) corroborated these results, finding no statistically significant difference between olaparib and talazoparib in terms of efficacy and safety. The results from McCrea *et al.*

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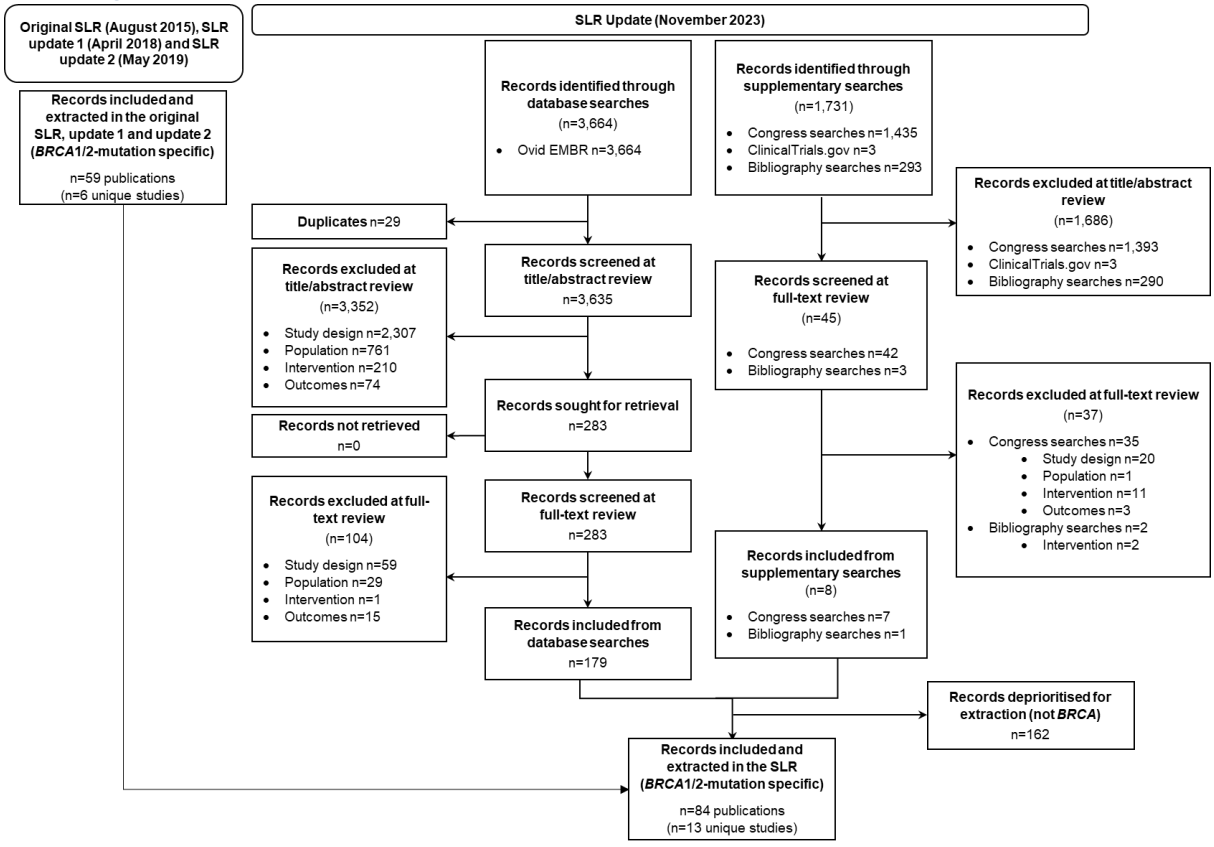
(2021) have been used to inform the economic model, and thus the ITC conducted in Wang *et al.* (2021) has not been reported in full here.[3]

B.3.8.1 Identification of comparator studies

As discussed in Section B.3.1, an SLR was conducted in May 2019, and updated in November 2023, to identify RCTs that reported data on efficacy and safety of interventions, including PARP inhibitors, for the treatment of patients with HER2− g*BRCA*m locally advanced or mBC (Figure 13). Overall, the searches identified a total of 84 relevant publications, reporting on 13 clinical trials: ASCENT, BRAVO, BROCADE, BROCADE 3, the California Cancer Consortium trial, CBCSG006, EMBRACA, Impassion130, NCT02849496, OlympiAD, S1416, SYNERGY and TNT.[84, 88, 98-108]

Only the OlympiAD and EMBRACA trials were considered eligible for ITC as they reported PFS outcomes for PARP inhibitors, olaparib and talazoparib, respectively (B.3.8.2).

Figure 13: Preferred reporting items for systematic reviews and meta-analysis (PRISMA) flow diagram



Abbreviations: HTA: Health technology assessment; PARP: Poly(ADP-ribose) polymerase; PFS: Progression-free survival; SLR: Systematic literature review; TNBC: Triple-negative breast cancer.

B.3.8.2 Studies of interest

For this ITC analysis, studies were only eligible if they investigated PARP inhibitor monotherapies in line with their respective marketing authorisations in patients with g*BRCA*m HER2− locally advanced or mBC. Besides the OlympiAD trial,[84] the SLR only identified a single study that met the eligibility criteria for the ITC: the EMBRACA trial.[88]

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The EMBRACA trial was a randomised, open-label, Phase III that compared the efficacy and safety of PARP inhibitor talazoparib (1 mg once daily) to TPC (capecitabine, eribulin, gemcitabine or vinorelbine in continuous 21-day cycles) in patients with HER2− g*BRCA*m locally advanced or mBC. Consistent with OlympiAD, the primary endpoint of EMBRACA was PFS (BICR) and was assessed on an ITT basis.[88]

As only two trials were identified and had a common comparator (standard chemotherapy treatment), a standard anchored ITC was used to compare the relative treatment effects (PFS).

B.3.8.3 Feasibility assessment

A feasibility assessment was performed to assess heterogeneity across the two trials. The trials were broadly comparable, however, some differences were identified, including heterogeneity in study design, differences in reporting of AEs, differences in chemotherapy agents used in the control arms of the studies, and the number of prior chemotherapies.

Study design

OlympiAD[84] and EMBRACA[88] had similar study designs: both were randomised, international, open-label, Phase III trials. The eligibility criteria across trials were also similar. Both trials enrolled HER2− patients with g*BRCA*m who were at least 18 years of age. Across trials, patients had to have received previous treatment with a taxane or anthracycline or both, unless this treatment was contraindicated. Both trials permitted previous neoadjuvant or adjuvant platinum-based therapy, provided at least 12 months or a disease-free interval of at last 6 months had elapsed since the last dose for OlympiAD and EMBRACA, respectively. Similarly, patients were excluded from both trials if they had disease progression while receiving platinum chemotherapy for mBC. In both trials, prior treatment with a PARP inhibitor was not permitted.

However, there were some differences in eligibility criteria. In the EMBRACA trial, patients had locally advanced and/or mBC (~95% of patients had mBC), whilst OlympiAD focussed only on patients with mBC. EMBRACA enrolled patients with an ECOG performance status ≤2, whereas OlympiAD enrolled patients with an ECOG score of ≤1. OlympiAD only permitted patients with HR+/HER2− breast cancer who had received at least one prior endocrine therapy (unless they are inappropriate for endocrine therapy), whereas there were no limits on prior endocrine therapy in EMBRACA. The maximum number of prior cytotoxic therapies was two for OlympiAD and three for EMBRACA. However, in all cases, these differences in eligibility criteria did not result in major differences in the enrolled patient populations, as shown in Table 17.

Treatment regimens/ dosing

The standard chemotherapy (TPC) regimen was comparable between OlympiAD (capecitabine, eribulin or vinorelbine) and EMBRACA (capecitabine, eribulin, gemcitabine or vinorelbine). Treatments were assigned in continuous 21-day cycles for both arms with talazoparib administered once daily (1 mg) in contrast to olaparib which was administered orally twice daily (300 mg).

Outcomes

The primary endpoint for both EMBRACA and OlympiAD was PFS by BICR which was used to assess efficacy of treatment. Safety assessments were also performed to provide a safety profile of each drug. OS was not evaluated as part of the ITC as there was no significant difference for either PARP inhibitor versus TPC in the OlympiAD and EMBRACA studies.[2] It is important to

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note that both studies were not powered to evaluate differences between the intervention and TPC in terms of OS and, as noted in Section B.3.5.2, analysis of OS in the trials was likely confounded by subsequent use of PARP inhibitors and/or platinum chemotherapy in the TPC group.

Population

There were differences in the baseline characteristics of the trials (Table 17). OlympiAD had a greater proportion of patients with an ECOG performance status of 0 (72.2%) than the EMBRACA study (53.3%) in the PARP inhibitor monotherapy arms. Whilst EMBRACA permitted patients with an ECOG performance status of 2, however these patients constituted only a very small proportion of enrolled patients (~2%). Similarly, whilst EMBRACA permitted patients with locally advanced breast cancer, these patients only constituted ~5% of enrolled patients. A higher proportion of patients in the OlympiAD trial had visceral disease when compared with the EMBRACA trial (80.5 vs 70.3% in EMBRACA) and a higher proportion of patients in EMBRACA were treated in the first-line setting (38.3 vs 28.8% in OlympiAD). The EMBRACA study also had a slightly higher proportion of patients with HR+/HER2− disease. There was no evidence that the variables with imbalances were effect modifiers for the PARP inhibitors and clinical experts consulted by AstraZeneca did not consider HR status to be a treatment effect modifier, therefore the studies were deemed comparable.

Table 17: Baseline patient characteristics in OlympiAD and EMBRACA studies

Treatment/Comparator Group	Total number (%) of patients			
	OlympiAD		EMBRACA	
	Olaparib (N=205)	TPC (N=97)	Talazoparib (N=287)	TPC (N=144)
Median age, years (range)	44 (22–76)	45 (24–68)	45 (27–84)	50 (24–88)
g*BRCA*m type, n (%)				
g*BRCA*1m	117 (57.1)	51 (52.6)	133 (46.3)	63 (43.8)
g*BRCA*2m	84 (41.0)	46 (47.4)	154 (53.7)	81 (56.2)
Both[a]	4 (2.0)	–	–	–
Receptor status, n (%)				
TNBC	102 (49.8)	48 (49.5)	130 (45.3)	60 (41.7)
HR+/HER2−	103 (50.2)	49 (50.5)	157 (54.7)	84 (58.3)
Breast cancer stage, n (%)				
Locally advanced	–	–	15 (5.2)	9 (6.2)
Metastatic	205 (100)	97 (100)	271 (94.4)	135 (93.8)
ECOG performance status, %				
0	72.2	63.9	53.3	58.3
1	27.8	36.1	44.3	39.6
2	–	–	2.1	1.4
Prior chemotherapy regimen for mBC, n (%)				
0	68 (33.2)	31 (32.0)	111 (38.7)	54 (37.5)
1	80 (39.0)	42 (43.3)	107 (37.3)	54 (37.5)
2	57 (27.8)	24 (24.7)	57 (19.9)	28 (19.4)
>3	–	–	12 (4.2)	8 (5.6)

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Prior platinum therapy, n (%)	60 (29.3)	26 (26.8)	46 (16.0)	30 (20.8)

[a]Four patients in the olaparib arm had both g*BRCA*1m and g*BRCA*2m.
Abbreviations: ECOG: Eastern Cooperative Oncology Group; g*BRCA*1m: Germline *BRCA*1 mutation; g*BRCA*2m: Germline *BRCA*2 mutation; mBC: metastatic breast cancer; TPC: Treatment of physician's choice; TNBC: Triple-negative breast cancer.
Source: McCrea *et al.* (2021)[2]

B.3.8.4 Methodology

Following identification of the RCTs of interest, an ITC of data from patients with g*BRCA*m HER2− locally advanced or mBC receiving treatment with PARP inhibitor monotherapy was performed to simulate comparative efficacy and safety.[2]

The ITC analysis was conducted by a Bayesian model, using the gemtc package in R. As only two relevant studies were identified for the ITC, there were not sufficient data from which to estimate between-study heterogeneity in a random effects model, and as such only fixed-effects analyses were run. In the absence of an appropriate comparative analysis, fit statistics are not informative and as such are not presented.

Efficacy analyses were performed on the log-hazard ratio scale using an identity link function and normal likelihood. Outcomes included the HR for PFS by BICR with 95% credible intervals (95% CrIs). Safety analyses were performed on an odds ratio scale using a logit link function and binomial likelihood. Safety outcomes including AEs, SAEs and discontinuations due to AEs were reported in ORs with 95% credible intervals.[2]

B.3.8.5 Results

Efficacy

The ITC of PFS by BICR suggested no difference in efficacy between olaparib and talazoparib based on data from the primary outcome of the studies (HR: 1.09; 95% CrI: 0.72–1.65). The results of the ITC therefore suggest that olaparib and talazoparib are comparable in terms of efficacy. The results of the ITC have further been validated by clinicians, all of whom stated that they would expect olaparib and talazoparib to have comparable efficacy.

Safety

The ITC found no notable difference in the risk of overall any-grade AEs between olaparib and talazoparib treatment, although the CrIs were wide (OR 1.07, CrIs: 0.13, 9.15). There was a trend favouring olaparib for any SAE (OR 0.88, CrIs: 0.40, 1.95) or treatment-related SAE (OR 0.47, CrIs: 0.12, 1.87), although not statistically significant (Figure 14).

As for specific AE of any grade, the ORs for alopecia and anaemia indicated higher risk in talazoparib-treated patients than olaparib-treated patients, while those of nausea and vomiting indicated higher risk in olaparib-treated patients.[2]

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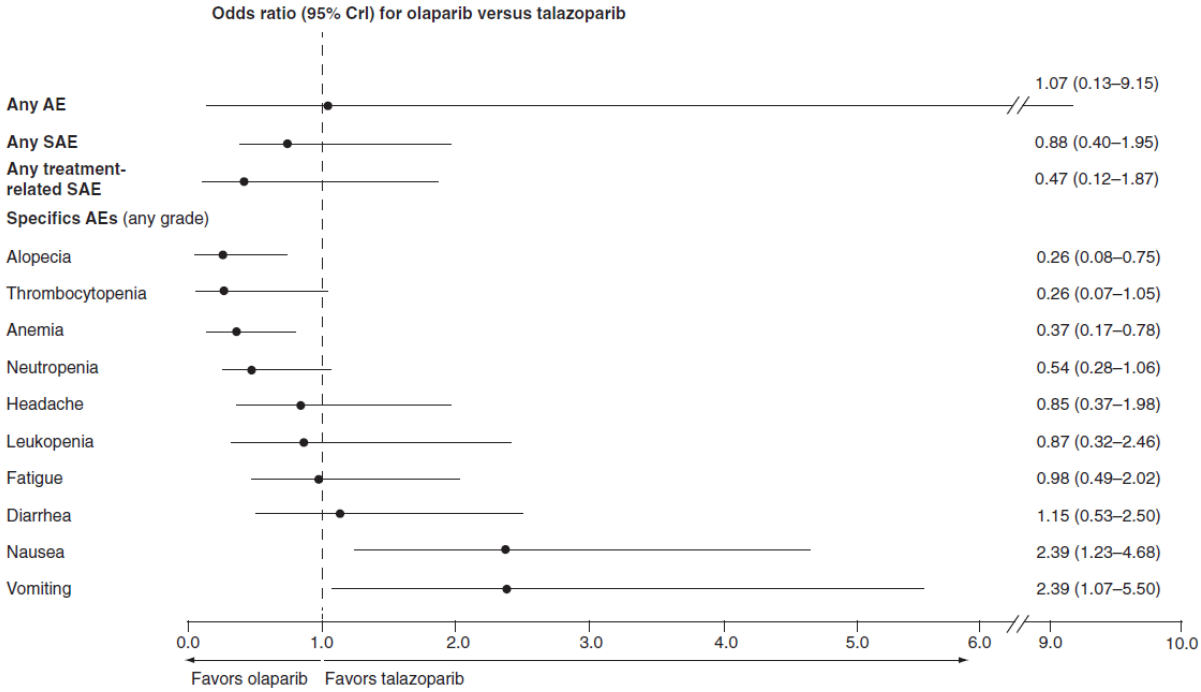
Figure 14: Forest plot of safety outcomes from ITC of olaparib versus talazoparib



Abbreviations: AE: Adverse event; CrI: Credible interval; ITC: Indirect treatment comparison; SAE: Serious adverse event.
Source: McCrea *et al.* (2021)[2]

B.3.8.6 Uncertainties in the indirect and mixed treatment comparisons

The ITC analysis was potentially limited by the heterogeneity in study design, differences in how AEs were reported and recorded, the different chemotherapy drugs used in the TPC comparator and the number of prior chemotherapies. Although the EMBRACA trial included patients with locally advanced breast cancer, whereas the OlympiAD trial only included patients with mBC, <5% of patients in the EMBRACA trial were locally advanced.[88] Overall, there is no evidence that the variables with imbalances were effect modifiers for the PARP inhibitors and as such the ITC is considered appropriate for decision making.[2]

Whilst the primary endpoint (PFS) and safety were comparable between studies, OS was not evaluated as part of the ITC. Median OS was not significantly different compared with TPC for olaparib in the OlympiAD study and talazoparib in the EMBRACA study, indicating no evidence of detrimental effect of PARP inhibitors versus TPC. Both studies were not powered to evaluate differences between the intervention and TPC in terms of OS and, as noted in Section B.3.5.2, analysis of OS in the trials was likely confounded by subsequent use of PARP inhibitors and/or platinum chemotherapy in the TPC group. Methods used to adjust OS in the presence of crossover are inherently uncertain and thus, performing an ITC for this endpoint was not considered appropriate. However, Wang *et al.* (2021) investigated the difference in OS between olaparib and talazoparib and found no statistically significant difference (HR: 1.18, 95% CrI: 0.61–2.31).[3]} Given the reported similarities in OS between PARP inhibitors and TPC, the lack of ITC evidence for OS from McCrea *et al.* (2021) should not considered a key source of uncertainty for decision-making.

B.3.8.7 Conclusions of ITC

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Overall, the findings from the ITC confirm the efficacy of PARP inhibitor monotherapy in the g*BRCA*m HER2− locally advanced or mBC setting are comparable between olaparib and talazoparib. A similar ITC was reported by Wang *et al.* (2021), which found no statistically significant difference between olaparib and talazoparib in terms of efficacy, safety, and acceptability.[3] The consistency of efficacy results between the OlympiAD and EMBRACA studies confirms the benefit of the PARP inhibitor class in the g*BRCA*m HER2− locally advanced or mBC setting.

The ITC found no notable difference in the overall risk of any-grade AEs between olaparib and talazoparib treatment. There was a trend favouring olaparib in the overall risk of any SAE and treatment-related SAEs, although the differences were not statistically significant. The PARP inhibitors did differ in risk of specific AEs, with olaparib having an increased risk of the GI events of nausea and vomiting, but a lower risk of alopecia and anaemia versus talazoparib. There was also a trend for a lower risk in thrombocytopaenia and neutropenia favouring olaparib, although the differences were not statistically significant. All clinical experts consulted as part of this appraisal stated that olaparib and talazoparib had broadly similar safety profiles, with half stating that they valued the slightly different distribution of AEs associated with olaparib, especially in terms of haematological events (Section B.4.5.1).

In both PARP inhibitor studies, GI toxicities were among the most commonly reported AEs, but they were mild to moderate in severity, well managed with supportive care, and resolved without dose modification, and are therefore unlikely to have a significant impact on overall HRQoL or resource use.[85, 109] In both the EMBRACA and OlympiAD studies, haematological toxicities were managed by supportive care (including transfusions) and dose modifications while ensuring that the majority of patients could remain on treatment.[85, 109, 110] The lower incidence of haematological grade 3 or 4 events, including anaemia, neutropenia and thrombocytopaenia reported for olaparib-treated patients versus talazoparib-treated patients may translate into cost savings for AE management, as discussed in Section B.3.4. Additionally, the AEs found to be more common for olaparib-treated patients versus talazoparib-treated patients are less costly than those reported in the EMBRACA trial (Section B.4.4.2).

B.3.9 Adverse reactions

B.3.9.1 Summary of adverse events

Safety data are presented for the final OS DCO (25th September 2017). The OlympiAD trial demonstrated that olaparib was generally well tolerated, consistent with other olaparib studies.[111] The median treatment duration for the primary DCO was 8.2 months (range: 0.5–28.7) in the olaparib arm and 3.4 months (range: 0.7–23.0) in the TPC arm which was similar to the overall treatment duration (7.5 months) which accounts for dose interruptions. Median treatment duration at the starting dose of olaparib 300 mg BID was 5.3 months.

For the olaparib group, the majority of AEs were Grade 1 or Grade 2 (Table 18). The TPC group had a higher rate of Grade ≥3 AEs (49.5%) than the olaparib group (38.0%) (Table 18).

The three different chemotherapies included as comparators within the TPC arm in OlympiAD have different toxicity profiles. It is also important to note that patient numbers were small and choice of chemotherapy treatment was not randomised.

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Table 18: Adverse events in any category – patient level (safety analysis set)

AE Category	Total number (%) of patients	
	Olaparib 300 mg bd (N=205)	TPC (N=91)
Any AE	200 (97.6)	87 (95.6)
Any AE causally related to study medication	178 (86.8)	74 (81.3)
Any AE of CTCAE grade 3 or higher	78 (38.0)	45 (49.5)
Any AE with outcome of death	1 (0.5)	0[a]
Any SAE (including events with outcome of death)	34 (16.6)	15 (16.5)
Any AE leading to discontinuation of olaparib/ chemotherapy	10 (4.9)	7 (7.7)

[a]An AE with outcome of death (dyspnoea) in the physician's choice arm was previously reported but was subsequently reassigned to disease progression by the investigator for the final DCO.
Abbreviations: AE: adverse event; bd: twice daily; CTCAE: Common Terminology Criteria for Adverse Events; DCO: data cut-off; OS: overall survival; SAE: Serious adverse event.
Source: Robson *et al.* (2019)[85]

B.3.9.2 Incidence of adverse events

The most common AEs reported during the OlympiAD trial are presented in Table 19. In the olaparib arm, these were mostly grade 1 or 2 in severity and rarely led to permanent discontinuation. Nausea, anaemia, vomiting, fatigue, cough, decreased appetite, back pain, and headache were reported at a relatively higher frequency (≥5%) in the olaparib arm compared with TPC. All-grade AEs of neutropenia, palmar plantar erythrodysesthesia (PPE), increased alanine aminotransferase, increased aspartate aminotransferase, and alopecia occurred at a higher frequency (≥5%) in the TPC arm compared with the olaparib arm.

Table 19: Incidence of the most common AEs occurring in >10% of patients in either treatment arm, by maximum reported CTCAE grade[a]

	Olaparib (n=205)				TPC (n=91)			
	All grades	Grade 1	Grade 2	Grade ≥3	All grades	Grade 1	Grade 2	Grade ≥3
Any AE	200 (97.6)	33 (16.1)	89 (43.4)	78 (38.0)	87 (95.6)	6 (6.6)	36 (39.6)	45 (49.5)
Nausea	119 (58.0)	92 (44.9)	27 (13.2)	0	32 (35.2)	26 (28.6)	5 (5.5)	1 (1.1)
Anaemia	82 (40.0)	19 (9.3)	30 (14.6)	33 (16.1)	24 (26.4)	9 (9.9)	11 (12.1)	4 (4.4)
Neutropenia	56 (27.3)	12 (5.9)	25 (12.2)	19 (9.3)	45 (49.5)	4 (4.4)	17 (18.7)	24 (26.4)
Vomiting	66 (32.2)	49 (23.9)	17 (8.3)	0	14 (15.4)	12 (13.2)	1 (1.1)	1 (1.1)
Fatigue	61 (29.8)	40 (19.5)	14 (6.8)	7 (3.4)	22 (24.2)	6 (6.6)	15 (16.5)	1 (1.1)
Diarrhoea	42 (20.5)	33 (16.1)	8 (3.9)	1 (0.5)	20 (22.0)	13 (14.3)	7 (7.7)	0
PPE	1 (0.5)	1 (0.5)	0	0	19 (20.9)	8 (8.8)	9 (9.9)	2 (2.2)
Decreased WBC	33 (16.1)	13 (6.3)	13 (6.3)	7 (3.4)	19 (20.9)	3 (3.3)	7 (7.7)	9 (9.9)

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Headache	42 (20.5)	28 (13.7)	12 (5.9)	2 (1.0)	14 (15.4)	8 (8.8)	4 (4.4)	2 (2.2)
Pyrexia	30 (14.6)	25 (12.2)	5 (2.4)	0	16 (17.6)	10 (11.0)	6 (6.6)	0
Increased ALT	24 (11.7)	15 (7.3)	6 (2.9)	3 (1.5)	16 (17.6)	8 (8.8)	7 (7.7	1 (1.1)
Cough	35 (17.1)	24 (11.7)	11 (5.4)	0	6 (6.6)	5 (5.5)	1 (1.1)	0
Increased AST	20 (9.8)	11 (5.4)	4 (2.0)	5 (2.4)	15 (15.6)	11 (12.1)	4 (4.4)	0
Decreased appetite	35 (17.1)	26 (12.7)	9 (4.4)	0	11 (12.1)	9 (9.9)	2 (2.2)	0
Constipation	26 (12.7)	19 (9.3)	6 (2.9)	1 (0.5)	12 (13.2)	9 (9.9)	3 (3.3)	0
Asthenia	19 (9.3)	11 (5.4)	6 (2.9)	2 (1.0)	12 (13.2)	6 (6.6)	6 (6.6)	0
Alopecia	7 (3.4)	6 (2.9)	1 (0.5)	0	12 (13.2)	7 (7.7)	5 (5.5)	0
URTI	27 (13.2)	17 (8.3)	9 (4.4)	1 (0.5)	9 (9.9)	4 (4.4)	5 (5.5)	0
Back pain	30 (14.6)	15 (7.3)	11 (5.4)	4 (2.0)	8 (8.8)	5 (5.5)	2 (2.2)	1 (1.1)
Stomatitis	16 (7.8)	14 (6.8)	2 (1.0)	0	10 (11.0)	6 (6.6)	4 (4.4)	0
Arthralgia	23 (11.2)	20 (9.8)	2 (1.0)	1 (0.5)	9 (9.9)	6 (6.6)	2 (2.2)	1 (1.1)
Leukopenia	23 (11.2)	4 (2.0)	16 (6.8)	5 (2.4)	9 (9.9)	3 (3.3)	3 (3.3)	3 (3.3)

[a]AEs of any cause; MedDRA-preferred terms are grouped for anaemia (anaemia, decreased Hb level, decreased haematocrit, decreased red blood cell count, and erythropenia) and neutropenia (febrile neutropenia, granulocytopenia, decreased granulocyte count, neutropenia, neutropenic sepsis, decreased neutrophil count, and neutropenic infection)
Abbreviations: AE: adverse event; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CTCAE: Common Terminology Criteria for Adverse Events; MedDRA: Medical Dictionary for Regulatory Activities; PPE: palmar plantar erythrodysesthesia; TPC: treatment of physician's choice; URTI: upper respiratory tract infection; WBC: white blood.
Source: Robson *et al.* (2019)[85]

B.3.9.3 Treatment discontinuation

Overall, the rate of discontinuation of olaparib treatment that occurred due to AEs was low (Figure 15). Discontinuation of olaparib was mainly due to anaemia (n=4, 2.0%) and decreased platelet count (n=2, 1.0%). Increased intracranial pressure, abdominal pain, dyspnoea, erythema nodosum, and thrombocytopenia each occurred in one patient who was treated with olaparib (all n=1, 0.5%). For the TPC, anaemia and neutropenia (both n=2, 2.2%), leukopenia, decreased neutrophil count, radiation skin injury, palmar- plantar erythrodysesthesia syndrome, peripheral motor neuropathy, and vomiting (all n=1, 1.1%) led to treatment discontinuation.

AEs also led to dose reduction (Figure 15). Anaemia (13.7%), neutropenia (4.9%), fatigue (2.4%), leukopenia (2.0%), increased alanine aminotransferase (1.5%), decreased platelet count (1.5%), thrombocytopenia (1.5%) and decreased white blood cell count (1.0%) led to dose reduction in ≥2 patients. Similar AEs led to dose reduction in the TPC arm and included ,

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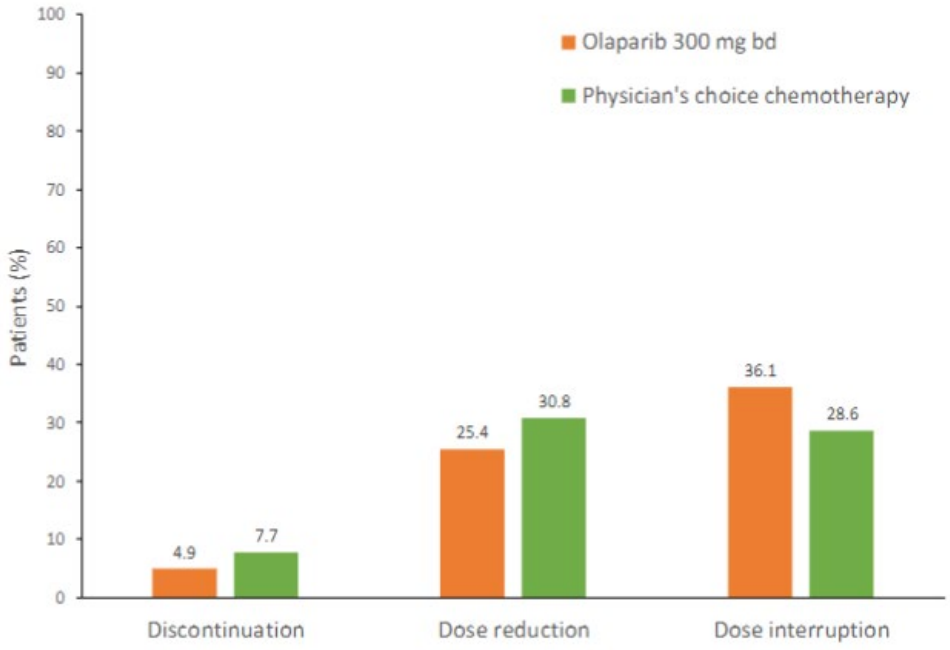
neutropenia (6.6%), decreased neutrophil count (n=6, 6.6%), decreased white blood cell count (4.4%), diarrhoea (3.3%), nausea (2.0%) and vomiting (2.2%). Additionally palmar-plantar erythrodysesthesia syndrome led to the discontinuation of 7.7% patients in in the TPC arm and no patients in the olaparib arm. Numerically, a greater number of olaparib patients had dose interruptions due to AEs. However, olaparib patients had longer exposure (2.5-times longer) to treatment.

Figure 15: Treatment interruptions,[a] dose reductions and discontinuations due to AEs in the OlympiAD study (safety analysis set, secondary DCO: 25th September 2017)



[a]Interruptions in olaparib treatment are considered comparable with delays in physician's choice chemotherapy
Abbreviations: AE, adverse event; bd, twice daily; DCO, data cut-off.
Source: Robson *et al.* (2019)[85]

B.3.9.4 Deaths

At the secondary DCO (25th September 2017), 63.4% of patients who received olaparib treatment and 63.9% of patients who received TPC had died whilst on treatment or follow-up. The majority of deaths were due to disease (Table 20). Other cause of death included sepsis (olaparib group, n=1) and disease progression (TPC group, n=1). This was not considered to be due to treatment by the investigator.

Table 20: Total number of deaths in the OlympiAD study (full analysis set, secondary DCO: 25th September 2017)

AE Category	Olaparib (n=205)	TPC (n=97)
Total number of deaths	**130 (63.4)**	**62 (63.9)**
Death related to disease under investigation only	3 (1.5)	4 (4.1)
Death related to disease under investigation only (including death > 30 days after last treatment)	117 (57.1)	57 (58.8)

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AE with outcome (death only)	1 (0.5)	0
AE related to disease under investigation and with AE outcome or death	0	0
Deaths >30 days after last treatment dose, unrelated to AE or disease under investigation	9 (4.4)	1 (1.0)

Abbreviations: AE, adverse event; DCO, data cut-off; TPC: treatment of physician's choice.
Source: AstraZeneca Data on File (OlympiAD CSR).[86]

B.3.10 Conclusions about comparable health benefits and safety

Principal results and conclusions

Efficacy

The OlympiAD trial was the first Phase III study to demonstrate the efficacy of olaparib in g*BRCA*m HER2− mBC , showing significantly longer median PFS in patients receiving oral olaparib monotherapy when compared with TPC (median PFS: 7.0 months vs. 4.2 months; HR 0.58; 95% CI: 0.43–0.80). In addition, risk of disease progression or death was 42% lower and the median PFS was 2.8 months longer with olaparib than with standard chemotherapy. Olaparib patients also had early mean time to onset of response that was similar to TPC patients and had double the rate of response (59.9% vs 28.8%). Olaparib also demonstrated benefits to patient quality of life with significantly less and delayed deterioration in HRQoL when compared with the TPC group. Treatment satisfaction was also higher in the olaparib group than the standard chemotherapy group.

The efficacy and safety of talazoparib, the most relevant comparator for this submission, for patients with g*BRCA*m HER2− locally advanced or mBC was investigated within the EMBRACA trial. In the study, PFS was found to be statistically significantly longer with talazoparib when compared with TPC (median PFS: 8.6 months vs. 5.6 months; HR: 0.54; 95% CI: 0.41–0.71; p<0.001).[88]

Overall, the results of the ITC confirm the efficacy of PARP inhibitor monotherapy in the g*BRCA*m HER2− locally advanced or mBC cancer setting are comparable between olaparib and talazoparib with no difference in efficacy found based on the primary outcome of the studies, PFS (HR: 1.09; 95% CrI; 0.72–1.65).[2] A similar ITC was reported by Wang *et al.* (2021), which found no statistically significant difference between olaparib and talazoparib in terms of efficacy, safety, and acceptability, measured by discontinuation rate and time to HRQoL discontinuation.[3] These results therefore justify the use of a cost-comparison analysis assuming clinical comparability.

Safety

Overall, the olaparib monotherapy was generally well tolerated in the patient population, consistent with previous studies that focus on olaparib monotherapy. When compared with TPC, olaparib patients had fewer Grade ≥3 AEs and lower rate of discontinuation due to AEs. AEs were mostly manageable through dose interruption or reduction and supportive treatment.

Within the EMBRACA trial, talazoparib was generally well-tolerated. Overall Grade ≥3 AEs were not reported for EMBRACA; however, Grade ≥3 SAEs were reported and were similar in both

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arms.[2] Most Grade 3–4 AEs reported in the talazoparib group were haematologic and most were successfully managed by supportive care (including transfusion) and dose modifications.[88]

The ITC found no notable difference in the overall risk of any-grade AEs between olaparib and talazoparib treatment. The PARP inhibitors did differ in risk of specific AEs, with olaparib having an increased risk of the GI events of nausea and vomiting, but a lower risk of alopecia and anaemia versus talazoparib.[2] All clinical experts consulted as part of this appraisal stated that olaparib and talazoparib had broadly similar safety profiles, with half stating that they valued the slightly different different distribution of AEs associated with olaparib, especially in terms of haematological events (Section B.4.5.1). These results therefore justify the use of a cost-comparison analysis assuming clinical comparability.

Strengths and limitations

The OlympiAD trial enrolled 302 patients who underwent randomisation (2:1) to receive either olaparib or standard therapy (TPC). Whilst the OlympiAD trial was designed to ensure the study was robust to biases, the open-label nature of the trial may have contributed to increased risk of bias. However, it is important to highlight the necessity of an open-label approach in this trial due to differences in treatments in the control arm (such as safety profile and dosing regimen) which are considered standard therapy. To mitigate bias in this circumstance BICR assessment was used for the ITT population.

At the time of the primary analysis for PFS, the OS data were immature (primary DCO: 9th December 2016). Therefore, analyses of OS and safety were performed in a follow-up study (secondary DCO: 25th September 2017). Given PFS data were already mature at the primary DCO (9th December 2016), PFS and the remaining secondary endpoints were not followed up at the follow-up analysis.

In addition, the trial was also not powered to detect statistical differences in efficacy and safety between subgroups, including hormone receptor status, previous use of chemotherapy or platinum-based treatments.

As there is a lack of head-to-head trial data between olaparib and talazoparib, a robust, anchored ITC was conducted to generate comparative efficacy data based on the OlympiAD and EMBRACA trials. These trials have broadly comparable study designs and patient populations. There may be some heterogeneity across the trials, but none of the identified differences were considered to be treatment effect modifiers.

Conclusions

In summary, olaparib demonstrated longer PFS, PFS2, TFST and TSST and doubled ORR when compared with standard therapy (TPC). This was associated with clinical benefits to patients with g*BRCA*m HER2− mBC by an improvement in quality of life (HRQoL). Olaparib was also generally well-tolerated.

The ITC demonstrates that olaparib and talazoparib are associated with comparable efficacy and safety. Clinical experts also noted that they would expect the efficacy of these two treatments to be similar and that they would be used similarly in clinical practice (Section B.4.5.1). These results can therefore be considered suitable for decision-making and justify the use of a cost-comparison analysis assuming clinical comparability, given olaparib offers similar health benefits to the most relevant technology already recommended by NICE in technology appraisal guidance

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in the specific population of g*BRCA*m HER2− locally advanced or mBC patients of relevance to this appraisal, talazoparib.

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B.4 Cost-comparison analysis

Summary of cost comparison

- A three health-state partitioned survival model was developed in Microsoft Excel® to assess the cost-savings of olaparib versus treatment with talazoparib. The health states included progression-free, progressed disease and death states
- The model is fully aligned with the NICE reference case and compares olaparib in its full licensed indication against the comparator listed in the NICE scope: talazoparib
- The OlympiAD trial provides the OS and PFS data for both arms in the model
- Based on the results of the indirect treatment comparison, which demonstrated that olaparib and talazoparib are associated with comparable efficacy (Section B.3.8) a hazard ratio of 1 is applied to the olaparib arm of the model to derive the talazoparib arm
- These data are extrapolated over a lifetime horizon using robust parametric modelling that was informed and validated by clinical experts and external data sources
- Treatment with olaparib (inclusive of commercial arrangement) is associated with cost savings of £[redacted] per patient compared to treatment with talazoparib (at list price)
- Extensive sensitivity and scenario analyses demonstrate that the base case model is robust to all key parameters and assumptions
- [redacted] olaparib is a plausibly cost-effective therapy option within its licensed indication.

B.4.1 Changes in service provision and management

Olaparib is an orally administered PARP inhibitor, and was the first genetically targeted treatment licensed for *BRCA*m BC. In line with the NICE scope, the proposed indication for olaparib in this submission is for patients with g*BRCA*m HER2− locally advanced or mBC and the most relevant comparator is talazoparib.

Both talazoparib and olaparib are administered orally. There are not anticipated to be any changes in service provision and management resulting from the reimbursement of olaparib.

B.4.2 Cost-comparison analysis inputs and assumptions

B.4.2.1 Features of the cost-comparison analysis

A *de novo* economic model was developed to assess the lifetime incremental cost savings of olaparib versus talazoparib in the treatment of g*BRCAm* HER2− locally advanced or mBC. The model was developed in line with the NICE reference case. A summary of the key features of the model is provided in Table 21.

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Table 21: Key features of cost-comparison analysis

Feature	Detail	Notes
Model structure	Three-state partitioned survival model	Consistent with previous evaluations in locally advanced or mBC
Time horizon	Up to 20 years (lifetime)	Assumed to capture all cost differences in the model
Cycle period	Weekly	To accurately capture treatment costs. Cycles were half cycle corrected.
Discounting	3.5% for costs and effects	Applied as annualised rates in line with annual budget cycles
Perspectives	NHS and PSS	In line with NICE guidelines
Outcomes	Costs (total and disaggregated) Incremental costs	Consistent with HTA requirements

Abbreviations: HTA: Health Technology Assessment; mBC: metastatic breast cancer; NHS: National Health Service; NICE: National Institute of Health and Care Excellence; PSS: Personal Social Service: PSS.

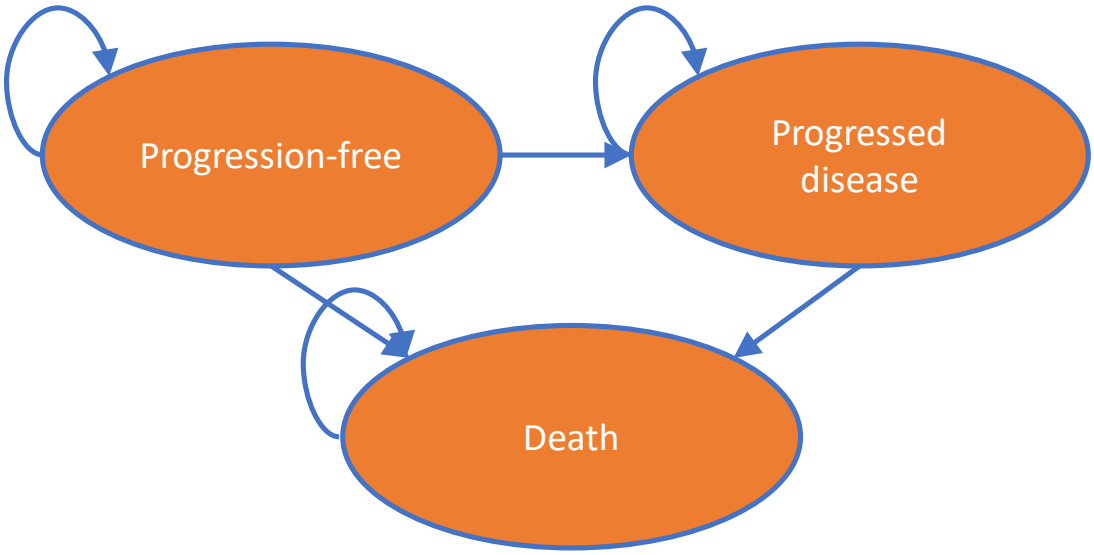
Clinician validation was also sought to validate modelling assumptions. One round of individual clinical expert interviews was conducted to validate the clinical assumptions underpinning the economic model. There were seven clinical experts consulted as part of the validation. Full details of the validation can be found in Section B.4.5.

B.4.2.2 Model structure

A conventional three-state partitioned survival model comprising health states for progression-free (PF), progressed disease (PD) and death was developed in Microsoft Excel 2016, in line with TA952.[1] The health states of PF and PD correspond to the periods before and after radiological progression, respectively, as defined according to the RECIST criteria (v1.1). PF and PD were modelled separately to accurately capture health state related monitoring costs. Progression of disease reflects an increase in tumour burden and/or spreading of disease. The death state captures all death events in the cohort, including deaths unrelated to cancer.

An illustration of the model flow is provided in Figure 16.

Figure 16: Illustration of partitioned survival model simulation technique from DSU report on partitioned survival analysis



Abbreviations: DSU: Decision Support Unit.

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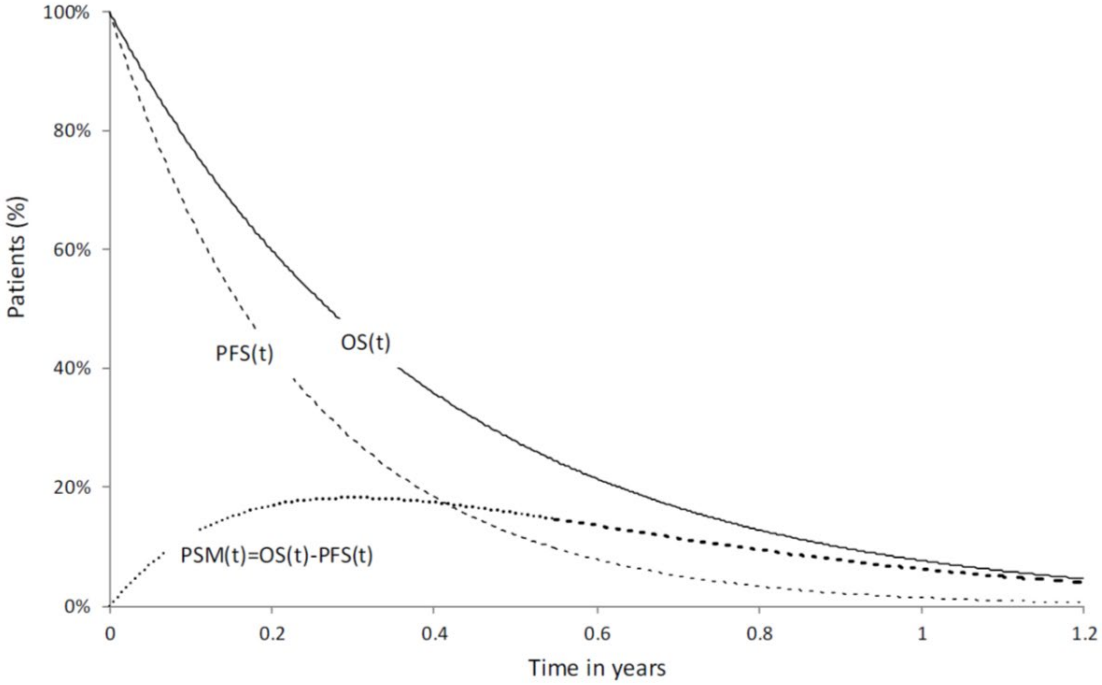
The cohort enter the model in the PF state, and initiate treatment with either olaparib or talazoparib. Over time, the cohort is at risk of experiencing radiological disease progression or death, and enter either the PD or death states. The transition to the death state can occur directly from PF or via the PD state. Death is an absorbing state.

The time spent on olaparib is modelled independently of PF status, in line with TA952,[1] using data on the time from randomisation to treatment discontinuation. This ensures that the model accurately reflects treatment exposure within OlympiAD. In TA952 time on treatment was modelled directly using the Kaplan–Meier (KM) curve,[1] however due to more immature data in OlympiAD, parametric curves were fitted to extrapolate time on treatment.

The partitioned survival method is used to simulate state occupancy over time. This approach estimates state membership from a set of non-mutually exclusive survival curves, PFS and OS, as illustrated in Figure 17. A weekly cycle period was adopted to accurately estimate drug uptake.

Figure 17: Partitioned survival simulated state membership.



Abbreviations: OS: overall survival; PFS: progression-free survival; PSM: partitioned survival model.

The proportion of patients alive over time are estimated directly from the OS curve. OS is then partitioned into the PF and PD states using the PFS curve. The proportion of patients occupying the PF state are derived directly from the cumulative survival probabilities of PFS, while the proportion occupying the PD state are derived from OS minus PFS. The proportion occupying the death state are estimated from one minus OS.

To avoid negative state membership, PFS is constrained to values that are less than or equal to OS over the lifetime of the model. The hazard for death is also constrained to values that are greater than or equal to the background all-cause mortality rate from the general population matched on age and gender. This is to avoid logical inconsistencies where survivorship in the locally advanced or mBC cohort exceeds that of the general population. Both OS and PFS are

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extrapolated beyond the follow-up of OlympiAD to a lifetime horizon using parametric survival functions.

B.4.2.3 Time horizon

In the base-case analysis, costs were modelled over an appropriate lifetime horizon, which was assumed to be 20 years and discounted at an annual rate of 3.5% as per the NICE reference case.

B.4.2.4 Model assumptions

A summary of key model assumptions is shown in Table 22.

Table 22: Key model assumptions

Assumption	Justification
Each cycle lasts for approximately 7 days, each year lasts for 52 cycles	To accurately capture treatment costs.
PFS and OS outcomes are extrapolated to a lifetime horizon using parametric functions fitted to the olaparib arm.	In line with NICE methods.
A hazard ratio of 1.0 was applied to the olaparib arm to derive the talazoparib	Olaparib and talazoparib are expected to have comparable efficacy. This is in line with the results of the ITC (see Section B.3.8) and clinical opinion.
Time to treatment discontinuation is modelled independently of PFS and OS	Decisions to withdraw treatment may include factors other than progression or mortality and include toxicity or patient preference. TTD was modelled independently of OS and PFS in line with TA952.[1]
Probability of death must be greater than or equal to the all-cause background mortality risk	To avoid cases where survival in the model cohort (stage IV BC) exceeds that of the general population implying cure of all diseases

Abbreviations: BC: breast cancer; OS: overall survival; PFS: progression-free survival.

B.4.3 Clinical parameters and variables

All clinical data were obtained from the olaparib arm of the OlympiAD study, which is summarised in section B.3. The model uses the latest data cut for each endpoint as summarised in Table 23.

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Table 23: Data cut-off and evidence maturity for ITT population

Endpoint	Data cut-off	Data set	Event maturity for ITT, %
PFS by BICR	Primary PFS (December 2016)	FAS	79.5% for olaparib
PFS by study investigator	Primary PFS (December 2016)	FAS	80.5% for olaparib
TTD	Primary OS (September 2017)	SAS	87.3% for olaparib
OS	Primary OS (September 2017)	FAS	63.4% for olaparib

Abbreviations: BC: breast cancer; BICR: blind independent central review: FAS: Full Analysis Set; ITT: intention to treat; IVRS: interactive voice response system; OS: overall survival; PFS: progression-free survival; SAS: Safety Analysis Set; TPC: treatment of physician's choice; TTD: time to treatment discontinuation.

As BICR scans of PFS were stopped after the primary analysis, all PFS analyses are based on the data collected up to the primary data cut-off of December 2016. The lifetime predictions of PFS, time to treatment discontinuation (TTD) and OS were estimated using parametric survival models fitted to patient level data from OlympiAD.

The best fitting parametric survival curve was selected in terms of visual fit. Fit statistics in terms of Akaike information criterion (AIC) and Bayesian information criterion (BIC) were also used to select the best fitting parametric curve. It is recommended that survival extrapolations are validated through comparison to alternative data sources. Published data on the long-term PFS and OS of patients with g*BRCA* locally advanced or mBC is limited. Key published sources include data from other clinical trials, and two observational studies by Kriege *et al*.[112, 113] None of these studies can be used to validate the lifetime predictions from the model as none reported event risks beyond the follow-up of OlympiAD.

In the absence of literature data, external clinical experts were consulted (Section B.4.5) and were asked to provide plausible benchmark probabilities for PFS and OS on olaparib at fixed intervals (e.g. 5, 10 and 15 years) in order to validate extrapolations.

The following sections outline the fitting of parametric models to PFS, OS and TTD.

B.4.3.1 PFS

PFS was modelled by investigator assessed data from the ITT population of OlympiAD. Investigator assessed PFS was selected as it had greater data maturity compared with BICR PFS (80.5% versus 79.5%). Table 24 summarises the total number of events and median and restricted mean survival times for PFS by study investigator in the ITT.

Table 24: Total number events and median time to event for PFS investigator in ITT

	Olaparib 300 mg bd (n=205)
Total number of events	165
Median time to event	7.79
Restricted mean survival time (up to last time point where each arm has an observation)	9.35 (5.78–8.41)

Abbreviations: bd: twice daily.

Following NICE Decision Support Unit (DSU) recommendations, a series of standard parametric functions were fitted to patient-level data from each arm of the OlympiAD study. A summary of the AIC and BIC statistics is provided in Table 25.

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Table 25: AIC and BIC statistics for the standard parametric functions fitted to patient level data for the olaparib arm of OlympiAD in the ITT population (PFS)

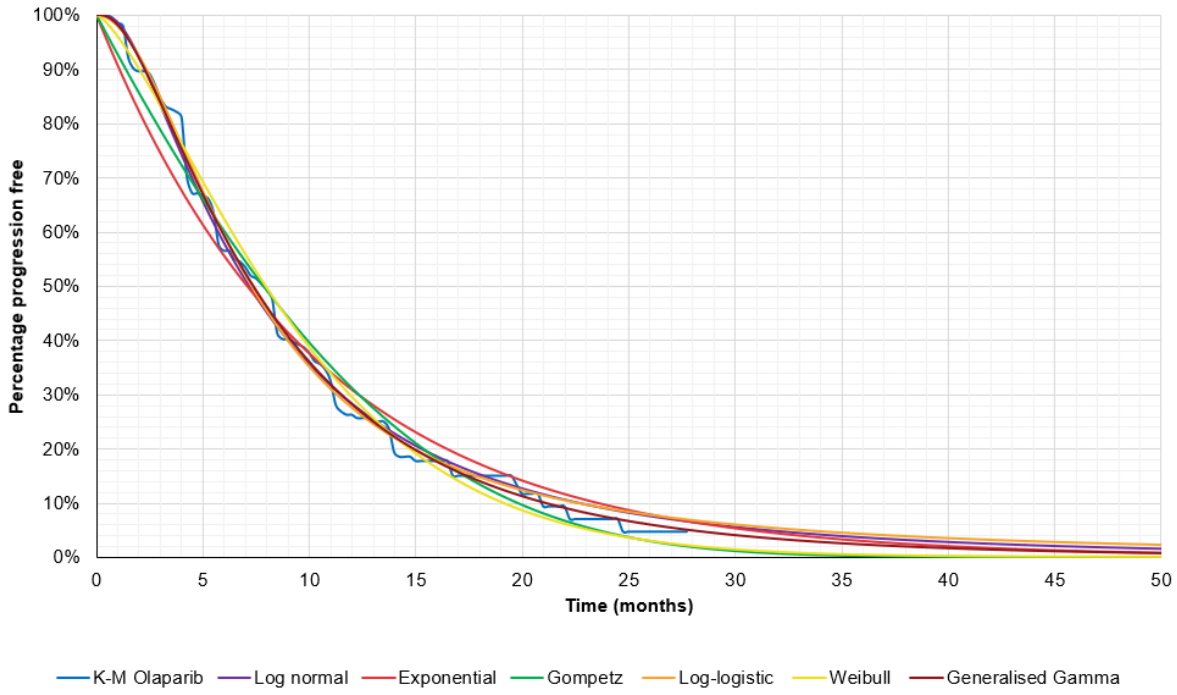
Model	Olaparib 300 mg bd	
	AIC	BIC
Generalised Gamma	1072.2	1082.2
Lognormal	**1071.4**	**1078.1**
Loglogistic	1072.0	1078.7
Exponential	1098.4	1101.7
Weibull	1078.8	1085.5
Gompertz	1092.4	1099.0

The model with the best fit according to AIC and BIC is highlighted bold.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; ITT: Intention to treat; PFS: progression-free survival.

The lognormal function was associated with the lowest AIC and BIC for olaparib, followed by the loglogistic function. All other models produced an inferior statistical fit to the observed data.

Figure 18 shows the visual fit of the standard functions versus the Kaplan–Meier plot for PFS based on investigator assessment. Despite the differences in fit statistics across models, the standard functions provided broadly equivalent visual fits to the data. Beyond study follow-up, the functions produced different estimates of long-term PFS (Table 26).

Figure 18: Comparison of predicted survival probabilities for PFS versus Kaplan–Meier curves for the ITT population (by investigator assessment)



Abbreviations: ITT: Intention to treat; PFS: progression-free survival.

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Table 26: Summary of predicted probabilities of PFS (based on investigator assessment) with olaparib at 6 months, 12 months, 18 months, 3, 5 and 10 years (ITT)

Model	Probability PFS with olaparib 300 mg bd				
Time point (years)	**0.5**	**1**	**1.5**	**3**	**5**
Trial	56.5%	26.3%	15.0%	-	-
Lognormal	55.1%	27.4%	15.2%	3.9%	1.1%
Exponential	54.5%	29.7%	16.2%	2.6%	0.2%
Gompertz	57.6%	29.6%	13.3%	0.4%	0.0%
Loglogistic	56.1%	26.8%	15.0%	4.8%	2.0%
Weibull	59.6%	28.2%	11.9%	0.5%	0.0%
Generalised Gamma	55.8%	27.3%	14.5%	3.2%	0.7%

Abbreviations: ITT: Intention to treat; PFS: progression-free survival.

Clinicians validated that all models produced viable results, however it was a common theme that clinicians had experience with rare patients considered to be super responders. Therefore, most clinicians agreed that models predicting 5-year PFS at 0% were probably too pessimistic. These models were therefore disregarded. Based on goodness of fit statistics and plausibility of extrapolation, the preferred function for the base case extrapolation of PFS by study investigator was the lognormal. This PFS curve selection is in line with TA952.[1]

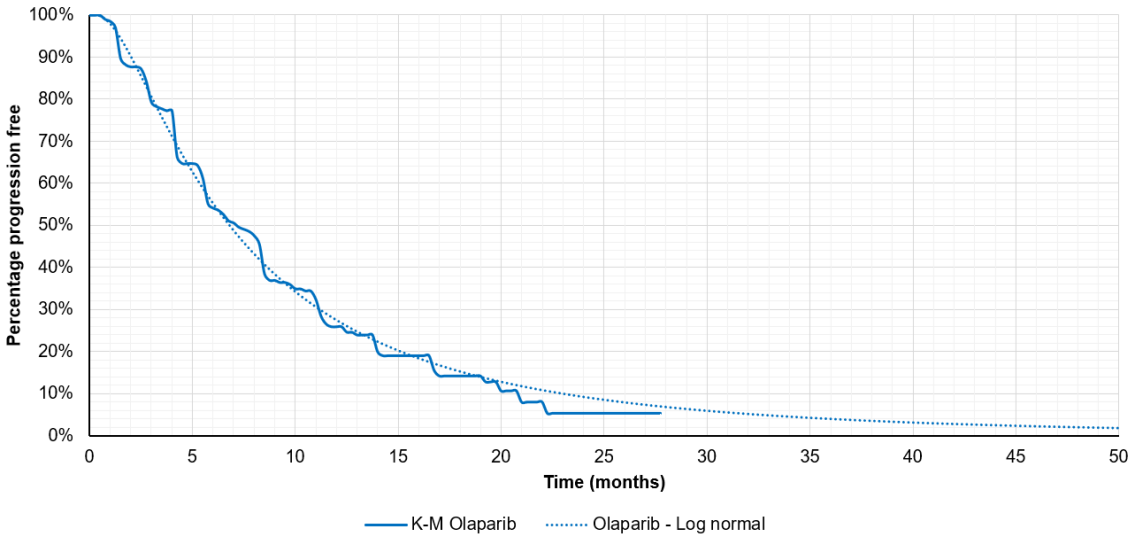
A summary of the estimated coefficients for the preferred model is provided in Table 27. Figure 19 presents the predicted PFS.

Table 27: Parameters of the lognormal PFS distribution

Parameter	Olaparib 300 mg bd
Shape	1.9131
Scale	0.9507

Abbreviations: PFS: progression-free survival.

Figure 19: Plot showing the Kaplan–Meier probabilities of PFS versus the best fitting model (lognormal)



Abbreviations: PFS: progression-free survival.

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B.4.3.2 OS

OS was modelled on data from the FAS of OlympiAD (secondary DCO [25th September 2017]) comprising all 205 patients randomised to olaparib. Table 28 summaries the total number of events and median and restricted mean survival times for OS in the ITT population.

Table 28: Total number events and median time to event for OS in ITT

	Olaparib 300 mg (n=205)
Total number of events	130
Median time to event	19.25 (17.15–21.55)
Restricted mean survival time (up to last time point where each arm has an observation)	21.69 (20.00–23.39)

Abbreviations: ITT: Intention to treat; OS: overall survival.

As for PFS, a series of standard parametric functions were fitted to patient-level data from each arm of the OlympiAD study. A summary of the AIC and BIC statistics is provided in Table 29.

Table 29: AIC and BIC statistics for the standard parametric functions fitted to patient level data from each arm of OlympiAD in the ITT population (OS)

Model	Olaparib 300 mg bd	
	AIC	BIC
Generalised Gamma	1088.44	1098.41
Lognormal	**1086.96**	**1093.61**
Loglogistic	1089.82	1096.47
Exponential	1135.76	1139.08
Weibull	1100.09	1106.74
Gompertz	1119.48	1126.13

The model with the best fit according to AIC and BIC is highlighted bold.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; ITT: Intention to treat; OS: overall survival; PFS: progression-free survival.

The lognormal function was associated with the lowest AIC and BIC for the olaparib arm. All other models produced an inferior statistical fit to the observed data.

Figure 20 shows the visual fit of the standard functions against the Kaplan–Meier plot for OS. The functions that performed worst on AIC and BIC (exponential, Weibull, and Gompertz) were found to poorly predict the Kaplan–Meier estimates of OS. The best fitting functions (according to AIC) of lognormal, generalised gamma and loglogistic accurately predicted OS over the study follow-up. Beyond study follow-up, the functions produced different estimates of long-term OS (Table 30).

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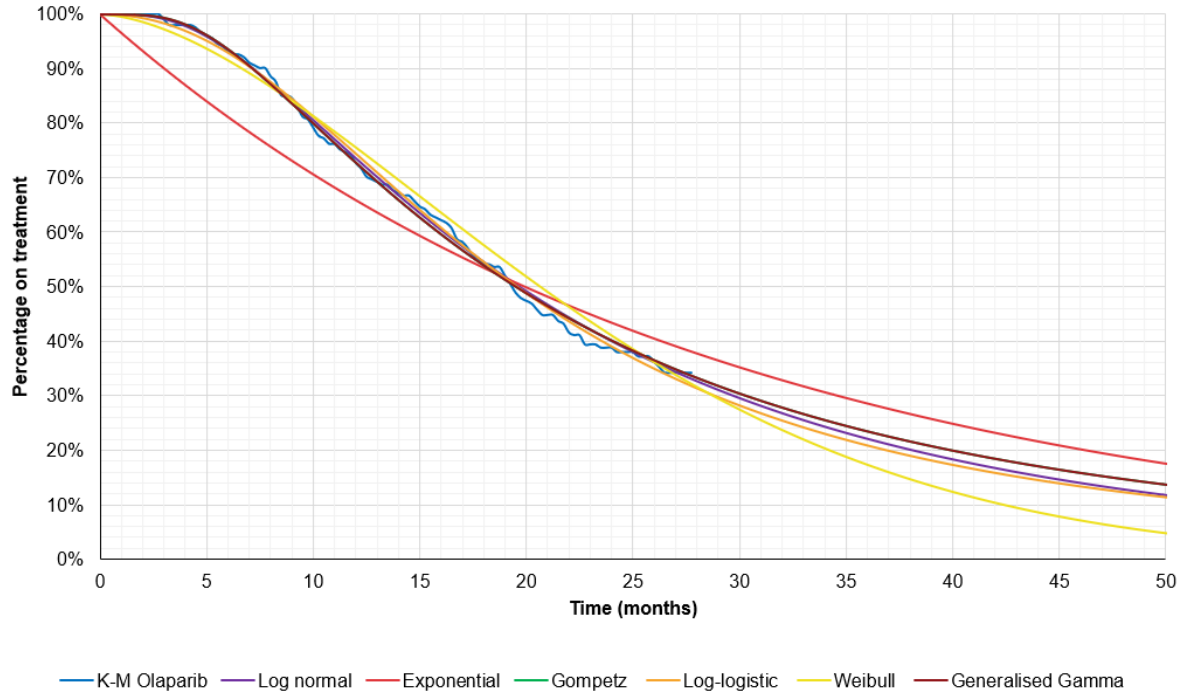
Figure 20: Comparison of predicted survival probabilities for OS versus Kaplan–Meier curves for the ITT population



Abbreviations: ITT: Intention to treat; OS: overall survival.

Table 30: Summary of landmark probabilities for OS with olaparib at 1, 2, 3, 5, 10, 15 and 20 years (ITT)

Model	Probability OS with olaparib 300 mg bd					
Time point (years)	**1**	**2**	**3**	**5**	**10**	**15**
Trial	72.7%	38.8%	26.5%	-	-	-
Log normal	73.6%	40.0%	22.1%	7.8%	1.1%	0.2%
Exponential	65.9%	43.5%	28.7%	12.5%	1.6%	0.2%
Gompertz	73.0%	42.8%	17.2%	0.3%	0.0%	0.0%
Log logistic	74.4%	39.1%	20.9%	8.0%	1.9%	0.8%
Weibull	75.6%	41.1%	17.4%	1.7%	0.0%	0.0%
Generalised Gamma	72.8%	40.1%	23.4%	9.7%	2.1%	0.7%

Abbreviations: ITT: Intention to treat; OS: overall survival.

The functions that best predicted the trial estimates of OS were the lognormal, generalised gamma and loglogistic functions. As for PFS, clinicians stated that all models produced viable results, however it was a common theme that clinicians had experience with rare patients considered to be super responders. Therefore, most clinicians agreed that models predicting 10-year OS at 0.0% were too pessimistic. Gompertz and Weibull functions were therefore disregarded. As a result, based on goodness of fit statistics and plausibility of model extrapolation, the preferred model for the base case of OS was lognormal. This OS curve selection is in line with TA952.[1]

A summary of the estimated coefficients for the preferred model is provided in Table 31. Figure 21 presents the predicted OS.

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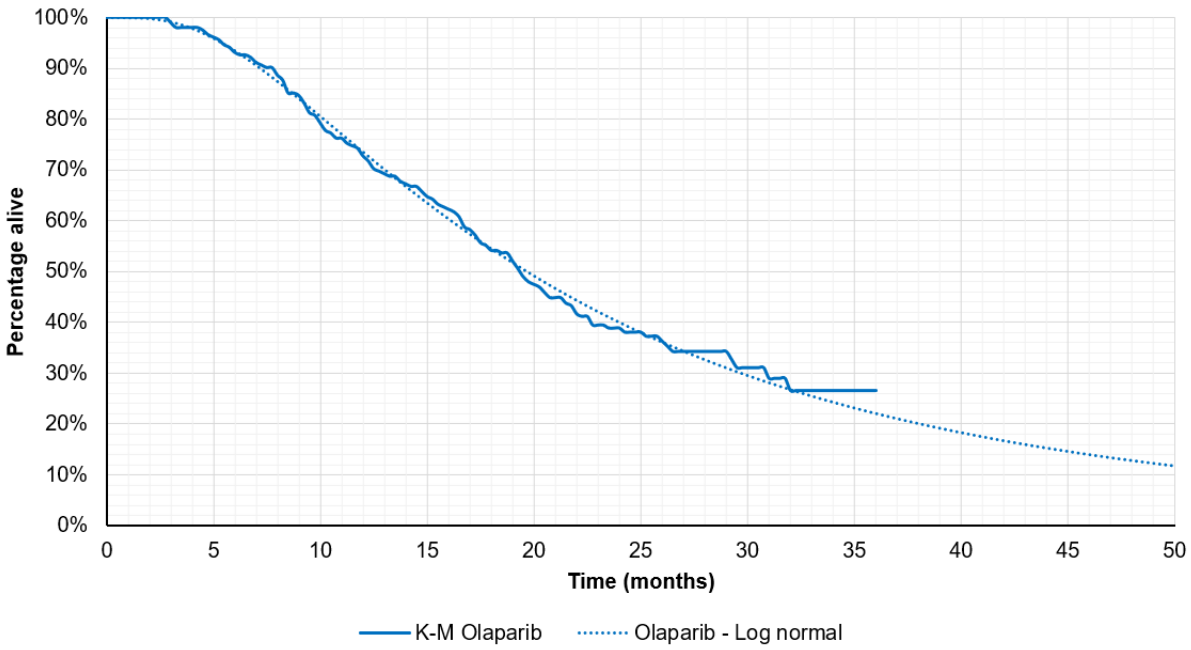
Table 31: Parameters of the lognormal OS distribution

Parameter	Olaparib 300 mg bd
Meanlog	2.9797
Sdlog	0.7840

Abbreviations: OS: overall survival.

Figure 21: Plot showing the Kaplan–Meier probabilities of OS versus the best fitting model (lognormal)



Abbreviations: OS: overall survival.

B.4.3.3 TTD

TTD for olaparib was modelled on exposure data from the SAS of OlympiAD, comprising all 205 patients randomised to olaparib.

Table 32 summaries the total number of events and median and restricted mean survival times for TTD in the ITT population.

Table 32: Total number events and median time to event for TTD in ITT

	Olaparib 300 mg bd (n=205)
Total number of events	163
Median time to event	8.28 (6.67–8.77)
Restricted mean survival time (up to last time point where each arm has an observation)	10.17 (9.14–11.21)

Abbreviations: ITT: Intention to treat; TTD: time to treatment discontinuation.

As for PFS and OS, a series of standard parametric functions were fitted to patient-level data from the olaparib arm of the OlympiAD study. A summary of the AIC and BIC statistics is provided in Table 33.

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Table 33: AIC and BIC statistics for the standard parametric functions fitted to patient level data from the olaparib arm of OlympiAD in the ITT population (TTD)

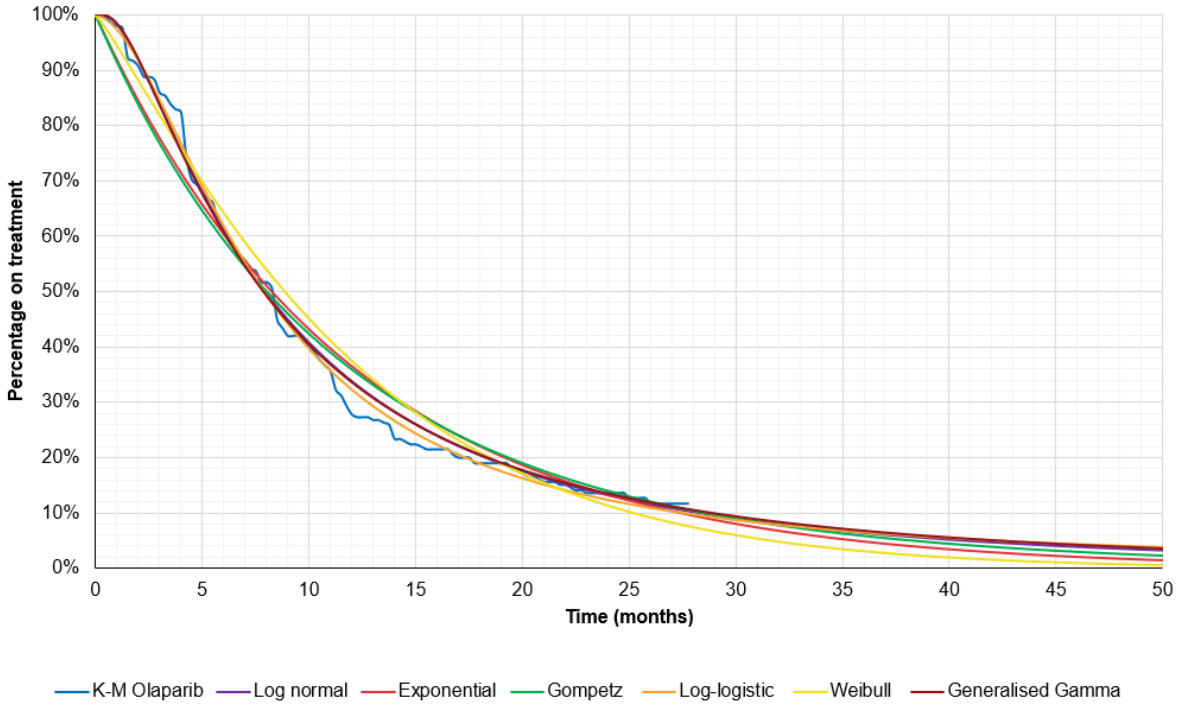
Model	Olaparib 300 mg bd	
	AIC	BIC
Generalized Gamma	1222.82	1232.79
Lognormal	1220.97	1227.61
Loglogistic	**1219.16**	**1225.81**
Exponential	1247.54	1250.87
Weibull	1244.51	1251.15
Gompertz	1249.12	1255.76

The model with the best fit according to AIC and BIC is highlighted bold.
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; ITT: Intention to treat; TTD: time to treatment discontinuation.

The function with the lowest AIC and BIC was the loglogistic. Lognormal was the second best-fitting function for olaparib, followed by the generalised gamma. All other models produced an inferior statistical fit to the observed data.

Figure 22 shows the visual fit of the standard functions versus the Kaplan–Meier plot for TTD. Despite the differences in AIC across models, all the standard functions produced a reasonable fit to the data based on visual inspection.

Figure 22: Comparison of predicted survival probabilities for TTD versus the Kaplan–Meier curves for the ITT population



Abbreviations: ITT: Intention to treat; TTD: time to treatment discontinuation.

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Table 34: Summary of predicted probabilities of TTD with olaparib at 6 months, 12 months, 18 months, 3, 5 and 10 years (ITT)

Model	Probability TTD with olaparib 300 mg bd				
Time point (years)	0.5	1	1.5	5	10
Generalised Gamma	60.6%	33.5%	20.4%	2.3%	0.4%
Lognormal	61.0%	33.7%	20.3%	2.0%	0.3%
Loglogistic	61.8%	32.2%	18.9%	2.7%	0.8%
Exponential	60.5%	36.6%	22.1%	0.7%	0.0%
Weibull	64.3%	37.5%	21.0%	0.2%	0.0%
Gompertz	59.4%	36.0%	22.3%	1.3%	0.1%
Trial	60.5%	27.8%	19.0%	-	-

Abbreviations: ITT: Intention to treat; TTD: time to treatment discontinuation.

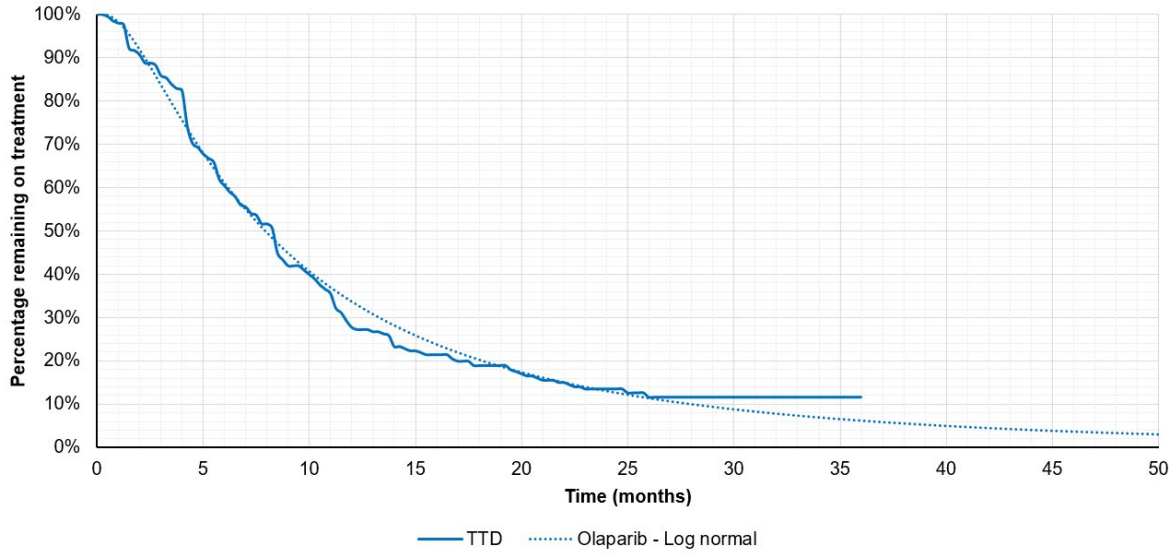
The function that best predicted the trial data for TTD was the lognormal distribution. Based on goodness of fit statistics, the preferred model for the base case of TTD was the lognormal distribution. A summary of the estimated coefficients for the preferred model is provided in Table 35. Figure 23 presents the predicted TTD up to 5-years.

Table 35: Parameters of the lognormal TTD distribution

Parameter	Olaparib 300 mg bd
Meanlog	2.0688
Sdlog	0.9884

Abbreviations: TTD: time to treatment discontinuation.

Figure 23: Plot showing the Kaplan–Meier probabilities of TTD versus the best fitting model (lognormal)



Abbreviations: TTD: time to treatment discontinuation.

B.4.3.4 Modelling clinical outcomes for talazoparib

A hazard ratio of 1.0 was adopted to model relative treatment effects for talazoparib versus olaparib. This reflects the perceived clinical equivalence between treatments and is in line with

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the results of the ITC (see Section B.3.8). Seven clinical experts were asked to comment on the comparable efficacy of olaparib versus talazoparib, all stated that they see olaparib and talazoparib to have similar efficacy.

A hazard ratio of 1.0 was applied to the extrapolated PFS, OS and TTD curves for olaparib from the OlympiAD trial to derive the respective survival curves for talazoparib.

B.4.3.5 Appropriateness of 1.0 Hazard Ratio

The ITC presented in Section B.3.8 was conducted on the log-hazard ratio scale, which may be confounded by the presence of non-proportional hazards in the trials informing the ITC. To validate the results of McCrea et al, an exploratory ITC using evidence from the post-hoc PFS analysis of OlympiAD, reported by Senkus et al, was conducted.[114] This approach uses an alternative method suitable for outcomes in the presence of non-proportional hazards.

Methods

Following previous ITCs, olaparib and talazoparib are compared via an anchored ITC using the TPC (SoC) control arms of OlympiAD and EMBRACA as the link in the network.

Restricted mean survival time (RMST) has been proposed as an alternative outcome measure to the hazard ratio in clinical trials with non-proportional hazards.[115] The RMST is the mean survival time up to a specified time point, t, corresponding to the area under the curve from time 0 to t. This measure yields a readily interpretable effect estimate, which can be compared across studies, and does not require the fitting of parametric models and associated assumptions on the distributional form of survival data. It provides a pragmatic estimate of the efficacy of therapy in studies where survival outcomes are relatively mature, and the proportional hazards assumption may be in doubt.

Analysis

The anchored ITC on the RMST scale was performed in three steps.

The first step involved estimating pseudo patient-level data from the EMBRACA study using the Guyot algorithm as implemented in the R package IPDfromKM (version 0.1.10).[116] The data points from the PFS Kaplan-Meier plot for EMBRACA were extracted using the online WebPlotDigitizer tool and combined with data on the numbers at risk and event numbers to estimate the pseudo data.

In the second step, the RMST was estimated for each arm of each study using the rmst2 function in the survRM2 R package (version 1.0-4). The RMST was estimated up to the minimum value of the largest observed survival time across trials. Due to data availability (i.e., requiring a Kaplan-Meier plot), it was only feasible to estimate the RMST for the PFS by blinded independent assessment for EMBRACA.[88] Therefore, in the primary analysis, the RMST for PFS by independent assessment was compared across studies using a time point of 24 months corresponding to the minimum value of the longest follow-up in the primary analysis of OlympiAD.[84] A second analysis was performed using the updated PFS by investigator from OlympiAD and comparing with the available PFS by blinded independent assessment in EMBRACA.[114] The RMST was assessed up to 27 months corresponding to the minimum value of the longest follow-up in the primary analysis of EMBRACA. Finally, a series of sensitivity analyses was performed using time points of 12, 18 and 24 months.

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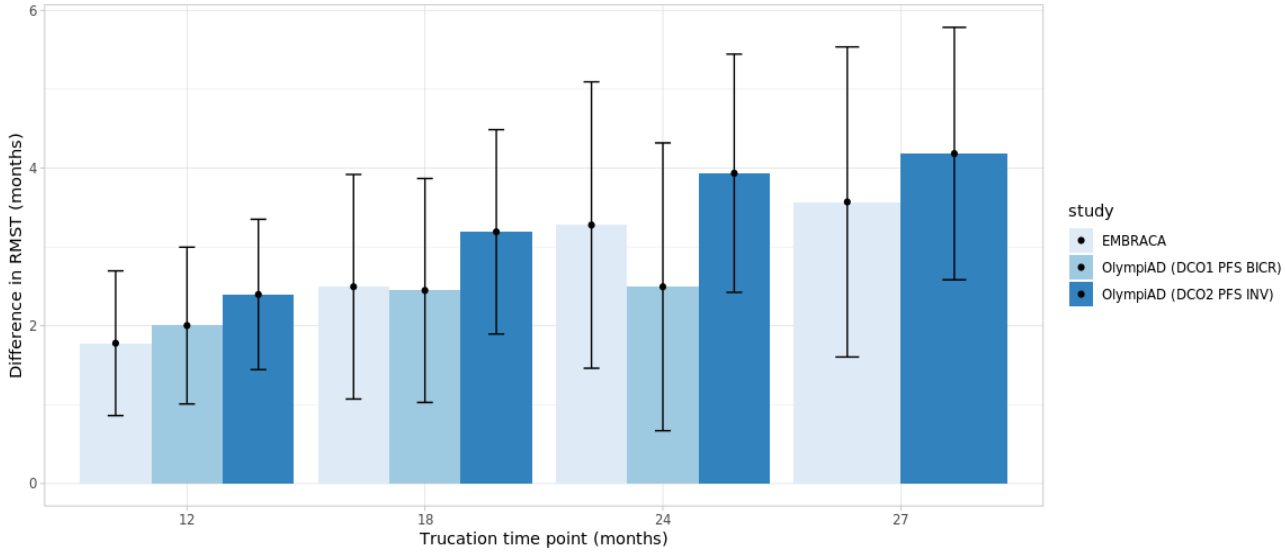
In the final step, the ITC of RMST was performed in a Bayesian framework using a fixed-effects arm-based model with normal-likelihood and identity link function.[117] The trial-specific baseline and treatment effect parameters were assigned vague prior distributions (e.g., normal(0,1000)). The reference arm of the comparison was SoC. The results of the ITC were summarized as the median RMST difference comparing olaparib versus talazoparib.

Results

A graph summarising the between-arm difference in RMST across studies and truncation points is provided in Figure 24. Across the two studies, there was clear overlap in the incremental RMST, at all truncation points, for PFS comparing PARP with SoC.

Figure 24: Difference in Restricted mean survival time (mean and confidence interval) for PFS comparing PARP inhibitor with SoC for truncation times of 12, 18, 24 and 27 months in OlympiAD and EMBRACA



PFS by blinded independent assessment

The results of the ITC on the RMST scale (up to month 24) using data from the primary endpoint of PFS by blinded independent assessment are presented in Table 36: Posterior RMST for PFS by blinded independent assessment from the ITC

Table 36: Posterior RMST for PFS by blinded independent assessment from the ITC

Parameter	Truncation time	Median	2.5%	97.5%	Rhat
d[Olaparib] vs d[talazoparib]	24 months	-0.79	-3.34	1.82	1.00
d[Olaparib] vs d[SoC]	24 months	2.52	0.69	4.35	1.00
d[Talazoparib] vs d[SoC]	24 months	3.26	1.53	5.09	1.00

Abbreviations: ITC: indirect treatment comparison; PFS: progression-free survival; RMST: restricted mean survival time; SoC: standard of care.

The ITC results suggest no significant difference in RMST for PFS by blinded independent assessment comparing olaparib with talazoparib (RMST up to 24 months=-0.79 months, 95% credible interval -3.34 to 1.82).

The Rhat statistic was equal to 1.0 indicating that the analysis had converged.

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PFS by investigator assessment

The results of the ITC on the RMST scale (up to month 27) using data from the endpoint of PFS by investigator assessment for OlympiAD (DCO2) and PFS by blinded independent assessment for EMBRACA (in lieu of a Kaplan-Meier plot for PFS by investigator in EMBRACA) are presented in Table 37.

Table 37: Posterior RMST for PFS by investigator assessment from the ITC

Parameter	Truncation time	Median	2.5%	97.5%	Rhat
d[Olaparib] vs d[talazoparib]	27 months	0.62	-1.94	3.13	1.00
d[Olaparib] vs d[SoC]	27 months	4.16	2.57	5.80	1.00
d[Talazoparib] vs d[SoC]	27 months	3.59	1.63	5.57	1.00

Abbreviations: ITC: indirect treatment comparison; PFS: progression-free survival; RMST: restricted mean survival time; SoC: standard of care.

The ITC results suggest no significant difference in RMST for PFS comparing olaparib with talazoparib (RMST=+0.62, 95% credible interval -1.94 to 3.13).

The Rhat statistic was equal to 1.0 indicating that the analysis had converged.

Conclusion

In summary, the results of the RMST ITCs demonstrate no evidence of a clinically meaningful difference in PFS between olaparib and talazoparib. The difference in RMST ranged from -0.79 months (in favour of talazoparib) to +0.62 months (in favour of olaparib). These results support the claim of non-inferiority between PARP inhibitors in this setting. The results support the appropriateness of using a hazard ratio of 1.0 to derive survival curves for talazoparib.

B.4.4 Cost and healthcare resource use identification, measurement and valuation

B.4.4.1 Intervention and comparator acquisition, administration, and monitoring costs

Acquisition costs

The dosing schedules were obtained from the SmPCs for each drug in the model. This included information on target dose, frequency of administration and maximum number of cycles, as summarised in Table 38.

The target daily dose of olaparib is 600 mg per day, as per its approved posology, with dose modifications permitted to manage adverse drug reactions.[6] The target daily dose of talazoparib is 1 mg per day, as per its approved posology, with dose modifications permitted to manage adverse drug reactions. Talazoparib and olaparib are taken until disease progression or unacceptable toxicity.[118]

For simplicity, the relative dose intensity (RDI) was assumed to be 100% across both arms. This is in line with the accepted assumptions from TA952.[1] It was also considered that alternative

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RDIs may bias the analysis in favour of talazoparib due to a high rate of dose interruptions seen in the EMBRACA trial.

The unit prices for comparators were obtained from the British National Formulary (BNF) 2024 for branded drugs. A summary is provided in Table 38.

Table 38: Summary of unit costs for interventions and comparators

Primary treatment	Pack unit strength (mg)	Pack size (n)	Price per pack	Source
Olaparib (oral)	150	56	List: £2,317.50 Net[a]: [redacted]	BNF 2024[119]
Talazoparib (oral)	1	30	£4,965.00	BNF 2024[120]

[a]A confidential commercial access agreement is in place for olaparib.
Abbreviations: BNF: British National Formulary.

Administration costs

Olaparib and talazoparib are both administered orally, and therefore are not anticipated to incur ongoing administration costs. However, for both olaparib and talazoparib, a one-off drug administration cost associated with delivering oral chemotherapy was applied, obtained from the National Schedule of NHS Costs 2021–2022 (Table 39).

Table 39: Summary of the unit costs for the administration of chemotherapy agents in the UK

Administration method	Cost per dose	Source
Oral	£237.09	NHS Costs (2021/22); currency code: SB11Z (deliver exclusively oral chemotherapy),[121] inflated to 2024 prices

Abbreviations: NHS: National Health Service.

Monitoring costs

For olaparib and talazoparib, 12 complete blood counts are included to capture the monthly monitoring of haematological toxicities during the first year of treatment. The unit costs for monitoring are captured within the health state costs in Table 42.

B.4.4.2 Adverse reaction unit costs and resource use

Seven clinical experts were asked to comment on the comparable efficacy of olaparib versus talazoparib, four of the clinicians stated that they had a similar safety profile, with three stating that they valued the slightly different safety profile of olaparib, especially in terms of haematological events. This is in line with the results of the ITC, where although there was no notable difference in the overall risk of any-grade AEs between olaparib and talazoparib treatment, a lower risk of anaemia for olaparib versus talazoparib was observed (Section B.3.8).[2] Therefore, adverse events were modelled separately for each treatment arm.

Treatment-related AE data for inclusion in the model for the olaparib arm were obtained from the OlympiAD trial; only Grade ≥3 AEs were included in the model. To account for heterogeneity between the trials, the odds ratio for each AE from the ITC (see Section B.3.8) was applied to determine AEs in the talazoparib arm.

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The cost impacts of AEs were assumed to apply during the first year of the model and were modelled as one-off events that occur at the start of the evaluation. This is justified on the basis that most AEs would occur soon after treatment initiation, and hence during the first 12 months of therapy. The total cost of AEs was calculated from the unit cost of each AE multiplied by the event rate.

Table 40: Unit costs associated with AE

AE	Cost per event	Source
Anaemia	£258.00	NHS payment scheme 2023/2025 (SA44A, single plasma exchange aged 19 years or over)
Neutropenia	£737.86	Cost of a 14-day single course of filgrastim for treating an episode of neutropenia (Accofil 70million units/0.73ml solution for injection pre-filled syringes Accord-UK Ltd, BNF 2024), as per TA952[1]
Diarrhoea	£307.00	NHS payment scheme 2023/2025 (FD01E Gastrointestinal infection without interventions, CC score 0-1, non-elective short stay)
Thrombocytopenia	£358.00	NHS payment scheme 2023/2025 (Thrombocytopenia, day case, average across CC scores, SA12G-K)
Headache	£0.70	Assumed that acute treatment would be provided using Imigran® (BNF 2024)
Leukopenia	£319.00	Assumed the same as outpatient visit (PSSRU 2022), inflated to 2024 prices

Abbreviations: AE: Adverse event; BNF: British National Formulary; CC score: comorbidity and complication split; CTCAE: Common Terminology Criteria for Adverse Events; PSSRU: Personal Social Service Research Unit; NHS: National Health Service.

Table 41: Incidence of AEs applied within the cost comparison model

AE	Olaparib	Talazoparib
Anaemia	16.1%	31.2%
Neutropenia	9.3%	12.3%
Diarrhoea	0.5%	0.3%
Thrombocytopenia	1.5%	4.0%
Headache	1.0%	0.8%
Leukopenia	2.0%	2.0%

Abbreviations: AE: adverse event.
Source: McCrea *et al.* (2021)[2]

B.4.4.3 Health state costs

The costs assigned to the states of PF and PD cover disease-related resource consumption including hospital visits, follow-up scans and consultations with clinicians. In OlympiAD, hospital-related resource use data were collected up to the date of last dose of olaparib. This included data on the frequency of hospital admissions, and the duration of stay by type of admission. In line with TA952,[1] a micro-costing approach was taken, a summary is provided in Table 42.

The health state costs for PF and PD in the base case are summarised in Table 42. The total weekly costs for PF and PD were estimated at £61.76 and £131.38, respectively.

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Table 42: Resource use (weekly) for PF and PD states, and unit costs

Resource	Weekly use in PF	Weekly use in PD	Unit cost	Notes	Data sources
Outpatient visit	0.00	0.00	£319.00	All outpatient costs captured in drug administration	NHS payment scheme 2023/2025 (370, medical oncology for outpatient, first attendance)
GP visit	0.25	0.50	£44.82	NICE CG 81, care package 1 and 2 (appendix): 1 per month GP surgery visit for PF, every 2 weeks for PD	PSSRU 2022 (per surgery consultation lasting 9.22 minutes, with qualification and direct staff costs), inflated to 2024 prices
Community nurse	0.50	1.00	£31.15	NICE CG 81, care package 1 and 2 (appendix): every 2 weeks community nurse visit for PF, every week for PD	PSSRU 2022 (per hour for band 6 nurse [consistent wage/salary to community nurses]), assuming 30 minute appointment time as per 2013 survey of community and district nursing, inflated to 2024 prices
Therapist	0.00	0.50	£34.43	NICE CG 81, care package 1 and 2 (appendix): No care required whilst PF and every 2 weeks whilst in PD	PSSRU 2022 (per hour for band 7 nurse in line with Macmillan costing fact sheet), assuming 30 minute appointment time as per 2013 survey of community and district nursing, inflated to 2024 prices
Cancer nurse	0.25	1.00	£54.65	NICE CG 81, care package 1 and 2 (appendix): 1 per month whilst PF and every week whilst in PD	PSSRU 2022 (per hour of community occupational therapist), inflated to 2024 prices
Complete blood count	0.00	0.00	£3.24	All drug related monitoring costs are captured separately	NHS reference costs 2021/2022 (DAPS05, pathology services), inflated to 2024 prices
Biochemistry	0.00	0.00	£1.69	All drug related monitoring costs are captured separately	NHS reference costs 2021/2022 (DAPS04, pathology services), inflated to 2024 prices
Computed tomography scan	0.11	0.11	£108.00	NICE CG 81, care package 1 and 2 (appendix): CT scan every 3 cycles (9 weeks) whilst in PF and PD	NHS payment scheme 2023/2025 (RD26Z, Computerised Tomography Scan of three areas, with contrast)

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Oncology visit	0.11	0.13	£176.00	NICE CG 81, care package 1 and 2 (appendix): consultation] every 3 cycles (9 weeks) whilst in PF and every 2 months whilst in PD	NHS payment scheme 2023/2025 (Consultant led Non-admitted face-to-face attendance, follow-up)
X-ray	0.00	0.00	£41.84	Not required	NHS reference costs 2021/2022 (DAPF, direct access plain film), inflated to 2024 prices

Abbreviations: GP: General Practitioner; NHS: National Health Service; NICE: National Institute of Health and Care Excellence; PD: progressive disease; PF: progression-free; PSSRU: Personal Social Service Research Unit.

B.4.4.4 *BRCA* mutation testing

Due to the recent reimbursement of talazoparib, olaparib reimbursement in the locally advanced or mBC setting is not expected to lead to an increase in g*BRCA*m testing volumes. Therefore, BRCA testing costs have not been included in the analysis.

B.4.4.5 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. The terminal care cost was calculated based on the weighted average approach used in the recent NICE evaluation of atezolizumab for TNBC (TA639).[76] The unit cost for each resource were sourced from PSSRU. This aligns with the approach used in TA952.[1] The weighted terminal care cost applied in the model was £7,952.60.

Table 43 summarises the unit cost and resource use of end of life care.

Table 43: Unit cost and resource use of end of life care

Setting	Unit costs	Proportion of patients in each setting
Hospital and social hospice care (combined)	£8,777	40%
Hospice	£22,238	10%
Home	£4,436	50%
		Total fixed cost: £7,952.60

Abbreviations: NICE: National Institute of Health and Care Excellence; TNBC: Tripple negative breast cancer.
Source: Atezolizumab NICE appraisal in TNBC (TA639).

B.4.5 Validation

B.4.5.1 Clinical validation

One round of individual clinical expert interviews was conducted to validate the clinical assumptions underpinning the economic model.[122] The interviews took place between March and

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April 2024. There were seven clinical experts and their areas of practice and working location are summarised in Table 44.

Table 44: Summary of clinical validation interviews supporting this submission

	Interview round 1
Number of clinical experts	7
Area of practice	Oncology
Geographical spread	London, Cardiff, Southampton, Bath

The following topics were included in the pre-specified interview agendas:

1. The UK clinical pathway advanced/metastatic g*BRCA*m HER2− breast cancer
2. Perceived efficacy and safety of OlympiAD
3. Olaparib versus talazoparib efficacy and safety profiles
4. Resource use
5. Long-term extrapolation of PFS and OS in OlympiAD

The UK clinical pathway g*BRCA*m HER2− locally advanced or mBC

Clinicians stated that factors including patient fitness, patient preference, presence of visceral crisis, biomarkers, oral vs IV drugs, would determine what treatment a patient would receive. Clinicians stated that if a patient had a known g*BRCA*m then they would look to prioritise treatment with a PARP inhibitor. All clinicians said that olaparib would be their PARP inhibitor of choice due to having experience with its use, as a result of reimbursement in early BC and the availability of an early access programme for locally advanced or mBC.

Perceived efficacy and safety of OlympiAD

All clinicians agreed that the OlympiAD patient population was representative of UK clinical practice. Clinicians valued the improvement in PFS and said that the HR was good. Clinicians were aware of the cross over and thus understood limitations in interpreting the OS benefit, however stated that they saw value in the observed numerical benefit. All clinicians agreed that the safety profile of olaparib was favourable compared to alternative cytotoxic treatments.

Olaparib versus talazoparib

All clinicians agreed that olaparib and talazoparib were clinically comparable in terms of efficacy. Three clinicians stated that olaparib had a more favourable safety profile, especially in terms of haematological events, compared to talazoparib. The remaining clinicians stated that they thought olaparib and talazoparib had similar safety profiles. All clinicians stated that they would use olaparib over talazoparib, due to olaparib having a favourable safety profile. Clinicians also stated that they were familiar with the use of olaparib due to reimbursement in early BC and the availability of an early access programme for locally advanced or mBC.

Resource use

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Clinicians stated that they would expect resource use to be the same for both drugs, with some stating that more blood transfusions may be required for talazoparib due to the incidence of haematological adverse events reported in the EMBRACA trial.

Long-term extrapolation of PFS and OS in OlympiAD

Clinicians thought that all models produced viable results, however it was a common theme that clinicians had experience with rare patients considered to be super responders. Therefore, most clinicians said that models predicting 5-year PFS at 0% were probably too pessimistic. In a similar vein, models predicting 10-year OS at 0% were also considered too pessimistic. Four clinicians singled out log-normal as the most appropriate curve to extrapolate PFS. Three clinicians singled out log-normal at the most appropriate curve selection for OS. In both cases, this was the most popular curve choice.

B.4.5.2 Technical validation

The model structure is consistent with the established approach to economic analysis in locally advanced or mBC and uses recommended mathematical functions for predicting lifetime PFS and OS. The results of the base case analysis, and associated sensitivity analyses are plausible considering the expected key drivers of results.

The model was subject to review and quality control before finalisation. An independent health economist, who not involved in the model development, reviewed the model for coding errors, inconsistencies, and plausibility of inputs and outputs. A range of extreme value and logic tests were conducted to examine the behaviour of the model and ensure that the results were logical.

In addition, internal validity was assessed by comparing the model predictions versus the Kaplan–Meier plots for PFS and OS, and the restricted mean survival time for OS up to the follow up of OlympiAD. In both cases, the model accurately replicated the survival endpoints from OlympiAD.

B.4.6 Base-case results

Total costs for olaparib [redacted] and talazoparib (at list price) are presented in Table 45, at list price. Olaparib is associated with a total cost per patient of £[redacted], whereas talazoparib is associated with a total cost per patient of £84,474. Olaparib is therefore associated with an incremental cost saving of £[redacted] per patient when compared to talazoparib. As expected, given equivalent health state occupancy and mode of administration costs were identical across olaparib and talazoparib for administration, monitoring, medical costs and end of life care. Cost differences were only observed for drug acquisition and adverse event costs.

Table 45: Cost-comparison base case results

Discounted	Olaparib	Talazoparib	Incremental
Drug acquisition	[redacted]	£62,854	[redacted]
Treatment administration	[redacted]	£237	[redacted]
Treatment monitoring	[redacted]	£39	[redacted]
Direct medical costs (PF)	[redacted]	£3,256	[redacted]

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Direct medical costs (PD)	[redacted]	£10,381	[redacted]
Direct medical end of life costs	[redacted]	£7,514	[redacted]
Adverse event costs	[redacted]	£193	[redacted]
Total	[redacted]	**£84,474**	[redacted]

Abbreviations: PD: progressive disease; PF: progression-free.

B.4.7 Sensitivity and scenario analyses

To identify key model drivers, one-way deterministic sensitivity analysis (DSA) was conducted. Parameters were varied one at a time between a +/- 20% variation around the mean.

The tornado plot showing the effect of varying parameters is displayed in Figure 25. Haematological adverse events, including anaemia and neutropenia had the largest impact on the incremental cost. As the majority of costs are applied equally to both arms of the model, most parameters did not impact the incremental costs.

Figure 25: Tornado plot showing results of the one-way sensitivity analysis

[redacted]

B.4.8 Interpretation and conclusions of economic evidence

The cost-comparison analysis has demonstrated that versus talazoparib, olaparib represents a plausibly cost-saving therapy option for patients with g*BRCA*m HER2− locally advanced or mBC. Treatment with olaparib in this indication is associated with a cost saving of £[redacted] per patient. Available evidence consistently indicates that olaparib and talazoparib are of comparable efficacy (Section B.4.3.4), and so the lower acquisition cost and alternative safety profile of olaparib would suggest that olaparib is a cost-saving treatment option versus talazoparib, whilst providing a different balance in side effect profile. Sensitivity and scenario analyses demonstrate that the base case model is robust to most parameters and assumptions.

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[redacted] olaparib is a plausibly cost-saving therapy option within its licensed indication.

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Appendices

Appendix C: Summary of product characteristics (SmPC) and UK public assessment report (EPAR)

Appendix D: Identification, selection and synthesis of clinical evidence

Appendix E: Subgroup analysis

Appendix F: Adverse reactions

Appendix G: Cost and healthcare resource identification, measurement and valuation

Appendix H: Checklist of confidential information

Appendix I: NGTD eligibility criteria

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Olaparib for treatment of *BRCA* mutation-positive HER2-negative metastatic breast cancer (Review of TA762)

ID3663

Summary of Information for Patients (SIP)

June 2024

File name	Version	Contains confidential information	Date
ID6336_Olaparib mBC_SIP_[CON]	Final	Yes	3rd June 2024

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Generic name: Olaparib

Brand name: Lynparza®

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

The population that this treatment will be used for is adults with **HER2**-negative **locally advanced or metastatic** breast cancer with **germline *BRCA* 1/2 mutations** that have previously been treated with an **anthracycline** and/or a **taxane** in the **(neo)adjuvant** or metastatic setting or for whom these treatments would not be suitable.

The terms used in the population are described in further detail in the sections below.

*Please note that further explanations for the words and phrases highlighted in **bold** are provided in the glossary (Section 4b). Cross-references to other sections are highlighted in pink.

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

Marketing authorisation is a licence required to place a medicinal product on the market, that sets out the conditions for use of a drug based on evidence of its safety and clinical

effectiveness. Olaparib has received a **marketing authorisation** from the **Medicines and Healthcare Product Regulatory Agency** in April 2019.[1]

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

AstraZeneca UK does engage the following patient groups relevant to this medicine with the aims of strengthening patient insights and responding to requests for information: Breast Cancer Now; MET UP UK; Make Seconds Count; UK Charity for TNBC. All patient group contributions are published annually on AstraZeneca UK's website: https://www.astrazeneca.co.uk/partnerships/working-with-patient-groups.

Since this publication, as of 31 May 2024 the following payments have been awarded:

- Breast Cancer Now: grant contributions towards helpline (2023)
- MET UP UK: grant contribution towards Metastatic Breast Cancer Conference in Manchester (June 2023)
- UK Charity for TNBC: sponsorship contribution towards patient experience roundtables (2024)
- UK Charity for TNBC: grant contribution towards establishment of Patient Forum (2024)

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

Olaparib is intended to treat locally advanced or metastatic breast cancer

What is locally advanced or metastatic breast cancer?

Breast cancer is the most common cancer diagnosed in the UK, accounting for 15% of new cancer cases.[2] About 685,000 women died from breast cancer in 2020, making it the most common cause of death amongst women.[3]

After someone is diagnosed with breast cancer, doctors will try to determine if it has spread in a process called staging. The stage of a cancer describes the size of a cancer and how far it has grown, including whether it has spread elsewhere in the body.[4] The

earliest stage breast cancers are stage 0 (where the cancer hasn't spread into the surrounding breast tissue). It then ranges from stage 1 through 4.[5]

Metastatic breast cancer is stage 4 breast cancer that has spread to another part of the body, most commonly the bones, lungs, brain, or liver.[6] Metastatic breast cancer is currently incurable and tends to progress rapidly. Locally advanced breast cancer describes where the cancer has spread to the area surrounding the tumour, such as the lymph nodes, skin or chest muscle, but not to more distant parts of the body.[7]

What are signs and symptoms of locally advanced or metastatic breast cancer?

The first symptom of breast cancer most people notice is a lump in their breast or some thickening. The following are also symptoms of breast cancer that people should look out for:

- a new lump or thickening in your breast or armpit
- a change in size, shape or feel of your breast
- skin changes in the breast such as puckering, dimpling, a rash or redness of the skin
- fluid leaking from the nipple in a woman who isn't pregnant or breastfeeding
- changes in the position of the nipple

The symptoms of metastatic breast cancer depend on which location in the body the cancer has spread to. For example, if the cancer has spread to the bones, people are likely to experience bone pain.[8]

What is the impact of locally advanced or metastatic breast cancer

People with metastatic breast cancer experience lower quality of life than the general population.[9] This is due to both the symptom burden, the toxicity associated with treatments taken and the emotional impact of the disease.

Metastatic breast cancer has a large economic burden in the UK.[10] The disease also impacts the ability of people to work and can impact people's personal finances.

What are *BRCA*1 and 2?

*BRCA*1 and 2 are breast cancer susceptibility **genes** that usually stop cells in our body from growing and dividing out of control. If there is a fault in these genes they may not function correctly, which can result in cells growing out of control.[11]

Germline *BRCA*1 and *BRCA*2 mutations (g*BRCA*m) increase the risk of developing breast cancer. Germline mutations are mutations that occur in sperm or egg cells and can be passed from parents to their children. For females with g*BRCA*1 or 2 mutations, their risk of developing breast cancer is substantially higher than females without this mutation, with approximately 70% developing the disease by the age of 80 years old.[12]

People with g*BRCA*1 or 2 metastatic breast cancer are likely to be younger at diagnosis, than people with breast cancer without the mutation.[13, 14] Therefore, they may be

establishing their careers and/or have childcare responsibilities, which will be affected by a breast cancer diagnosis.

Survival outcomes are also reduced for these patients compared to breast cancer without *BRCA* mutations, and there is a high unmet need for effective targeted treatments.[15] A specific class of treatments, called PARP inhibitors, are able to target cancers with g*BRCA*m (see Section 3a).

What is HER2 status and why is it important?

Outcomes in metastatic breast cancer are also influenced by whether the cancer has a **protein** called **human epidermal growth factor receptor 2 (HER2)**.[16] Cancer cells that have too many copies of the *HER2* gene (HER2-positive cancers) produce too much of the protein called HER2 which promotes their growth.[17] These types of breast cancer can be treated with drugs that target the HER2 protein. Cancers with a low amount of HER2 protein are known as HER2-negative breast cancers.

What is hormone receptor status and why is it important?

Some breast cancers are sensitive to the body's naturally occurring female **hormones**: oestrogen or progesterone. The breast cancer cells have hormone **receptors** on the outside of their walls that can bind to the oestrogen and progesterone that circulate through the body.[17]

Cancers that have hormone receptors (for oestrogen or progesterone or both) are known as hormone receptor positive, and whilst those that do not have hormone receptors are known as hormone receptor negative. Knowing if a breast cancer is sensitive to hormones gives doctors a better idea of how best to treat the cancer or prevent cancer from recurring. Hormone receptor positive cancers can be treated with drugs that target oestrogen and progesterone (see Section 2a), reducing their effect on cell growth.[6, 8]

If a cancer has a low amount of HER2 protein and does not have hormone receptors present, it can be called triple-negative breast cancer (TNBC). There are limited treatment options for patients with TNBC, and therefore patients with TNBC often have poorer survival outcomes.[18]

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

Most people are diagnosed with breast cancer at early stages of the disease (stage 1 and 2). However, about 15% of people are first diagnosed with stage 3 or 4 breast cancer.[19]

People may notice symptoms of breast cancer (as described in Section 2a), such as the a lump or a change in appearance or texture of the skin, which leads to an assessment by a doctor and subsequent investigations.[20] This may include blood tests, imaging and biopsies. Depending on the results of these tests, a diagnosis of breast cancer can be

given. In the UK, breast cancer screens are also performed as a part of the National Health Service (NHS) breast cancer screening programme, with women aged between 50 and <71 invited to take part.

People can sometimes be offered a genetic test, using samples of saliva or blood, to test whether they have a g*BRCA*1 or 2 mutation.[21, 22] This helps people to understand their risk of breast cancer and if they develop the disease, helps doctors to decide on the most suitable treatment for their cancer. This is particularly relevant for olaparib, as it works by targeting the *BRCA*1 or 2 mutation in the cancer cell. These genetic tests are given in the UK when it is suspected that a person could have the g*BRCA*1 or 2 mutation; for example if there is a family history of *BRCA* mutated breast cancer.

One of the key investigations performed by doctors is a **biopsy**, where a sample of the tumour is collected and is tested for the presence of hormone receptors in a pathology laboratory. This helps doctors understand a person's cancer, to find out which treatment could be most appropriate. As described in **Section 1b and 2a**, olaparib can be given to people with HR+/HER2−, or TNBC.

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
    - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
    - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

The aim of treatment for metastatic breast cancer is to extend life and provide a good quality of life. Treatment options are specific to each patient and depend on which treatments were used in early breast cancer.

Non-targeted treatments

The treatment for HER2-negative metastatic breast cancer with g*BRCA*m currently includes **non-targeted treatments**. These include hormone (endocrine) therapy or chemotherapy.

Chemotherapy can be given as a combination treatment, which is several chemotherapy drugs together, or as a single agent, which is one type of chemotherapy drug alone. The type of chemotherapy given depends on the type of breast cancer.

If the breast cancer is hormone receptor positive (see Section 2a), hormone therapy can be given. Hormonal therapies lower the amount of oestrogen or progesterone in the body or reduce their effect on cell growth.[6, 8] Examples of hormonal therapies for breast cancer include fulvestrant and aromatase inhibitors.

Targeted treatments

There are various targeted treatments available for HER2-negative breast cancer patients, which can be given alone or alongside non-targeted treatments such as endocrine therapies.[23] The choice of targeted treatment depends on a patient's hormone receptor status, previous treatments they have received and whether they have *BRCA* mutations. These targeted treatments include:

- CDK4/6 inhibitors such as palbociclib, ribociclib, and abemaciclib, which block proteins in cancer cells called cyclin-dependent kinases (CDKs). Blocking these proteins in HR+ breast cancer cells helps stop the cells from dividing and can slow cancer growth.

- The mTOR inhibitor, everolimus, which blocks mTOR, a protein in cells that normally helps them grow and divide. Everolimus may also stop tumours from developing new blood vessels, which can help limit their growth.

- The PI3K inhibitor, alpelisib, which blocks a form of the PI3K protein in cancer cells that can help stop them from growing.

- Immunotherapies, such as pembrolizumab or atezolizumab, which targets PD-1 (a protein on immune system T cells that normally helps keep them from attacking other cells in the body). By blocking PD-1, these drugs boost the immune response against breast cancer cells.[24]

- The antibody-drug conjugate, sacituzumab govitecan, which is a **monoclonal antibody** joined to a chemotherapy drug. The antibody helps direct the chemotherapy directly to the cancer by attaching to a specific protein on cancer cells.

- The PARP inhibitor, talazoparib, which was recently recommended for people with HER2-negative locally advanced or metastatic breast cancer, specifically for people with g*BRCA*m.[25]

Like talazoparib, olaparib is a PARP inhibitor (see Section 3a) intended for use in the same group of people with HER2-negative locally advanced or metastatic breast cancer and g*BRCA*m. This submission therefore compares olaparib to talazoparib.

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or

experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Mertz *et al.* (2022) explored the perspectives of breast cancer patients on progression-free survival and quality of life in metastatic breast cancer, holding virtual roundtables in Europe and the United States and interviews in Japan with breast cancer patients, patient advocates, and thought leaders.[26]

The study found that the most important treatment goal for was patients with metastatic breast cancer was extending their length of life without negatively impacting quality of life. Time when the disease is not progressing (referred to as progression-free survival) was also considered meaningful to patients when associated with improvements in quality of life and no added treatment toxicity. Patients with metastatic breast cancer valued relief from cancer-related symptoms and treatment-related toxicities as well as the ability to pursue personal goals.[26]

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Olaparib is a targeted treatment also known as a PARP inhibitor. PARPs are proteins that help damaged cells repair themselves. Some cancer cells, such as cancer cells with *BRCA* mutations, rely on PARP to keep their DNA healthy. Olaparib blocks how PARP proteins work and without PARP proteins, cancer cells may become too damaged to survive, and therefore die.[27]

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy

(3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.
No.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for. How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?
How is olaparib taken? Olaparib is taken as a hard capsule by mouth, also known as orally, twice per day. The recommended dose is 600 milligrams (mg) per day.[1] People should be treated with olaparib until either their disease progresses, or they have too many harmful side effects from treatment.

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.
The key **clinical trial** providing clinical evidence for olaparib in patients with HER2-negative metastatic breast cancer with g*BRCA*1/2 mutations is the OlympiAD trial.[28, 29] The OlympiAD trial assessed the ability of olaparib to improve **progression-free survival** and **overall survival** of patients (i.e., its **efficacy**), as well as improve patient quality of life, compared to the **comparator,** chemotherapy. The trials also assessed the safety and tolerability of olaparib compared to chemotherapy, including the frequency of severity of side effects and whether patients had to stop treatment. The comparator in the OlympiAD trial was a basket of chemotherapy. Patients could be prescribed any of the following three chemotherapies, as chosen by their doctor: • Capecitabine • Eribulin • Vinorelbine The trial was an international **Phase 3** trial conducted in 19 countries. A total of 302 patients started the trial with 205 patients assigned to receive olaparib and 97 patients assigned to receive chemotherapy. The trial was **open-label**, which means that all participants knew whether they were receiving olaparib or the comparator, chemotherapy.

Data collected from OlympiAD have been reported in the journal articles by Robsen *et al.* (2017), which presents data collected by December 2016, and Robsen *et al.* (2019), which presents the latest data collected in September 2017.[28, 30]

More information on this trial can be found in **Document B** in **Section B.3.1**.

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

Trial results

The OlympiAD clinical trial measured the effectiveness of olaparib for the treatment of HER2-negative metastatic breast cancer with g*BRCA*1/2 mutations. It demonstrated that olaparib provided a significant benefit over chemotherapy.[28, 29]

Progression-free survival

Progression-free survival is the time between the start of the trial and signs that the cancer has started to grow again (i.e. the length of time before the disease starts to progress), or death due to any cause.

The median progression-free survival was 2.8 months longer when people were treated with olaparib (7.0 months) compared to those treated with chemotherapy (4.2 months).[28]

Objective response rate

Objective response rate is the percentage of patients whose cancer shrinks (by at least 30%) or disappears completely after treatment. A benefit in objective response rate was observed for patients treated with olaparib (59.9%) compared to chemotherapy (28.8%).[28]

Overall survival

Overall survival is measured as the time between the start of the trial and death due to any cause. At the final analysis of overall survival, treatment with olaparib (median overall survival: 19.3 months) was associated with numerically longer overall survival than chemotherapy (median OS: 17.1 months). However, this difference was not statistically significant; potential reasons for this are detailed in **Document B, Section B.3.5.2**.[29]

Indirect treatment comparison

As discussed in **Section 2c**, it is anticipated that olaparib will be used as an alternative treatment option to talazoparib for people with HER2-negative metastatic breast cancer and g*BRCA*m. However, no clinical trials have been conducted that directly compare both olaparib and talazoparib. Therefore, an analysis called an **indirect comparison** was done to compare olaparib to talazoparib. This is a common approach in the evaluations of new medicines. This statistical analysis is explained in further detail in **Document B, Section B.3.6.**

Overall, compared to talazoparib, the indirect comparison showed that olaparib was similarly effective when considering progression-free survival, and is a well-**tolerated** treatment option for the HER2-negative metastatic breast cancer with g*BRCA*m.[31]

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D)

was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

The OlympiAD trial measured the quality of life of patients using the **EORTC QLQ-C30** measure.[28] This is a specific measure for quality of life in people living with cancer.

Treatment with olaparib was associated with a significant improvement in quality of life compared to chemotherapy. Also, more than one-third of people taking olaparib reported a meaningful improvement in quality of life during the trial.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Every medicine has **side effects** and the same medicine can produce different reactions in different people.

In the OlympiAD trial, olaparib was generally well tolerated and most side effects were of a low grade.[29] There was also a low rate of people stopping treatment due to side effects (4.9%). 16.6% of patients who received olaparib and 16.5% of patients who received chemotherapy reported a serious side effect. Importantly, the risk of **anaemia** (where the body does not have enough healthy red blood cells) did not increase with olaparib treatment.

Information on other potential side effects is available in the Patient Information Leaflet, and results from the OlympiAD trial are reported in **Document B, Section B.3.7**.[1]

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

There is a need for targeted treatments for HER2-negative metastatic breast cancer with g*BRCA*m

There are currently limited treatment options for people with this disease and non-targeted treatments are associated with significant toxicity. Other than talazoparib, olaparib is the only other targeted treatment specifically for people with HER2-negative metastatic breast cancer with g*BRCA*m, and will therefore help address this unmet need.

Olaparib is effective for HER2-negative metastatic breast cancer with g*BRCA*m

According to robust clinical trial evidence, olaparib is effective in treating HER2-negative metastatic breast cancer with g*BRCA*m, and was associated with improved progression-free survival and objective response rate when compared to chemotherapy (see **Section 3e**). Quality of life was also improved for people taking olaparib within the OlympiAD trial, with trial participants experiencing a significant improvement in in quality of life when taking olaparib compared to chemotherapy.[29] Treatment satisfaction, measured using a questionnaire in the OlympiAD trial, was also higher in people taking olaparib than people taking chemotherapy.[28]

Olaparib is administered by mouth

Olaparib is administered as a hard capsule by mouth, which can be taken at home.[1] This could be convenient for people taking it and reduce the time required for people and their supporting caregivers to attend hospital visits.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

Olaparib is generally well-tolerated and effective. However, like all existing breast cancer treatments, olaparib does not work for everyone and some patients might not experience any improvement in their disease.

Additionally, like all treatments for breast cancer, some patients may experience side effects while they are taking the treatment. The side effects are usually manageable, and most patients do not need to stop treatment because of side effects. These have been summarised in **Section 3g**.

Beyond these points, there are no additional key disadvantages with olaparib treatment.

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

Introduction to the economic model built for this submission

A cost-comparison model was developed for olaparib with the aim of comparing the costs associated with treatment when using this treatment, compared with using talazoparib. It was designed to reflect the usual way that HER2-negative metastatic breast cancer with g*BRCA*m is treated with either olaparib or talazoparib within the NHS.

Talazoparib was considered the principal comparator for the model as it is recommended for use in the same population for which olaparib is intended. In addition, both olaparib and talazoparib are PARP inhibitors. For these reasons, it is anticipated that olaparib would be considered by doctors as an alternative treatment to talazoparib in the proposed treatment population.

Based on the results from the indirect treatment comparison (see response to **Section 3e**), the efficacy of olaparib was assumed to be similar to talazoparib. The costs associated with treatment using olaparib were therefore compared with the costs of using talazoparib to determine whether olaparib would be a cost-effective treatment.

Clinical trial outcomes used in the model

Given the assumption of similar efficacy between olaparib and talazoparib, a cost-comparison model was developed for this submission. As such, no clinical outcomes were considered within the model, only costs.

How the costs of treatment differ between olaparib and talazoparib

The following costs were included within the cost-comparison model:

- The cost to purchase the medicine itself and how much it costs to administer the medicine (e.g., healthcare professional time)
- The cost of starting treatment and the cost of monitoring the patients during treatment
- The cost of side effects that happen during treatment
- The cost of diagnostic testing to identify patients with g*BRCA*m who would be suitable for treatment with olaparib or talazoparib

Olaparib will be provided to the NHS at a confidential discounted price which has been considered in the results because it is known to AstraZeneca. It should be noted that a confidential discount may apply to talazoparib as well, but this cannot be included in the analysis because it is unknown to AstraZeneca.

Cost-comparison results

When assuming similar efficacy for olaparib and talazoparib, the cost-comparison model predicts olaparib (at its discounted price) to be associated with reduced costs compared with talazoparib (at its full price). This means that the introduction of olaparib to clinical practice may represent a cost saving. However, it should be noted that these results are based on company-preferred assumptions and do not account for the confidential discount available for talazoparib.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations. If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)
Olaparib is one of the first targeted treatments for people with HER2-negative metastatic breast cancer with g*BRCA*m to be available on the NHS.

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here
There are no equality issues that are anticipated for the use of olaparib in HER2-negative metastatic breast cancer with g*BRCA*m.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc. Where possible, please provide open access materials or provide copies that patients can access.

Further information on HER2-negative metastatic breast cancer with g*BRCA*m

- What is cancer?: https://www.cancerresearchuk.org/about-cancer/what-is-cancer
- Inherited cancer genes and cancer risk: https://www.cancerresearchuk.org/about-cancer/causes-of-cancer/inheritedcancer-genes-and-increased-cancer-risk
- Breast cancer: https://www.cancerresearchuk.org/about-cancer/breast-cancer
- Metastatic breast cancer: https://breastcancernow.org/informationsupport/support-you/secondary-metastatic-breast-cancer
- Genetic testing for *BRCA*1 or *BRCA*2 mutations: https://breastcancernow.org/about-breast-cancer/awareness/breast-cancer-in-families/genetic-testing-for-altered-breast-cancer-genes/
- Targeted therapies for breast cancer: https://www.cancer.org/cancer/types/breast-cancer/treatment/targeted-therapy-for-breast-cancer.html#:~:text=Olaparib%20can%20be%20given%20to,help%20some%20women%20live%20longer
- PARP inhibitors for breast cancer: https://breastcancernow.org/informationsupport/facing-breast-cancer/going-through-breast-cancer-treatment/parpinhibitors-in-breast-cancer-treatment
- Olaparib: https://www.macmillan.org.uk/cancer-information-and-support/treatments-and-drugs/olaparib

Further information on NICE and the role of patients:

- Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE
- NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE
- EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/
- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

This glossary explains terms highlighted in black bold text in this summary of information for patients. At times, an explanation for a term might mean you need to read other terms to understand the original terms.

Anaemia	A condition in which the body does not have enough healthy red blood cells
Anthracycline	A class of drugs used in cancer chemotherapy

Biopsy	A procedure to remove a piece of tissue or a sample of cells from your body so that it can be tested in a laboratory
***BRCA* 1/2**	*BRCA*1 and *BRCA*2 genes usually protect people from developing breast cancer. However, inheriting an alteration in one of these genes increases the risk of developing cancer.
Chemotherapy	A type of cancer therapy that uses drugs to kill cancer cells.
Clinical trial	A type of research study that tests how well new medical approaches work in people. These studies test new methods of screening, prevention, diagnosis or treatment of a disease. Also called a clinical study.
Comparator	The standard (for example, another medicine or usual care) against which a medicine is compared in a study. The comparator can be no intervention (for example, best supportive care).
Efficacy	The ability of a medicine to produce a desired positive effect on your disease or illness in a clinical trial.
EORTC QLQ-C30	A measure of health-related quality of life used within a clinical trial
Genes	A gene is an inherited part of a cell in a living thing that controls physical characteristics, growth and development.
Germline	gene change in a body's reproductive cell (egg or sperm) that becomes incorporated into the DNA of every cell in the body of the offspring
HER2	a protein that helps breast cancer cells grow quickly
Hormones	Chemical substances that carry messages within the body to help coordinate different bodily functions.
Indirect comparison	An analysis that compares medicines that have not been compared directly in a head-to-head, randomised trial.
Marketing authorisation	The legal approval by a regulatory body that allows a medicine to be given to patients in a particular country.
Medicines and Healthcare Product Regulatory Agency	The regulatory body that evaluates, approves and supervises medicines throughout the European Union.
Metastatic	Cancer that has spread to other parts of the body beyond its original origin.
Monoclonal antibody	A type of protein that is made in the laboratory and can bind to certain targets in the body

Mutations	Our genes pick up mistakes that happen when cells divide. These mistakes are called genetic mutations. It is usual for cells to repair faults in their genes or to remove them from the body. Cancer happens when cells with genetic mutations are not repaired or removed from the body and instead multiply out of control.
(neo)adjuvant	Chemotherapy that a person with cancer receives before their primary course of treatment
Objective response rate	The percentage of patients whose cancer shrinks or disappears after treatment.
Open-label	A clinical trial where participants know what treatment they receive.
Overall survival	The length of time from either the date of diagnosis or the start of treatment for a disease, such as cancer, that patients diagnosed with the disease are still alive. In a clinical trial, measuring the OS is one way to see how well a new treatment works. Also called overall survival.
PARP inhibitor	A type of targeted cancer drug
Phase 3	This type of clinical trial that tests the safety and how well a new treatment works compared with a standard treatment. For example, it evaluates which group of patients has better survival rates or fewer side effects.
Progression-free survival	The length of time during and after the treatment of a disease, such as cancer, that a patient lives with the disease but it does not get worse. In a clinical trial, measuring the PFS is one way to see how well a new treatment works. Also called progression-free survival.
Protein	These are structures inside all cells of our body that are important for many activities including growth, repair and signalling
Receptors	A structure on the surface of a cell that detects stimuli.
Side effects	An unexpected medical problem that arises during treatment. Side effects may be mild, moderate or severe.
Targeted treatments	Targeted cancer drugs work by ‘targeting’ the differences between a cancer cell and normal cell that help cancer cells survive and grow. As these therapies target cancer cells specifically, they limit damage to healthy parts of the body.
Taxane	A type of drug that blocks cell growth by stopping cell division

Tolerated	The ability of a patient to put up with the side effects of treatment.

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

1. European Medicines Agency. Olaparib (Lynparza®) Summary of Product Characteristics. Available at: https://www.ema.europa.eu/en/documents/product-information/lynparza-epar-product-information_en.pdf (Accessed: 16/02/2024).
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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Olaparib for treating BRCA mutation-positive HER2-negative advanced breast cancer after chemotherapy (Review of TA762) [ID6336]

Clarification questions

JUNE 2024

File name	Version	Contains confidential information	Date
[ID6336] olaparib - Clarification Responses - [CON]	V1	Yes	27/06/2024

Notes for company
Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

Decision problem

A1. CS Section B.1.2.2. CS Figure 4 (treatment pathway) specifies metastatic BC (mBC) in the title. Please confirm whether this pathway also applies to locally advanced disease.

Response:
The treatment pathway presented in Figure 4 applies to both locally advanced and metastatic breast cancer. Treatment for both locally advanced and metastatic disease is the expected to be the same, as supported by clinical guidelines. Guidelines for the management of advanced BC are available from NICE (CG81, last updated in 2017)[1] and for mBC from the European Society for Medical Oncology (ESMO, 2021).[2]

A2. Talazoparib has a marketing authorisation and NICE recommendation for patients previously treated with an anthracycline and/or a taxane (CS Section B.1), while the olaparib marketing authorisation is restricted to patients previously treated with an anthracycline and a taxane (CS Table 2 and Section B.1.2.4).

a) Please provide an estimate of the proportion of patients eligible for talazoparib who are not eligible for olaparib.
b) Would only having one of an anthracycline or a taxane, rather than both, affect the relative efficacy of talazoparib?

Response:

a) Proportion of UK patients treated with an anthracycline and a taxane

Although the marketing authorisation for talazoparib is technically slightly broader than that for olaparib (due to the and/or phrasing in relation to prior chemotherapy regimens), in UK clinical practice the vast majority of eligible patients would be expected to have received a prior anthracycline ***and*** a taxane, as this aligns with NICE guidelines (as outlined below).

It should be highlighted that in the UK the vast majority of breast cancer patients are initially diagnosed with early-stage disease (83% diagnosed at stage 1 or 2 in 2020)[3], which further increases the likelihood that they would have received both a taxane and an anthracycline by the time they are being considered for either talazoparib or olaparib in the advanced

setting. Therefore, only a very small proportion of patients would be eligible for talazoparib who are not also eligible for olaparib.

NICE recommendations on the choice of chemotherapy regimen in breast cancer patients:

NICE guideline on "early and locally advanced breast cancer: diagnosis and management" [NG101][4] makes the following recommendations: • *For people with breast cancer where chemotherapy is indicated, offer a regimen that contains both a taxane and an anthracycline. Refer to the summaries of product characteristics for individual taxanes and anthracyclines to check for differences in licensed indications.*	*NICE guideline on "advanced breast cancer: diagnosis and treatment" [CG81][1] makes the following recommendations:* • *Consider using combination chemotherapy to treat patients with advanced breast cancer for whom a greater probability of response is important and who understand and are likely to tolerate the additional toxicity.* • *For patients with advanced breast cancer who are not suitable for anthracyclines (because they are contraindicated or because of prior anthracycline treatment either in the adjuvant or metastatic setting), systemic chemotherapy should be offered in the following sequence:* o *first line: single-agent docetaxel* o *second line: single-agent vinorelbine or capecitabine* o *third line: single-agent capecitabine or vinorelbine (whichever was not used as second-line treatment).*

b) Impact of prior chemotherapy regimen on treatment effect of PARP inhibitors

Treatment with only an anthracycline or a taxane alone is not expected to affect the relative efficacy of PARP inhibitors (PARPis). This is due to PARPis having a different mode of action compared to taxanes and anthracyclines and therefore a different target. PARPis mechanism of action includes inhibition of PARP1/2 enzymes directly, and therefore has a unique target that is different to that of anthracyclines and taxanes.

A3. CS Section B.1.2.4. The company's intended population is locally advanced or metastatic breast cancer. However, the OlympiAD trial is only in metastatic breast cancer. Please confirm:

a) Whether there is any data for olaparib in locally advanced breast cancer, and

b) Whether you expect efficacy or safety of olaparib to differ between metastatic and locally advanced disease.

Response:
The scope of the appraisal as defined by NICE is in 'adult patients with germline BRCA1/2 mutations, who have human epidermal growth factor receptor 2 negative (HER2−) locally advanced or metastatic breast cancer (mBC)' which is in line with the EMA license for olaparib in this setting. Although there were no patients with locally advanced breast cancer (LABC) included in the OlympiAD trial, the CHMP concluded that it was appropriate to

extend the EMA marketing authorisation to this group “given a similar clinical management for locally advanced and metastatic disease and based on a biological and pharmacological rationale”.[5]

AstraZeneca do not believe that the lack of data specifically exploring the use of olaparib in LABC should impact decision-making for this appraisal because:

a) There is no evidence or clinical rationale to suggest that LABC versus mBC is a treatment effect modifier for PARP inhibitors in this setting.
b) The EMBRACA trial was also heavily weighted towards mBC (rather than LABC) patients and was deemed suitable for decision making by NICE.

a) LABC versus mBC not considered to be a treatment effect modifier

LABC and mBC are distinct stages of breast cancer, which may have prognostic implications. However, there is no evidence to suggest that they are treatment effect modifiers for PARP inhibitor (i.e. that the stage of disease would impact the relative effectiveness of a treatment).

This is because both stages of the disease share key underlying biological mechanisms, such as gBRCA mutations and hormone receptor status. Treatments targeting these mechanisms are expected to be similarly effective regardless of whether a patient has distant metastases or not. This concept is reflected in clinical practice guidelines, which generally recommend similar systemic therapies for both LABC and mBC.

b) Limited proportion of LABC patients enrolled within EMBRACA

The numbers of locally advanced breast cancer patients in EMBRACA was extremely limited, and such patients represented less than 6% of the total enrolled population (n= 24 patients with locally advanced disease versus n= 406 patients with metastatic disease).[6] The impact of the ITT efficacy in EMBRACA is therefore unlikely to be driven by the inclusion of LABC patients, hence a cost-comparison route remains appropriate. Furthermore, in TA952[7], the ITT analysis was used to inform decision making rather than splitting the analysis into LABC and mBC subgroups, suggesting that LABC and mBC were not considered to be significant treatment effect modifiers.

Indirect treatment comparison (ITC)

A4. CS Section B.3. Please provide effectiveness data (e.g. PFS and OS with Kaplan-Meier plots) and safety data for the EMBRACA trial of talazoparib.

Response:

The data is publicly available and can be found within the following publications:

- Litton, J.K. et al. (2018) ‘Talazoparib in patients with advanced breast cancer and a germline BRCA mutation’, New England Journal of Medicine, 379(8), pp. 753–763. doi:10.1056/nejmoa1802905.[6]
- Litton JK, Hurvitz SA, Mina LA, et al. Talazoparib versus chemotherapy in patients with germline BRCA1/2-mutated HER2-negative advanced breast cancer: final overall survival results from the EMBRACA trial. Ann Oncol 2020;31:1526-1535.[8]

A5. CS Table 17 presents baseline patient characteristics for OlympiAD and EMBRACA, However, the text in CS Section B.3.8.3 contains additional information not presented in Table 17.

a) Please update Table 17 for OlympiAD and EMBRACA to cover all the patient characteristics covered in Section B.3.8.3 (including how many previously had a taxane, anthracycline or both; and how many HR+ patients had prior endocrine therapy) and any other important characteristics.
b) Please also provide a table of key study characteristics (in addition to patient characteristics) for both trials. Please include all the study characteristics covered in Section B.3.8.3 and any other important characteristics.
c) On the tables above, please provide summary data for each trial for all randomised patients (across both arms) as well as per arm. This will facilitate easier comparison between the overall trial populations.

Response:

a) The updated version of Table 17 from the CS is provided in Table 1 below. With regards to the specific requests for additional detail on prior treatments which patients had received, it is worth noting that:
    i. Prior endocrine therapies: all HR+ve patients in both trials had received prior endocrine therapy.
    ii. Prior chemotherapy agents: All patients in OlympiAD must have received both an anthracycline and a taxane (as per the inclusion criteria). The EMBRACA trial inclusion criteria specified that patients had to receive an anthracycline, a taxane or both; however, there is no published data on the proportion of patients who received these agents as monotherapy or in combination, so it has not been possible to include this level of granularity in Table 1. Receiving either an anthracycline or a taxane alone prior to treatment with either olaparib or talazoparib is not expected to affect the relative efficacy (see response to A2).

Table 1: Baseline patient characteristics in OlympiAD and EMBRACA studies

Treatment/Comparator Group	Total number (%) of patients					
	OlympiAD [9,10]			EMBRACA [6,8]		
	Olaparib (N=205)	TPC (N=97)	Total % of trial	Talazoparib (N=287)	TPC (N=144)	Total % of trial
Median age, years (range)	44 (22–76)	45 (24–68)	29.5	45 (27–84)	50 (24–88)	22.0
g*BRCAm* type, n (%)						
gBRCA1m	117 (57.1)	51 (52.6)	55.6	133 (46.3)	63 (43.8)	45.5
gBRCA2m	84 (41.0)	46 (47.4)	43.0	154 (53.7)	81 (56.2)	54.5
Both	4 (2.0)	–	1.3	–	–	-
Receptor status, n (%)						
TNBC	102 (49.8)	48 (49.5)	49.7%	130 (45.3)	60 (41.7)	44.1
HR+/HER2−	103 (50.2)	49 (50.5)	50.3%	157 (54.7)	84 (58.3)	55.9
Breast cancer stage, n (%)						
Locally advanced	–	–	-	15 (5.2)	9 (6.2)	5.6
Metastatic	205 (100)	97 (100)	100.0	271 (94.4)	135 (93.8)	94.2
ECOG performance status, %						
0	72.2	63.9	45.1	53.3	58.3	25.9
1	27.8	36.1	21.2	44.3	39.6	19.5
2	–	–	-	2.1	1.4	0.8
Prior chemotherapy regimen for mBC, n (%)						
0	68 (33.2)	31 (32.0)	32.8	111 (38.7)	54 (37.5)	38.3
1	80 (39.0)	42 (43.3)	40.4	107 (37.3)	54 (37.5)	37.4
2	57 (27.8)	24 (24.7)	26.8	57 (19.9)	28 (19.4)	19.7
>3	–	–	0.0	12 (4.2)	8 (5.6)	4.6
Prior platinum therapy, n (%)	60 (29.3)	26 (26.8)	28.5	46 (16.0)	30 (20.8)	17.6
Visceral disease	165 (80.5)	84 (86.6)	82.5	200 (69.7)	103 (71.5)	70.3
Treatment with anthracycline, taxane, or both	205 (100)	97 (100)	100.0	287 (100)	144 (100)	100.0

Prior endocrine therapy if HR+ve (OlympiAD: n= 152, EMBRACA: n = 241)	103 (100)	49 (100)	100.0	157 (100)	84 (100)	100.0

[a]Four patients in the olaparib arm had both g*BRCA*1m and g*BRCA*2m.
Abbreviations: ECOG: Eastern Cooperative Oncology Group; g*BRCA*1m: Germline *BRCA*1 mutation; g*BRCA*2m: Germline *BRCA*2 mutation; mBC: metastatic breast cancer; TPC: Treatment of physician's choice; TNBC: Triple-negative breast cancer.
Source: McCrea *et al.* (2021)

b) Table 2 displays a comparison of the key study characteristics of OlympiAD and EMBRACA that are relevant to this appraisal.

Table 2: Key Study characteristics

Trial name	OlympiAD [9,10]	EMBRACA [6,8]
Location	OlympiAD was conducted across 19 countries worldwide including: Bulgaria, China, Czech Republic, France, Hungary, Italy, Japan, Korea, Mexico, Peru, Poland, Romania, Russia, Spain, Switzerland, Taiwan, Turkey, United Kingdom and United States	EMBRACA was conducted across Australia, Belgium, Brazil, France, Germany, Ireland, Israel, Italy, Republic of Korea, Poland, Russia, Spain, Taiwan, Ukraine, United Kingdom and United States
Trial design	The OlympiAD trial was a high-quality, international, Phase III, multicentre, open-label, controlled trial that assessed the efficacy and safety of olaparib in comparison with SOC chemotherapy for patients with g*BRCA*m HER2− mBC	The EMBRACA trial was a high-quality, international, Phase III, multicentre, open-label, controlled trial that assessed the efficacy and safety of talazoparib in comparison with SOC chemotherapy for patients with g*BRCA*m HER2− mBC
Eligibility criteria for participants	Patients were deemed eligible for inclusion in the OlympiAD trial if they were: • ≥18 years of age • Had HER2− mBC • Both HR+/HER2− and TNBC patients were permitted • Had confirmed deleterious or suspected deleterious g*BRCA*m • Patients were required to have received no more than two previous chemotherapy regimens for metastatic disease and had received chemotherapy treatment in the neoadjuvant, adjuvant or metastatic setting with an anthracycline (unless it was contraindicated) and a taxane • At least one endocrine therapy was administered to	Patients were deemed eligible for inclusion in the EMBRACA trial if they were: • Histologically or cytologically confirmed carcinoma of the breast • Locally advanced breast cancer that is not amenable to curative radiation or surgical cure and/or metastatic disease appropriate for systemic single cytotoxic chemotherapy • Documentation of a deleterious, suspected deleterious, or pathogenic germline BRCA1 or BRCA2 mutation from Myriad Genetics or other laboratory approved by the Sponsor • No more than 3 prior chemotherapy-inclusive regimens for locally advanced and/or metastatic disease (no limit on

	patients with HR+/HER2− mBC unless contraindicated • Previous neoadjuvant or adjuvant platinum treatment was allowed if ≥12 months had passed since it was last given. If no evidence of disease progression had occurred during treatment, platinum treatment was also permitted for patients with metastatic disease • Patients were required to have normal baseline organ and bone marrow function, as well measurable disease. Measurable disease was defined as at least one lesion suitable for baseline and subsequent assessment for disease according to modified RECIST, version 1.1	prior hormonal therapies or targeted anticancer therapies such as mechanistic target of rapamycin (mTOR) or CDK4/6 inhibitors, immune-oncology agents, tyrosine kinase inhibitors, or monoclonal antibodies against CTL4 or VEGF) • Prior treatment with a taxane and/or anthracycline in the neoadjuvant, adjuvant, locally advanced, or metastatic setting unless medically contraindicated • Have measurable or non-measurable, evaluable disease by the revised response evaluation criteria in solid tumors (RECIST) v.1.1 • Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2
Intervention	Olaparib administered orally at a dose of 300 mg twice daily	Talazoparib administered at a dose of 1mg once daily
Comparator	Three pre-specified standard chemotherapies (repeated every 21 days) were prescribed according to TPC: • Capecitabine administered orally at a dose of 2,500 mg per square meter of body-surface area daily (divided into two doses) for 14 days • Eribulin mesylate administered intravenously at a dose of 1.4 mg per square meter on day 1 and day 8 • Vinorelbine administered intravenously at a dose of 30 mg per square meter of body surface area on day 1 and day 8	Three pre-specified standard chemotherapies: • Capecitabine administered orally at a dose of 2,500 mg per square meter of body-surface area daily (divided into two doses) for 14 days • Eribulin mesylate administered intravenously at a dose of 1.4 mg per square meter on day 1 and day 8 • Vinorelbine administered intravenously at a dose of 30 mg per square meter of body surface area on day 1 and day 8 • Gemcitabine administered intravenously at a dose of 1250 per square meter of body-surface area IV over 30 minutes on Day 1 and 8 of each 21-day cycle in combination with paclitaxel 175 mg/m2 IV over 3 hours on Day 1 before gemcitabine administration.

A6. Please comment on why the indirect treatment comparison (ITC) results in Wang et al. are slightly different to the results in McCrea et al.

Response:

The ITCs conducted by McCrea et al.[11] and Wang et al.[12] have slight differences in methodological approaches and different statistical models, which can lead to different results, for example:

- McCrea et al conducted a Bayesian fixed-effects ITC using individual patient level data from the OlympiAD trial.
- Wang et al. conducted an ITC using a random-effect model within a Bayesian framework using pseudo data derived via Montel Carlo simulation methods.

Despite slight differences in the results of the ITCs, both yield the same conclusion, that olaparib and talazoparib have equivalent efficacy. McCrea et al. and Wang et al. both suggests no difference in PFS between olaparib and talazoparib, estimating a HR of 1.09 and 1.08, respectively. Both ITCs are therefore useful to act as evidence to inform decision making and support the case for a cost-comparison of olaparib versus talazoparib.

A7. Please elaborate on the decision to use the ITC presented in McCrea et al. as opposed to Wang et al. to primarily support the assessment of equal efficacy of olaparib and talazoparib.

Response:

McCrea et al. was used as the main evidence base within the submission as it was based on individual patient level data directly from the OlympiAD trial, whereas Wang et al. was based on aggregate published data from EMBRACA, using pseudo data derived via Monte Carlo simulation. ITCs conducted using individual patient level data are potentially more reliable than those based on aggregate data.[13] Furthermore, McCrea et al. was the most recently published ITC.

However, as discussed in A6, both studies yield the same conclusion and act as evidence to support the equivalent efficacy of talazoparib and olaparib. Both ITCs are therefore useful to act as evidence to inform decision making and support the case for a cost-comparison of olaparib versus talazoparib.

A8. Please provide an ITC for subgroup analyses of PFS for any important clinical subgroups, including HR+ and TNBC.

Response:

It is not appropriate to conduct ITCs in the prespecified subgroups for several reasons:

- Olaparib demonstrated clinical benefit in the full ITT population.
- The subgroups are not powered in the OlympiAD trial.
- Talazoparib received reimbursement in the full ITT population.
- There is no biological plausibility for HR-status to be a treatment modifier.

Firstly, olaparib demonstrated clinical benefit in the full ITT population, as such this should remain the population of interest for this appraisal.

The results of the subgroup analysis in both the OlympiAD and EMBRACA trials showed no statistical evidence that treatment effect on PFS was different across pre-specified subgroups. However, neither of the trials were powered to demonstrate a significant treatment effect in subgroups. Underpowered studies tend to provide imprecise estimates of treatment effects, the results of the subgroup analysis should therefore be interpreted with caution. Performing an ITC on studies that are not powered appropriately can lead to misleading or unreliable results. It was noted in TA952[7] that any analyses in pre-specified subgroups would add additional uncertainty.

Talazoparib was deemed cost-effective in the full ITT-population, it would therefore not be suitable to conduct a cost-comparison for a drug reimbursed in the ITT population against a subgroup for a comparator considered equivalent.

Finally, there is no biological rationale for HR status to be considered a treatment effect modifier, as HR status is not the drug target. In TA886[14], the evaluation of adjuvant olaparib in the early setting, it was noted that there was no statistical evidence of a differential treatment effect by HR subgroup, with the benefit of olaparib being observed irrespective of HR status. This supports that the treatment effect is driven by the BRCA mutation rather than the HR status, given that this is the biological target for PARPi.

Based on the above, AstraZeneca believe that the conclusions drawn from the ITT ITCs are applicable to and appropriate for decision making in this appraisal and additional analyses in distinct subgroups are unlikely to provide meaningful insight. For these reasons, AstraZeneca has chosen not to conduct an ITC on the pre-specified subgroups.

Adverse event data

A9. CS Section B.4.4.2 states that Grade ≥3 adverse events (AEs) from OlympiAD were included in the model (and presumably in CS Table 40 and 41).

a) Please explain why not all of the Grade ≥3 AEs presented in CS Table 19 are included in CS Tables 40 and 41. Please include all AEs regardless of assumed cost.

b) Please clarify whether Grade ≥3 AEs from the EMBRACA trial have been incorporated via the ITC. If not, please include any additional AEs as appropriate.

Response:

a) To standardise these between trial differences, only adverse events that were included in McCrea et al were included in the model. The AEs included in McCrea et al. were those identified as being the most commonly reported for olaparib and talazoparib in either the OlympiAD or EMBRACA studies, respectively, and are included in their respective drug labels. These were considered to be the most important AEs to compare olaparib and talazoparib, and thus other AEs not listed were excluded.

b) Grade ≥3 AEs from EMBRACA have been incorporated indirectly via the ITC. Treatment-related AE data for inclusion in the model for the olaparib arm were obtained from the OlympiAD trial, the odds ratio for each AE from the ITC (see Section B.3.8.) was applied to determine AE frequency in the talazoparib arm.

A10. CS Table 41 provides the incidence of each AE, and CS Section B.4.4.2 states that AE data were obtained from the OlympiAD trial and that odds ratios from the ITC were applied in order to determine AEs in the talazoparib arm. However, the data in Table 41 do not appear to match the data in CS Figure 14 (safety ITC) in terms of the direction of effect of some AEs. For example, headache favours olaparib in the ITC but favours talazoparib in Table 41, and leukopenia favours olaparib in the ITC but is the same in both arms in Table 41.

For AEs without an assumed cost, there also appears to be inconsistency; for example, fatigue marginally favours olaparib in Figure 14, whereas this favours talazoparib in the model. Please check the calculations for AEs and ensure consistency between the data in Table 41 and Figure 14, and between Figure 14 and incidence of AEs within the model.

Response:

Thank you for highlighting this error within the model. The model has now been updated to correct for this error and the updated model results are shown in Table 3. This correction has minimal effect on the model results. The incidence of AEs applied within the cost-comparison model are displayed below in Table 4.

Table 3: Results of cost comparison analysis

Cost type	Olaparib	Talazoparib	Incremental
Drug acquisition	[redacted]	£62,854	[redacted]
Treatment administration	[redacted]	£237	[redacted]
Treatment monitoring	[redacted]	£39	[redacted]
Direct medical costs (PF)	[redacted]	£3,256	[redacted]
Direct medical costs (PD)	[redacted]	£10,381	[redacted]
Direct medical end of life costs	[redacted]	£7,514	[redacted]
Adverse event costs	[redacted]	£337	[redacted]
Total	[redacted]	£84,618	[redacted]

Table 4: Incidence of AEs applied within the cost comparison model

AE	Olaparib	Talazoparib
Anaemia	16.10%	43.51%
Neutropenia	9.30%	25.14%
Nausea	0.00%	0.00%
Vomiting	0.00%	0.00%
Diarrhoea	0.50%	1.35%
Fatigue	3.40%	9.19%
Alopecia	0.00%	0.00%
Thrombocytopenia	1.50%	4.05%
Headache	1.00%	2.70%
Leukopenia	2.40%	6.49%

Abbreviations: AE: adverse event.
Source: McCrea *et al.* (2021)

Section B: Clarification on cost-effectiveness data

B1. Please provide a table which shows the cost per month of treatment for olaparib (at PAS price) and for talazoparib (at list price) and other relevant costs which differ between the two drugs; these appear to be only the costs of AEs (Tables 40 and 41 in the CS assuming all AEs with costs are included).

Response:

[redacted]

Table 5: Monthly costs per patient

Monthly cost per patient (30 day)	Olaparib [redacted]	Talazoparib (at list price)	Incremental
Drug acquisition	[redacted]	£4,965.00	[redacted]
Adverse Event (one-off cost)	£124.73	£337.10	-£212.37

B2. Please provide the likely QALY losses associated with all AEs (not just those in Table 40 and 41 in the CS) rated as Grade 3 or greater.

Response:

The estimated QALY losses associated with each arm of the model are displayed in Table 6. The adverse events of interest, as specified in McCrea et al.[11] were those identified as being the most commonly reported for olaparib and talazoparib in either the OlympiAD or EMBRACA studies, respectively, and are included in their respective drug labels. Utility decrements were sourced from previous TAs or the literature. Each adverse event was assumed to last 14-days. Treatment with olaparib and talazoparib was associated with a QALY loss due to adverse events of 0.0009 and 0.0024, respectively. The results of the analysis support the case that olaparib has a more favourable safety profile compared to talazoparib.

Table 6: Estimated Utility Decrement

Adverse events, n (%)	QALY decrement	OlympiAD		EMBRACA		Source
		Grade ≥3	Estimated QALY loss	Grade ≥3	Estimated QALY loss	
Nausea	0.103	0.00%	0.0000	0.30%	0.0000	TA819
Anaemia	0.01	16.10%	0.0001	39.20%	0.0002	TA819
Vomiting	0.103	0.00%	0.0000	2.40%	0.0001	TA819
Fatigue	0.115	3.40%	0.0001	1.70%	0.0001	TA819
Neutropenia	0.124	9.30%	0.0004	20.90%	0.0010	TA819
Diarrhea	0.103	0.50%	0.0000	0.70%	0.0000	TA819
Headache	0.115	1.00%	0.0000	1.70%	0.0001	Assumed the same as fatigue
Thrombocytopenia	0.124	1.50%	0.0001	0.15%	0.0007	Assumed the same as neutropenia
Leukopenia	0.124	2.40%	0.0001	0.07%	0.0003	Assumed the same as neutropenia
Alopecia	0.114	0.00%	0.0000	0.00%	0.0000	Lloyd et al

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NICE National Institute for Health and Care Excellence

Cost Comparison Appraisal

Olaparib for treating BRCA mutation-positive HER2-negative advanced breast cancer after chemotherapy [ID6336]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	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 company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	Breast Cancer Now has received funding from a number of drug companies towards our support services. However, we do not receive any pharmaceutical funding for our Policy, Evidence and Influencing work, which includes our work on access to drugs. Over the last 12 months (May 2023-May 2024) we have received funding from the following companies listed in the final stakeholder list for this appraisal: AstraZeneca – we have received £42,314.55 to support our helpline and Ask Our Nurses service (May 2023) Breast Cancer Now hosts the UK Interdisciplinary Breast Cancer Symposium (UKIBCS) alongside a number of partners including professional bodies and charities. The meeting is held every 2 years and the UKIBCS provides a space to bring together those with an interest in breast cancer research and treatment to advance understanding of the disease. The event is managed by a third party who receive and process sponsorship on behalf of the host and partners. Sponsors have no control over the running of the event and editorial control has been retained by the UKIBCS executive board. In the past 12 months (since May 2023), this has included the following listed on this appraisal matrix: Pfizer - £6k for an exhibitors package, November 2023

	Breast Cancer Now-funded researchers contributed to the discovery of a targeted use for PARP inhibitors. The charity receives a share of royalties from the Institute of Cancer Research for sales of PARP inhibitor drugs being used in a targeted way to treat cancers with changes in BRCA genes, or other similar defects which mean that cancer cells are unable to properly repair their DNA. Income raised through the royalties/payments for PARP inhibitor drugs is invested back into the charity, so that Breast Cancer Now can continue to fund world-class research and life-changing support for everyone affected by breast cancer.
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 use our various networks of people affected by breast cancer to gather information about patient experience. This includes our online Breast Cancer Now Forum and our online and face to face services.

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?	Secondary breast cancer, also known as advanced or metastatic breast cancer, occurs when cancer originating in the breast spreads to other parts of the body, most commonly the lungs, brain, bones or liver. There is no cure for secondary breast cancer. Treatment aims to control and slow the spread of the cancer, relieve symptoms and give people the best quality of life for as long as possible. Someone can be diagnosed with secondary breast cancer from the start, or they can be diagnosed with the condition subsequent to a primary breast cancer diagnosis. Approximately 5-10% of women with breast cancer are thought to carry an altered gene, with BRCA being the most common. Patients with an inherited BRCA mutation may be diagnosed at a younger age. Some have young children and face the frightening prospect of the uncertainty of knowing whether they will see key milestones. Patients with BRCA tell us that they can feel an additional burden knowing that children and family members may also have the altered gene. Triple negative breast cancer can be more aggressive and harder to treat than other types of breast cancer, resulting in potentially poorer outcomes and short life expectancy Some patients with triple negative breast cancer would be eligible for this treatment if it is made available. Secondary breast cancer symptoms can have a major impact on people's quality of life. They will vary depending on where the cancer has spread to, but general symptoms can include feeling constantly tired (fatigue), nausea, weight loss and loss of appetite. Headaches, nausea, seizures and confusion can occur if cancer has spread to the brain. People who develop brain metastases will likely have to give up their driving licence, which can have a major impact on independence and ability to carry out day-to-day activities. Symptoms such as breathlessness and pain while breathing can occur if cancer has spread to the lungs. Breast cancer treatments themselves can also cause side effects, which is a significant source of concern for patients. These side effects can have a major impact on people's day-to-day lives, quality of life, health and wellbeing. Different patients will react differently to drugs, so side-effects are not easy to predict. Diagnosis with secondary breast cancer can have a significant emotional toll for patients and those around them. After their diagnosis, patients may feel overwhelmed, anxious, depressed and isolated. The practicalities of

	managing their condition (which often involves travelling to regular hospital appointments) alongside day-to-day activities like work, household and parental responsibilities can be difficult to manage. Patients with secondary breast cancer have a significant desire to find treatments that will halt progression and extend life for as long as possible. They also have a strong desire to retain quality of life and spend time with their loved ones.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	The PARP inhibitor talazoparib was approved by NICE to treat HER2-negative secondary breast cancer with germline BRCA mutations in February 2024. Breast Cancer Now strongly welcomed this decision as it was the first targeted treatment made available on the NHS in England specifically for certain people with locally advanced or secondary breast cancer who have inherited an altered BRCA gene. Patients welcomed the fact that the treatment offers them precious extra time before their disease progresses, compared to chemotherapy. Its administration method – a daily tablet – means that patients now need fewer hospital visits (compared to intravenous chemotherapy) freeing up valuable time for patients, as well as capacity in oncology units. Prior to the approval of talazoparib, for the triple negative cohort of patients, for many years chemotherapy was the mainstay of treatment and there were significantly limited treatments and progress for this group of patients. In recent years, we have seen the introduction of some new treatments such as atezolizumab/pembrolizumab and sacituzumab govitecan for certain patients which have been hugely welcomed. However, patients are still desperate for new treatments which can increase the time before their disease progresses and improve survival. Prior to the approval of talazoparib, for the hormone-receptor positive cohort of patients, for a number of years hormone treatment alone was a key treatment, however, we have seen the welcome introduction of a number of CDK 4/6 inhibitors as well as treatments for certain subgroups of patients such as alpelisib. New and effective treatment options post CDK/46 inhibitor are still lacking as patients become resistant to these treatments so new medicines that can increase the options available for these group of patients are still urgently needed and patients welcome treatments that are easy to take, such as oral tablets and can enable them to have a good quality of life.
8. Is there an unmet need for patients with this condition?	While the approval of talazoparib has been a great step forward for patients with an inherited altered BRCA gene, additional treatment options will always be welcomed. Making an additional PARP inhibitor available will offer valuable choice to both patients and clinicians. Olaparib could be used to treat patients experiencing intolerable side effects on the existing treatments.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	The OlympiAD phase 3 clinical trial compared Olaparib to clinician's choice of chemotherapy to treat HER2-negative secondary breast cancer with a germline BRCA mutation. Data published at the time showed greater progression free survival compared to chemotherapy (7.0 months vs. 4.2 months). Follow-up data showed median overall survival of 19.3 months for olaparib, versus 17.1 months for chemotherapy. A key benefit of this treatment is its administration method. An oral tablet can be easy for patients to take and although routine appointments will still be required for monitoring and scans, there will be fewer trips required to hospital compared to IV treatments. Patients tell us that this can make them feel like they can get on with their 'normal lives' much easier and can feel less like a patient which is important for this group of patients that are on constant treatment.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	In the OlympiAD clinical trial, patients receiving olaparib reported nausea, anaemia, vomiting, fatigue, cough, decreased appetite, back pain and headache at a relatively higher frequency than the comparator. These potential side effects will be of concern to patients. However, all treatments come with side-effects and patients experience these side effects in different ways. It is important that they are offered choice to balance side-effects against the potential benefit of treatments. Many patients would welcome an additional treatment option at this stage in the pathway, particularly if they need to discontinue alternative treatments as a result of their side effects. Olaparib is taken twice daily, while the current treatment option, talazoparib, is taken once daily. This regime may be slightly more onerous to patients.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Not known

Other issues

13. Are there any other issues that you would like the committee to consider?	

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• A diagnosis of secondary breast cancer has significant implications for the length and quality of a patient's life and can take a major emotional and practical toll. • Approximately 5-10% of people with breast cancer carry an altered gene, most commonly BRCA – these patients may be diagnosed at a younger age, presenting additional challenges for patients with young children. • Patients with an altered BRCA gene have greatly benefited from the approval of talazoparib in early 2024. This was the first targeted treatment made available on the NHS in England for certain people with locally advanced or secondary breast cancer who have inherited an altered BRCA gene. The treatment offers precious extra time before their disease progresses and its administration method as an oral tablet was very appealing to patients. • The approval of olaparib would offer a valuable additional treatment option for patients and clinicians. Results from the OlympiAD clinical trial showed follow-up showed greater progression free survival compared to chemotherapy (7.0 months vs. 4.2 months). Follow-up analysis showed median overall survival of 19.3 months for olaparib, versus 17.1 months for chemotherapy. • Patients receiving olaparib may experience side effects, including nausea, anaemia, vomiting, fatigue, cough, decreased appetite, back pain and headache. Its administration method is much less onerous than IV treatments, but slightly more onerous than talazoparib as it is taken orally twice a day, rather than once.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - YES or NO

For more information about how we process your personal data please see our privacy notice.

Olaparib for treating BRCA mutation-positive HER2-negative advanced breast cancer after chemotherapy (Review of TA762) [ID6336]. A Cost-comparison Technology Appraisal

Produced by	Sheffield Centre for Health and Related Research (SCHARR), The University of Sheffield
Authors	Katy Cooper, Senior Research Fellow, SCHARR, University of Sheffield, Sheffield, UK Matt Stevenson, Professor of Health Technology Assessment, SCHARR, University of Sheffield, Sheffield, UK Jessica Forsyth, Research Associate, SCHARR, University of Sheffield, Sheffield, UK Ruth Wong, Information Specialist, SCHARR, University of Sheffield, Sheffield, UK Kate Ren, Senior Research Fellow, SCHARR, University of Sheffield, Sheffield, UK Uzma Asghar, Consultant Medical Oncologist, The Royal Marsden NHS Foundation Trust, UK. Nicolò Matteo Luca Battisti, Consultant Medical Oncologist, The Royal Marsden NHS Foundation Trust, UK. Carlo Palmieri, Consultant Medical Oncologist, The Clatterbridge Cancer Centre, Liverpool, UK.
Correspondence to	Katy Cooper, Senior Research Fellow, SCHARR, University of Sheffield, Sheffield, UK
Date completed	17 July 2024

Source of funding: This report was commissioned by the NIHR HTA Programme as project number 168094.

Declared competing interests of the authors

None of the authors has any conflicts of interest to declare.

Acknowledgements

We would like to thank Mon Mon Yee (SCHARR) for providing comments on the draft report, and Andrea Shippam (Programme Manager, SCHARR) for providing administrative support and in preparing and formatting the report.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

Cooper KL, Stevenson M, Forsyth J, Wong R, Ren K, Asghar U, Battisti NML, Palmieri C. Olaparib for treating BRCA mutation-positive HER2-negative advanced breast cancer after chemotherapy (Review of TA762) [ID6336]. A Cost-comparison Technology Appraisal. Sheffield Centre for Health and Related Research (SCHARR), 2024.

Contributions of authors

Katy Cooper was project lead. Ruth Wong critiqued the company's search strategy. Katy Cooper summarised and critiqued the clinical effectiveness data reported within the company's submission. Jessica Forsyth and Kate Ren critiqued the indirect treatment comparison within the submission. Matt Stevenson critiqued the cost data submitted by the company. Uzma Asghar, Nicolò Battisti and Carlo Palmieri provided clinical advice. All authors were involved in drafting and commenting on the final report. Copyright belongs to The University of Sheffield.

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Abbreviations

AE	Adverse event
BICR	Blinded independent central review
BRCA	Breast cancer susceptibility gene
CDK4/6 inhibitor	Cyclin-dependent kinase 4 and 6 inhibitor
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CRD	Centre for Reviews and Dissemination
CrI	Credible interval
CS	Company submission
EAG	External Assessment Group
EMA	European Medicines Agency
ECOG PS	Eastern Cooperative Oncology Group performance status
HER2+/-	Human epidermal growth factor receptor 2 positive/negative
HR	Hazard ratio
HR+/-	Hormone receptor positive/negative
HRQoL	Health-related quality of life
IPD	Individual patient-level data
ITC	Indirect treatment comparison
ITT	Intention-to-treat
mBC	Metastatic breast cancer
NICE	National Institute for Health and Care Excellence
OR	Odds ratio
ORR	Objective response rate
OS	Overall survival
PARP inhibitor	Poly(ADP-ribose) polymerase inhibitor
PAS	Patient Access Scheme
PFS	Progression-free survival
PFS2	Progression-free survival 2 (time from randomisation to a second progression event or death after a first progression event)
RCT	Randomised controlled trial
SAE	Serious adverse event
TFST	Time to first subsequent cancer therapy
TNBC	Triple negative breast cancer
TPC	Treatment of physician's choice
TSST	Time to second subsequent cancer therapy

1. EXECUTIVE SUMMARY

The National Institute for Health and Care Excellence (NICE) cost-comparison approach is suitable for technologies which are likely to provide similar or greater health benefits at similar or lower cost than comparator(s) recommended in published NICE guidance for the same population.

The External Assessment Group (EAG) highlights that the company updated its percentage discount for olaparib, in this indication, after the factual accuracy check; this report only considers the new discounted price unless explicitly stated.

The EAG considers that this topic broadly meets the criterion for providing similar or greater health benefits as clinical advisors to the EAG considered olaparib and talazoparib to have similar mechanisms of action and similar clinical effectiveness, although there may be some differences in safety profiles and rates of specific side effects between the two drugs. However, when the Patient Access Scheme (PAS) price of talazoparib and the updated percentage discount price for olaparib are considered, olaparib has a greater acquisition price, so appears not to meet the similar or lower cost criterion.

The EAG highlights a potential difference in the marketing authorisation between olaparib and talazoparib that needs to be considered by NICE. For talazoparib, both the marketing authorisation[1] and NICE recommendation [TA952][2] require patients to have received an anthracycline **and/or** a taxane (unless contraindicated), while the marketing authorisation for olaparib[3] specifies that patients must have received both an anthracycline **and** a taxane (unless contraindicated). This means that any recommendation for olaparib would be slightly narrower than that for talazoparib. This is discussed further in Section 3 of this report.

2. BACKGROUND

2.1. Why the cost-comparison approach has been considered

Olaparib is being considered for the cost-comparison approach because it is in the same drug class as talazoparib, which recently received a NICE recommendation [TA952] in a very similar population as that intended for olaparib; and because indirect treatment comparisons (ITCs) suggest that olaparib and talazoparib provide similar health benefits, as outlined in the NICE final scope.[4]

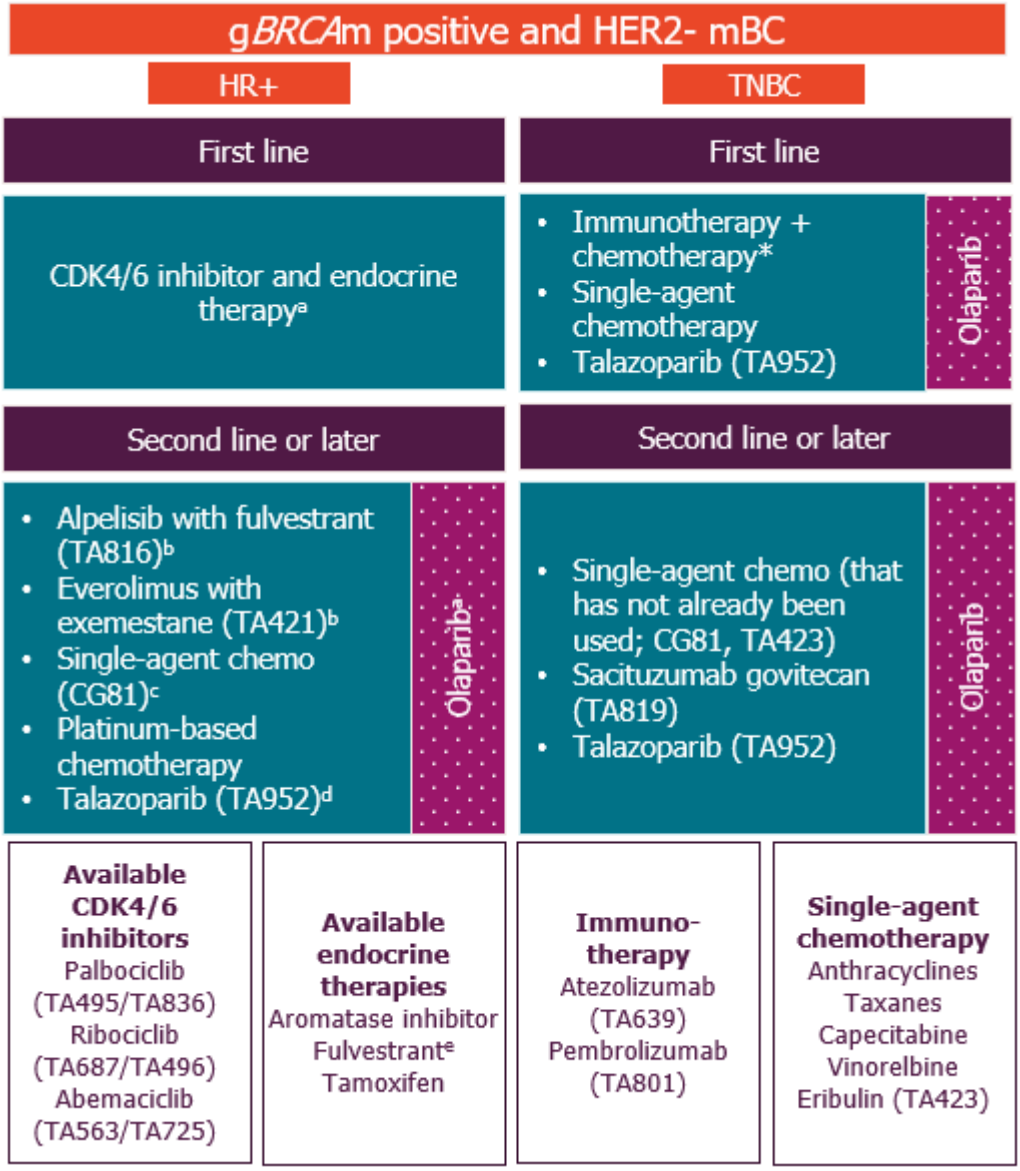
2.2. Company description of disease area and treatment pathway

The EAG considers that the company has provided an acceptable description of the disease area and the treatment pathway (company submission [CS] Section B.1.2).[5] Clinical advisors to the EAG considered the company's treatment pathway diagram (reproduced in Figure 1) to be accurate. The EAG noted that the pathway diagram header only specifies metastatic breast cancer (mBC); however, the company noted in their clarification response[6] (A1) that the pathway applies to both locally advanced and metastatic breast cancer, and clinical advisors to the EAG agreed.

Breast cancer can be classed as human epidermal growth factor receptor 2 positive or negative (HER2+ or HER2-) and as hormone receptor positive or negative (HR+ or HR-), where hormone receptors include the oestrogen and progesterone receptors. Breast cancer that is both HER2- and HR- is known as triple negative breast cancer (TNBC). The population in the CS[5] and the NICE final scope[4] is people with HER2- locally advanced or metastatic breast cancer previously treated with chemotherapy, with germline mutations in breast cancer susceptibility (*BRCA*) genes. The EAG notes that the term "pathogenic variant" rather than "mutation" may be preferred when referring to germline mutations; however, the term "mutation" is used in this report for consistency with the NICE final scope.[4]

The population for this appraisal includes two key sub-populations: HER2-/HR+ breast cancer and TNBC. The CS (Section B.1.2.1) states that in England, approximately 69% of breast cancer cases are HR+/HER2- while 10% are TNBC (the remainder are HER2+ and are out of scope for this appraisal). Within the company's treatment pathway, for HER2-/HR+ disease, talazoparib (and potentially olaparib) are listed as options for second-line treatment of advanced disease, since first-line treatment would usually be cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors plus endocrine therapy (Figure 1). Conversely, for TNBC, talazoparib (and potentially olaparib) are listed as options for either first-line or second-line treatment of advanced disease.

Figure 1: Current treatment pathway



[a] Endocrine monotherapy may be considered in first line in a small group of patients with comorbidities or a performance status that prevents the use of CDK4/6 inhibitor combinations. For patients whose disease is imminently life-threatening or requires early relief of symptoms because of significant visceral organ involvement, chemotherapy may be considered as first-line treatment; [b]Therapies typically used at second-line in patients who progress following first-line therapy but remain sensitive to endocrine therapy; [c]Single-agent chemotherapy is an option for patients who are not (or are no longer) responsive to endocrine therapy at second or later line; [d]For patients with HR+ disease, talazoparib is recommended only in patients with mBC who have had prior endocrine therapy (i.e. second line or later), unless this is not suitable. Olaparib is positioned in the same population for which talazoparib received a recommendation. [e]Fulvestrant monotherapy is not recommended by NICE. *The EAG notes that no footnote is provided for "*" in the CS.

Abbreviations: CDK: cyclin-dependent kinase; g*BRCA*m: germline breast cancer susceptibility gene mutation; HR: hormone receptor; mBC: metastatic breast cancer; TNBC: triple negative breast cancer.

Source: Reproduced from CS Figure 4. **Source in CS:** TA816; TA421; TA423; TA81; TA819; TA495; TA836; TA687; TA496; TA563; TA725; TA639; ´TA801.

2.3. Testing for breast cancer subtypes and mutation status

The CS[5] (Section B.1.2.1.2) covers testing for HR status, HER2 status and germline *BRCA* mutations. In terms of germline *BRCA* mutation testing, the CS states that some patients would be routinely tested due to age, family history or tumour characteristics. The CS also states that it was noted within the talazoparib appraisal (TA952)[2] that the cost of *BRCA* testing should be included for some patients with HER2−/HR+ locally advanced or metastatic breast cancer. The CS states that olaparib reimbursement in the locally advanced or metastatic setting is not expected to lead to an increase in germline *BRCA* mutation testing volumes.

2.4. Mechanism of action of olaparib and talazoparib

Olaparib belongs to the class of poly(ADP-ribose) polymerase (PARP) inhibitors (CS Section B.1.1).[5] Olaparib is an oral selective inhibitor of PARP enzymes (PARP1 and PARP2), which play a role in DNA repair. Mutations in *BRCA1* and *BRCA2* also inhibit DNA repair. Olaparib's inhibition of DNA repair, particularly in cells with a *BRCA* mutation, increases genomic instability and can eventually lead to cell death.

Talazoparib is also a PARP inhibitor (PARP1 and PARP2).[2] Both olaparib and talazoparib are orally administered. Clinical advisors to the EAG considered olaparib and talazoparib to have a similar mechanism of action.

3. CRITIQUE OF THE DECISION PROBLEM IN COMPANY'S SUBMISSION

3.1. Marketing authorisations and NICE recommendations for olaparib and talazoparib

The olaparib marketing authorisation is as follows: "*Lynparza (olaparib) is indicated as monotherapy for the treatment of adult patients with germline BRCA1/2 mutations, who have human epidermal growth factor receptor 2 negative (HER2−) locally 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 hormone receptor positive (HR+) breast cancer should also have progressed on or after prior endocrine therapy, or be considered unsuitable for endocrine therapy*."[3]

The talazoparib marketing authorisation is as follows: "*Talzenna (talazoparib) is indicated as monotherapy for the treatment of adult patients with germline BRCA1/2-mutations, who have HER2-negative (HER2-) locally advanced or metastatic breast cancer. Patients should have been previously treated with an anthracycline and/or a taxane in the (neo)adjuvant, locally advanced or metastatic setting unless patients were not suitable for these treatments. Patients with hormone receptor positive (HR+) breast cancer should have been treated with a prior endocrine-based therapy, or be considered unsuitable for endocrine-based therapy.*"[1]

Talazoparib was recommended by NICE in February 2024 for the following indication [TA952]: "*Talazoparib is recommended, within its marketing authorisation, for treating HER2-negative, locally advanced or metastatic breast cancer with germline BRCA1 or BRCA2 mutations in adults who have had an anthracycline or a taxane, or both, unless these treatments are not suitable, and endocrine therapy if they have hormone receptor (HR)-positive breast cancer, unless this is not suitable. Talazoparib is only recommended if the company provides it according to the commercial arrangement*".[2]

3.2. Licensed indication for olaparib vs. talazoparib

The CS[5] (Section B.1) states that the intended population in the CS covers the full marketing authorisation for olaparib. The EAG notes that olaparib has a slightly different indication to talazoparib. For talazoparib, both the marketing authorisation[1] and NICE recommendation [TA952][2] require patients to have received an anthracycline **and/or** a taxane (unless contraindicated), while the marketing authorisation for Olaparib specifies that patients must have received both an anthracycline **and** a taxane (unless contraindicated). This means that any recommendation for olaparib[3] would need to be slightly narrower than that for talazoparib. Clinical advisors to the EAG considered that the two patient populations (those having had both prior therapies, or one or the other) were unlikely to be substantially different in terms of their characteristics or response to PARP inhibitors.

The company clarification response[6] (A2) states that the vast majority of eligible patients for olaparib or talazoparib would have received a prior anthracycline **and** a taxane as this aligns with NICE guidance for early and advanced breast cancer.[7, 8] The clarification response (A2) also states that prior treatment with only an anthracycline or a taxane alone, rather than both, is not expected to affect the relative efficacy of PARP inhibitors, since PARP inhibitors have a different mode of action compared to taxanes and anthracyclines.

3.3. Company decision problem: similarity to NICE final scope

The company decision problem (CS[5] Table 1) is aligned with the NICE final scope[4] in terms of the population, intervention, comparator and outcomes. In summary, the population is adults with HER2− locally advanced or metastatic breast cancer with germline *BRCA* 1/2 mutations, previously treated with an anthracycline and a taxane in the (neo)adjuvant or metastatic setting (unless contraindicated), and previously treated with endocrine therapy in the case of HR+ disease (unless contraindicated). The intervention is olaparib monotherapy and the comparator is talazoparib. Outcomes include overall survival (OS), progression-free survival (PFS), objective response rate (ORR), adverse events (AEs) and health-related quality of life (HRQoL).

3.4. Clinical evidence and relevance to patient population in England

The clinical data for this appraisal is based on the OlympiAD trial of olaparib[9, 10] and the EMBRACA trial of talazoparib.[11, 12] Clinical advisors to the EAG considered that both trials are generalisable to clinical practice for the relevant patient populations in England and Wales. These trials are discussed further in Section 4 of this report.

3.5. Relevance of comparator

Talazoparib is the only comparator in the NICE final scope[4] and in the CS.[5] The EAG considers talazoparib to be a relevant comparator for this appraisal. The CS (Section B.1) states that talazoparib is the most appropriate comparator for the following reasons: talazoparib is the first reimbursed targeted treatment for the proposed target population; clinical experts consulted by the company stated that they would prioritise treatment with a PARP inhibitor for patients with a known germline *BRCA* mutation; two published ITCs suggest that talazoparib and olaparib have comparable efficacy and safety;[13, 14] and clinical experts consulted by the company noted that they would expect the two treatments to have similar efficacy and safety. Clinical advisors to the EAG considered that talazoparib is likely to become commonly used in clinical practice in its NICE-reimbursed population.

4. SUMMARY OF THE EAG'S CRITIQUE OF CLINICAL EFFECTIVENESS EVIDENCE SUBMITTED

4.1. Critique of company systematic review methods

The reported searches (original followed by update searches) in the CS[5] (Appendix D.1) are transparent and fully reported (provision of full search strategies, detailed PRISMA diagrams) across database, trials registry and supplementary conference and HTA agency searches. Overall, the EAG considers that the company search was comprehensive and that there were no observable and/or consequential errors in the search approach and strategies, although a small number of inconsequential errors were identified by the EAG in relation to reproducibility and reporting inconsistencies (not detailed here).

4.2. Overview of trials of olaparib and talazoparib

The CS[5] (Section B.3.8.1) states that two trials were identified which assessed the relevant intervention or comparator in the relevant population, and reported PFS. These included the OlympiAD trial of olaparib (Robson *et al.*[9] and Robson *et al.*[10]) and the EMBRACA trial of talazoparib (Litton *et al.*[11] and *Litton et al.*[12]). The EAG considers these to be the most relevant source of clinical effectiveness and safety evidence for this appraisal.

4.3. Key differences in trial design and baseline characteristics

The CS[5] (Section B.3.8.3) provides a comparison between trials as a feasibility assessment prior to ITC. The key characteristics of the OlympiAD[9, 10] and EMBRACA[11, 12] trials are tabulated in Appendix 1 of this report, and baseline patient characteristics in Appendix 2. The trials were generally similar in design. Both trials enrolled HER2− patients with germline *BRCA* mutations and compared oral PARP inhibitor monotherapy versus single-agent chemotherapy treatment of physician's choice (TPC). The CS[5] (Section B.4.5.1) states that of the seven clinical experts consulted by the company, all agreed that the OlympiAD patient population was representative of UK clinical practice. Clinical advisors to the EAG considered that both trials were generalisable to clinical practice for the relevant patient populations in England and Wales.

Differences between trials included the following. OlympiAD only included metastatic breast cancer, while in EMBRACA 94% had metastatic disease and 6% locally advanced disease. Patients in OlympiAD had received a prior anthracycline and a taxane, while patients in EMBRACA had received a prior anthracycline and/or a taxane (the proportion receiving one or both in EMBRACA is not publicly available, according to clarification response[6] A5). Slightly fewer patients had HR+ disease in OlympiAD (50%) than EMBRACA (56%). The Eastern Cooperative Oncology Group performance status (ECOG PS) was more favourable in OlympiAD (across both arms, 70% had PS=0 and 30% had PS=1, while in EMBRACA 55%

had PS=0, 43% had PS=1 and 2% had PS=2). More patients in OlympiAD had visceral disease (82%) than in EMBRACA (70%). The maximum number of prior cytotoxic therapies for metastatic disease was two in OlympiAD and three in EMBRACA, although only 5% had three prior therapies in EMBRACA. Conversely, EMBRACA had more patients with no prior therapies for metastatic disease (38% in EMBRACA, 33% in OlympiAD). Patients in the OlympiAD comparator arm had a choice of three chemotherapies (capecitabine, eribulin or vinorelbine) while those in EMBRACA had a choice of four (capecitabine, eribulin, vinorelbine or gemcitabine); however, only 8% received gemcitabine in EMBRACA.

The CS[5] (Section B.3.8.3) states that there was no evidence that the variables with imbalances were effect modifiers for the PARP inhibitors, and that clinical experts consulted by the company did not consider hormone receptor status to be a treatment effect modifier; therefore the studies were deemed comparable by the company. In relation to OlympiAD only including patients with metastatic disease, the company notes (in clarification response[6] A3) that there is no evidence that locally advanced versus metastatic disease is a treatment effect modifier for PARP inhibitors; that clinical practice guidelines generally recommend similar systemic therapies for both subgroups; and that the Committee for Medicinal Products for Human Use (CHMP) considered it appropriate to extend the European Medicines Agency (EMA) marketing authorisation for olaparib to patients with locally advanced disease "*given a similar clinical management for locally advanced and metastatic disease and based on a biological and pharmacological rationale*".[15] Overall, clinical advisors to the EAG considered that the two trial populations were broadly comparable, with one advisor noting that EMBRACA has slightly wider inclusion criteria.

4.4. Quality assessment of trials

Quality assessment (critical appraisal) of the two trials was conducted by the company using the Centre for Reviews and Dissemination (CRD) checklist for RCTs (CS[5] Section B.3.4 for OlympiAD and CS Appendix D.3 for EMBRACA). Both studies scored low risk of bias for the following: randomisation methods, similarity of groups at baseline, imbalances in drop-outs, reporting of all relevant outcomes, and appropriate intention-to-treat (ITT) analysis. Both studies scored "No" for blinding since both trials were open-label; however, PFS was assessed via blinded independent central review (BICR) in both trials. For EMBRACA, the company stated that concealment of treatment allocation was not adequate; however, the EAG considers this was likely to be adequate since randomisation was centralised. The EAG considers both studies to be of low risk of bias overall.

4.5. Results of individual trials

Results for OlympiAD are reported in the CS[5] (Section B.3.5). These include PFS, OS, ORR, HRQoL, time from randomisation to second progression event or death after first progression event (PFS2), time to first subsequent cancer therapy (TFST), time to second subsequent cancer therapy (TSST), and treatment satisfaction score. Results for EMBRACA are reported in Litton *et al.*[11] and Litton *et al.*[12]. A summary of PFS, OS and ORR are provided in Table 1. Kaplan-Meier plots for PFS and OS for each trial are provided in Appendix 3 of this report.

Table 1: Summary of PFS, OS and ORR

Outcome	OlympiAD			EMBRACA		
	Olaparib (n=205): median	**TPC (n=97): median**	**HR/OR (95% CI), p-value**	**Talazoparib (n=287): median**	**TPC (n=144): median**	**HR/OR (95% CI), p-value**
PFS (by BICR)	7.0 mo	4.2 mo	HR 0.58 (0.43 to 0.80), p=0.0009	8.6 mo	5.6 mo	HR 0.54 (0.41 to 0.71), p<0.001
OS	19.3 mo	17.1 mo	HR 0.90 (0.66 to 1.23), p=0.513	19.3 mo	19.5 mo	HR 0.85 (0.67 to 1.07), p=0.17
ORR (of evaluable patients)	100/167 (60%)	19/66 (29%)	-	137/219 (63%)	31/114 (27%)	OR 5.0 (2.9 to 8.8), p<0.001

Abbreviations: BICR: blinded independent central review; CI: confidence interval; HR: hazard ratio; mo: months; OR: odds ratio; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; TPC: treatment of physician's choice.
Source: Adapted from CS Table 14, Litton *et al.* [11], Litton *et al.* [12] **Source in CS:** PFS and ORR for olaparib: CS, Robson *et al.*[9] (cut-off Dec 2016); OS for olaparib: CS, Robson *et al.*[10] (cut-off Sept 2017); PFS and ORR for talazoparib: Litton *et al.*[11] (cut-off Sept 2017); OS for talazoparib: Litton *et al.*[12] (cut-off Sept 2019).

4.6. Overview of indirect treatment comparisons of olaparib vs. talazoparib

The company[5] performed a Bayesian fixed effect ITC to inform the estimation of the comparative efficacy and safety between olaparib and talazoparib based on the OlympiAD and EMBRACA trials. This ITC analysis was reported in McCrea *et al.*[13] The CS also highlighted that Wang *et al.*[14] conducted a similar ITC using a Bayesian random effects model. The EAG sought clarification regarding the company's choice to use the ITC presented in McCrea *et al.*[13] as the primary evidence for the ITC. The company justified their choice[6] by stating that (i) McCrea *et al.*[13] was based on individual patient-level data (IPD) from the OlympiAD trial which are potentially more reliable than aggregate data which were used by Wang *et al.*[14] and (ii) that McCrea *et al.*[13] was the most recently published ITC. After examining the methods used in McCrea *et al.*[13] and Wang *et al.*[14] the EAG believes that both ITC analyses were based on the same Bayesian hierarchical model, and that having access to IPD does not impact the results. The main difference between the two ITCs is that McCrea *et al.*[13] used a fixed effect model, while Wang *et al.*[14] employed a random effects model.

The EAG argues that the justification by the company "*As only two relevant studies were identified for the ITC, there were not sufficient data from which to estimate between-study*

heterogeneity in a random effects model" is not a valid reason for conducting a fixed effect analysis. Heterogeneity is expected in evidence synthesis, and using a fixed effect model would underestimate uncertainty associate with the estimated treatment effect. In the case of limited studies in the analysis, incorporating external information through an informative prior distribution[16] can help estimate the between-study heterogeneity as suggested by the NICE Methods Guide.[17] The EAG also highlights that a lack of a statistically significant difference between the two treatments does not imply equivalence. The EAG believes that a better approach is to obtain the probability of the point estimate for the relative treatment effect falling within a clinical equivalence range using the CODA samples from the ITCs.

4.7. Comparative effectiveness results from ITCs

The CS[5] (Section B.2.1) states that the key efficacy outcomes in the talazoparib appraisal were PFS and OS; the EAG agrees with this conclusion. ITC results for PFS, OS and ORR from McCrea *et al.*[13] and Wang *et al.*[14] are summarised in Table 2, in the form of hazard ratios (HRs) or odds ratios (ORs) with 95% credible intervals (CrI). The ITC for PFS (by BICR) was non-significant in both analyses, with a HR for olaparib vs. talazoparib of 1.09 (95% CrI 0.72 to 1.65) in McCrea *et al.*[13] and a HR of 1.08 (95% CrI 0.34 to 3.45) in Wang *et al.*[14] based on the same raw data from the two trials. Wang *et al*.[14] also reported an ITC for ORR, giving a non-significant OR for olaparib vs. talazoparib of 0.83 (95% CrI 0.05 to 12.64).

An ITC for OS was not reported in McCrea *et al.*[13] but was reported in Wang *et al.*[14] with a non-statistically significant HR for olaparib vs. talazoparib of 1.18 (95% CrI 0.61 to 2.31). The CS (Section B.3.8.6) states that neither study was powered to evaluate OS, and that OS may be confounded by subsequent use of PARP inhibitors and/or platinum chemotherapy in TPC arms. In OlympiAD, subsequent therapies included PARP inhibitors in 1% and 8%, and platinum chemotherapy in 43% and 45%, of the olaparib and TPC arms, respectively (CS Table 15). In EMBRACA, subsequent therapies included PARP inhibitors in 5% and 33%, and platinum chemotherapy in 46% and 42%, of the olaparib and TPC arms, respectively (Litton *et al.*[12]).

Table 2: Summary of ITCs for effectiveness

Outcome (olaparib vs. talazoparib)	McCrea *et al.*[13]		Wang *et al.*[14]	
	HR/OR (95% CrI)	Favours	HR/OR (95% CrI)	Favours
PFS (by BICR)	HR 1.09 (0.72 to 1.65)	Tala (NS)	HR 1.08 (0.34 to 3.45)	Tala (NS)
OS	-	-	HR 1.18 (0.61 to 2.31)	Tala (NS)
ORR	-	-	OR 0.83 (0.05 to 12.64)	Olap (NS)

Abbreviations: BICR: blinded independent central review; CrI: credible interval; HR: hazard ratio; NS, non-significant; olap: olaparib; OR: odds ratio; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; tala: talazoparib.

4.8. Subgroup analyses

Pre-specified subgroup analyses for PFS for OlympiAD and EMBRACA are provided in Appendix 4 of this report (CS[5] Section B.3.6 and Litton *et al.*[11] respectively). All subgroups demonstrated a numerical benefit for olaparib or talazoparib over TPC, though the effect was not statistically significant in some analyses. The CS notes that neither trial was sufficiently powered for subgroup analyses. Clinical advisors to the EAG agreed that it was not possible to determine a lack of effectiveness in any specific subgroup, based on these data.

The CS[5] did not report an ITC for subgroup analyses. The EAG requested subgroup analyses for PFS, but the company stated in their clarification response[6] (A8) that they did not consider this to be appropriate for the following reasons: olaparib demonstrated clinical benefit in the full ITT population; the subgroups are not sufficiently powered in OlympiAD; talazoparib received reimbursement in the full ITT population; and there is no biological plausibility for hormone receptor status to be a treatment modifier since it is not the target of PARP inhibitors. Conversely, Wang *et al.*[14] did conduct an ITC for subgroup analyses of PFS; all analyses were non-statistically significant (Table 3). The EAG considers that it is not possible to conclude whether PFS is better for olaparib or talazoparib within any specific subgroup.

Table 3: Summary of ITCs for subgroup analyses of PFS

Subgroup for PFS (olaparib vs. talazoparib)	Wang *et al.*[14]	
	HR (95% CrI)	Favours
HR+	1.74 (0.43 to 6.96)	Tala (NS)
TNBC	0.72 (0.15 to 3.50)	Olap (NS)
Prior platinum	0.90 (0.32 to 2.49)	Olap (NS)
No prior platinum	1.14 (0.35 to 3.82)	Tala (NS)
BRCA1 mutation	0.91 (0.28 to 3.01)	Olap (NS)
BRCA2 mutation	1.46 (0.35 to 6.03)	Tala (NS)
No prior chemotherapy	1.01 (0.30 to 3.41)	Tala (NS)

Abbreviations: CrI: credible interval; HR: hazard ratio; HR+: hormone receptor positive; NS, non-significant; olap: olaparib; PFS: progression-free survival; tala: talazoparib; TNBC: triple negative breast cancer.

4.9. Comparative safety results from ITCs

The ITCs of safety presented in the CS[5] (Section B.3.8.5) are those reported in McCrea *et al.*[13] while Wang *et al.*[14] also present ITCs of safety. These results are summarised in Table 4. The company state in their clarification response[6] (A9) that the AEs included in McCrea *et al.*[13] were those identified as being the most commonly reported in either the OlympiAD or EMBRACA studies. The ITCs of safety were non-significant for any-grade AEs, any serious adverse event (SAE), any treatment-related SAE, and treatment discontinuation. ITCs for haematological AEs all showed an increased risk with talazoparib, the majority being non-

statistically significant (anaemia was significantly higher with talazoparib in the McCrea *et al.*[13] analysis). In terms of non-haematological AEs, the ITCs for alopecia, nausea and vomiting showed a statistically significantly increased risk with olaparib, while ITCs for headache and fatigue did not show a significant difference. The EAG notes that the AE data in CS Table 41 contains errors; the corrected version appears in the clarification response[6] (A10 Table 4).

Table 4: Summary of ITCs for safety

Outcome (olaparib vs. talazoparib)	McCrea *et al.*[13]		Wang *et al.*[14]	
	OR (95% CrI)	Favours	OR (95% CrI)	Favours
Summary AEs				
Any-grade AEs	1.07 (0.13 to 9.15)	Tala (NS)	-	-
Any SAE	0.88 (0.40 to 1.95)	Olap (NS)	-	-
Any treatment-related SAE	0.47 (0.12 to 1.87)	Olap (NS)	-	-
Treatment discontinuation	-	-	0.93 (0.20 to 4.37)	Olap (NS)
Haematological AEs				
Anaemia (any grade)	0.37 (0.17 to 0.78)	Olap (sig)	0.37 (0.02 to 6.84)	Olap (NS)
Anaemia (grade 3-4)	-	-	0.34 (0.00 to 34.7)	Olap (NS
Neutropenia (any grade)	0.54 (0.28 to 1.06)	Olap (NS)	0.54 (0.09 to 3.26)	Olap (NS)
Neutropenia (grade 3-4)	-	-	0.57 (0.06 to 5.87)	Olap (NS)
Thrombocytopenia (any grade)	0.26 (0.07 to 1.05)	Olap (NS)	-	-
Leukopenia / decreased white cell count (any grade)	0.87 (0.32 to 2.46)	Olap (NS)	0.55 (0.20 to 1.50)	Olap (NS)
Leukopenia / decreased white cell count (grade 3-4)	-	-	0.42 (0.04 to 4.22)	Olap (NS)
Non-haematological AEs				
Alopecia (any grade)	0.26 (0.08 to 0.75)	Olap (sig)	-	-
Headache (any grade)	0.85 (0.37 to 1.98)	Olap (NS)	0.82 (0.25 to 2.75)	Olap (NS)
Headache (grade 3-4)	-	-	0.14 (0.00 to 4.04)	Olap (NS)
Fatigue (any grade)	0.98 (0.49 to 2.02)	Olap (NS)	1.01 (0.42 to 2.41)	Tala (NS)
Fatigue (grade 3-4)	-	-	6.82 (0.46 to 240.0)	Tala (NS)
Diarrhoea (any grade)	1.15 (0.53 to 2.50)	Tala (NS)	-	-
Nausea (any grade)	2.39 (1.23 to 4.68)	Tala (sig)	-	-
Vomiting (any grade)	2.39 (1.07 to 5.50)	Tala (sig)	-	-

Abbreviations: AE: adverse event; CrI: credible interval; NS, non-significant; olap: olaparib; OR: odds ratio; SAE: serious adverse event; sig, significant; tala: talazoparib.

4.10. Clinical expert views on comparative effectiveness and safety

Effectiveness: The CS[5] (Section B.4.5.1) states that all seven clinical experts consulted by the company agreed that they would expect the two treatments to have comparable efficacy. Clinical advisors to the EAG stated that they expected the two treatments to have similar effectiveness.

Safety: The CS[5] (Section B.4.5.1) states that, of seven clinical experts consulted by the company, four considered that olaparib and talazoparib have overall similar safety profiles, while three stated that olaparib had a more favourable safety profile than talazoparib, especially in terms of haematological events, and that they valued the slightly different safety profile of olaparib. The CS also states that the clinical experts consulted by the company were familiar with prescribing olaparib due to use in the early breast cancer setting; clinical advisors to the EAG agreed with this. Of the clinical advisors to the EAG, one noted that the two treatments appear to have distinct safety profiles, which may have advantages when tailoring treatment for patients.

4.11. Summary of comparative clinical effectiveness

Overall, the EAG considers that olaparib is likely to result in similar overall health outcomes to talazoparib. All three clinical advisors to the EAG stated that they would wish to have the option to choose between the two drugs.

5. SUMMARY OF THE EAG'S CRITIQUE OF COST COMPARISON EVIDENCE SUBMITTED

The company provided the EAG with a fully executable economic model but as this is beyond the remit of cost-comparison appraisals the EAG largely ignored this. The EAG did look at specific sections which provided insight into the cost and AE components where these appeared incorrect in the company submission or were ambiguous.

In its clarification response,[6] the company provided a table (CS Table 3) which compared the costs of an olaparib strategy with a talazoparib strategy from the full economic model, which assumed [redacted].

After factual accuracy check, the company provided the list price of 28 days of olaparib and the updated discount ([redacted] of the list price) from which the EAG could calculate the cost of 30 days of treatment to allow comparison with the cost of talazoparib (£4965.00 at list price for 30 days). This value, and the list price for 30 days of talazoparib are shown in Table 5, although these costs are misleading as the PAS for talazoparib has not been considered, as advised by NICE. Table 5 also includes the estimated total costs of treatment with olaparib and talazoparib using the treatment duration the company estimated in its model (using a lognormal (2.0688, 0.9884)) which is approximately 12.90 months (or approximately 393 days).

The company assumes that both drugs have a relative dose intensity of 1.00, citing the final appraisal determination for talazoparib (TA952[2]) Section 3.20, and assuming this for olaparib. The EAG are comfortable with this assumption.

In the clarification response[6] (answer B1), the company estimates the difference in the costs of AEs between patients receiving olaparib and patients receiving talazoparib; in the clarification response (answer B2), the company estimates the difference in QALY losses due to AEs between patients receiving olaparib and patients receiving talazoparib.

6. COMPANY AND EAG COST COMPARISON RESULTS

The acquisition costs provided by the company are shown in Table 5.

Table 5: 30-day drug acquisition costs for olaparib and talazoparib

Cost type	Olaparib ([redacted])	Talazoparib (list price)
Drug acquisition costs over 30-days	[redacted]	£4965.00
Drug acquisition costs over 12.90 months	[redacted]	£64,985.14

In addition, the company estimated that the costs of AEs were £212.37 lower for patients receiving olaparib, which were assumed to be a one-off cost.

The company also estimates that there would be a small increase in QALYs due to fewer AEs for patients receiving olaparib, with olaparib estimated to have a reduction in QALYs of 0.0009 and talazoparib having a reduction in QALYs of 0.0024. The EAG has converted this health gain into monetary terms assuming a threshold of £30,000 per QALY, which equates to a cost saving for olaparib of approximately £45 (£30 using a threshold of £20,000 per QALY). In total the net advantage of olaparib compared with talazoparib in relation to AEs is less than £300. This is a small saving compared with the costs of a course of treatment, which is [redacted] for olaparib.

The EAG is content with the analyses undertaken by the company. The clinical experts consulted by the EAG indicated that they did not anticipate there being a material difference in the non-drug acquisition costs between patients receiving olaparib and patients receiving talazoparib and the EAG has therefore focussed on drug acquisition costs.

The EAG has provided in a confidential appendix a revised version of Table 5 when the PAS for talazoparib is considered. In this confidential analysis, [redacted]

7. EQUALITIES AND INNOVATION

No equality or innovation considerations were noted in the CS.

8. EAG COMMENTARY ON THE ROBUSTNESS OF EVIDENCE SUBMITTED BY THE COMPANY

As noted in Section 1, the indications specified in the marketing authorisations for olaparib and talazoparib are slightly different. However, overall, the EAG considers that olaparib is likely to result in similar health outcomes to talazoparib.

9. REFERENCES

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10. APPENDICES

Appendix 1: Study characteristics

Table 6: Study characteristics for OlympiAD and EMBRACA

Study characteristics	OlympiAD	EMBRACA
Trial design	Phase III, multicentre, randomised, open-label	Phase III, multicentre, randomised, open-label
Location	19 countries worldwide including UK	16 countries worldwide including UK
Population (key criteria)	• Metastatic breast cancer • HR+/HER2− or TNBC • Germline *BRCA* mutation • Received anthracycline and taxane in (neo)adjuvant or metastatic setting (unless contraindicated) • No more than 2 previous chemotherapy regimens for metastatic disease • If HR+, at least 1 prior endocrine therapy (unless contraindicated) • ECOG performance status ≤ 1	• Locally advanced or metastatic breast cancer • HR+/HER2− or TNBC • Germline *BRCA* mutation • Received anthracycline and/or taxane in (neo)adjuvant or metastatic setting (unless contraindicated). • No more than 3 previous chemotherapy regimens for locally advanced or metastatic disease • ECOG performance status ≤ 2
Intervention	Olaparib (300 mg twice daily orally; N=205)	Talazoparib (1mg once daily orally; N=287)
Comparator	Standard chemotherapy (N=97) with a single-agent treatment of physician's choice (TPC) of: • Capecitabine • Eribulin • Vinorelbine	Standard chemotherapy (N=144) with a single-agent treatment of physician's choice (TPC) of: • Capecitabine • Eribulin • Vinorelbine • Gemcitabine
Outcomes in decision problem	• Progression-free survival (PFS) by BICR • Overall survival (OS) • Response rate (ORR) • Adverse events (AEs) • Health-related quality of life (HRQoL)	• Progression-free survival (PFS) by BICR • Overall survival (OS) • Response rate (ORR) • Adverse events (AEs) • Health-related quality of life (HRQoL)
Other outcomes	• Time from randomisation to a second progression event or death after a first progression event (PFS2) • Time to first subsequent cancer therapy (TFST) • Time to second subsequent cancer therapy (TSST) • Treatment satisfaction score	• Not reported in CS
Data cut-offs and follow-up	• Primary cut-off for PFS: Dec 2016 (median FU 14.5mo for olaparib and 14.1mo for TPC) • Updated OS and safety: Sept 2017 (median FU 25.3mo for olaparib and 26.3mo for TPC)	• Primary cut-off for PFS: Sept 2017 (median FU 11.2mo • Updated OS and safety: Sept 2019 (median FU 44.9mo for talazoparib and 36.8 for TPC)

Abbreviations: AE: adverse events; *BRCA*: breast cancer susceptibility gene; HER2: human epidermal growth factor receptor type 2; HR+: HR-positive; HRQoL: health-related quality of life; mBC: metastatic breast cancer; ORR: objective response rate; OS overall survival; PFS: progression-free survival; SOC: standard of care; TPC: treatment of physician's choice.
Source: Adapted from CS Table 7 and clarification response Table 2. **Source in CS:** Robson *et al.*[9], Robson *et al.*[10]

Appendix 2: Baseline patient characteristics

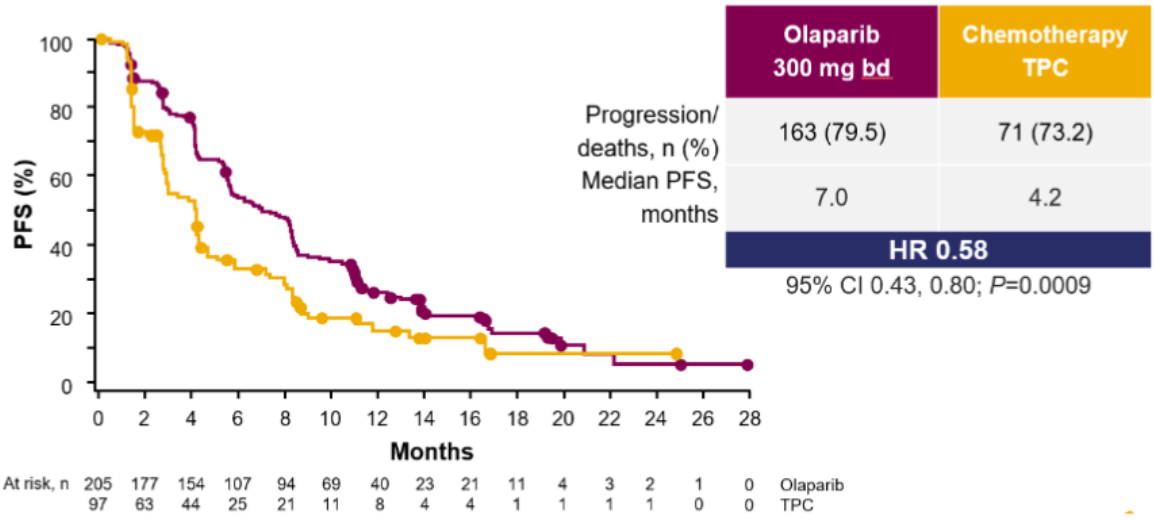
Table 7: Baseline patient characteristics in OlympiAD and EMBRACA

Baseline characteristics	Total number (%) of patients					
	OlympiAD			EMBRACA		
	Olaparib (N=205)	TPC (N=97)	Total % of trial	Talazoparib (N=287)	TPC (N=144)	Total % of trial
Median age, years (range)	44 (22–76)	45 (24–68)	-	45 (27–84)	50 (24–88)	-
g*BRCAm* type, n (%)						
gBRCA1m	117 (57)	51 (53)	(56)	133 (46)	63 (44)	(45)
gBRCA2m	84 (41)	46 (47)	(43)	154 (54)	81 (56)	(55)
Both	4 (2)	–	(1)	–	–	-
Hormone receptor status, n (%)						
TNBC	102 (50)	48 (49)	(50)	130 (45)	60 (42)	(44)
HR+/HER2−	103 (50)	49 (51)	(50)	157 (55)	84 (58)	(56)
Breast cancer stage, n (%)						
Locally advanced	–	–	-	15 (5)	9 (6)	(6)
Metastatic	205 (100)	97 (100)	(100)	271 (94)	135 (94)	(94)
ECOG performance status, %						
0	72	64	(70)	53	58	(55)
1	28	36	(30)	44	40	(43)
2	–	–	-	2	1	(2)
Prior chemotherapy regimens for mBC, n (%)						
0	68 (33)	31 (32)	(33)	111 (39)	54 (38)	(38)
1	80 (39)	42 (43)	(40)	107 (37)	54 (38)	(37)
2	57 (28)	24 (25)	(27)	57 (20)	28 (19)	(20)
>3	–	–	(0)	12 (4)	8 (6)	(5)
Prior platinum therapy, n (%)	60 (29)	26 (27)	(28)	46 (16)	30 (21)	(18)
Visceral disease	165 (80)	84 (87)	(82)	200 (70)	103 (72)	(70)
Prior anthracycline, taxane, or both	205 (100)	97 (100)	(100)	287 (100)	144 (100)	(100)
Prior endocrine therapy if HR+ve (OlympiAD: n=152, EMBRACA: n=241)	103 (100)	49 (100)	(100)	157 (100)	84 (100)	(100)
Receipt of randomised intervention	Olaparib: 205 (100)	Cape: 41 (42) Erib: 34 (35) Vino: 16 (16) None: 6 (6)	-	Talazoparib: 286 (99.7)	Cape: 55 (38) Erib: 50 (35) Vino: 9 (6) Gem: 12 (8) None: 18 (13)	

[a]Four patients in the olaparib arm had both g*BRCA*1m and g*BRCA*2m.
Abbreviations: cape: capecitabine; ECOG: Eastern Cooperative Oncology Group; erib: eribulin; g*BRCA*1m: Germline *BRCA*1 mutation; g*BRCA*2m: Germline *BRCA*2 mutation; gem: gemcitabine; mBC: metastatic breast cancer; TPC: Treatment of physician's choice; TNBC: Triple-negative breast cancer; vino: vinorelbine.
Source: Adapted from clarification response Table 1. **Source in CS:** McCrea *et al.*[13]

Appendix 3: PFS and OS in OlympiAD and EMBRACA

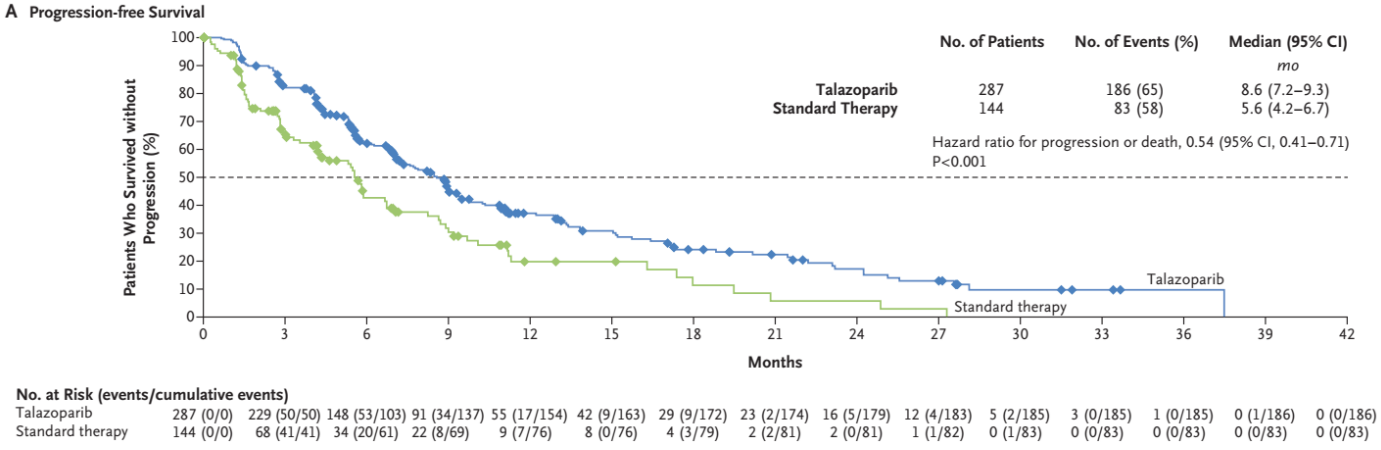
Figure 2: PFS by BICR in OlympiAD trial of olaparib vs. TPC



Abbreviations: bd: twice daily; BICR: blinded independent central review; PFS: progression-free survival; HR: hazard ratio; TPC; treatment of physician's choice.

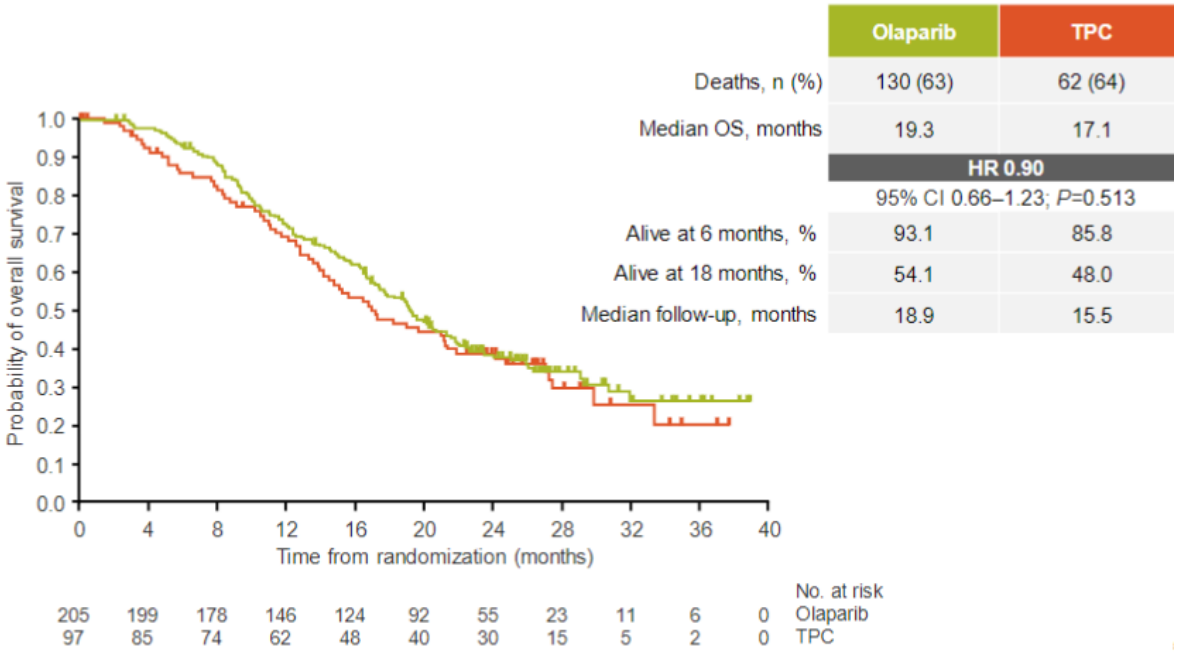
Source: Robson *et al.*[9], data cut-off Dec 2016

Figure 3: PFS in EMBRACA trial of talazoparib vs. TPC



Abbreviations: mo, months.
Source: Litton *et al.*[11], data cut-off Sept 2017

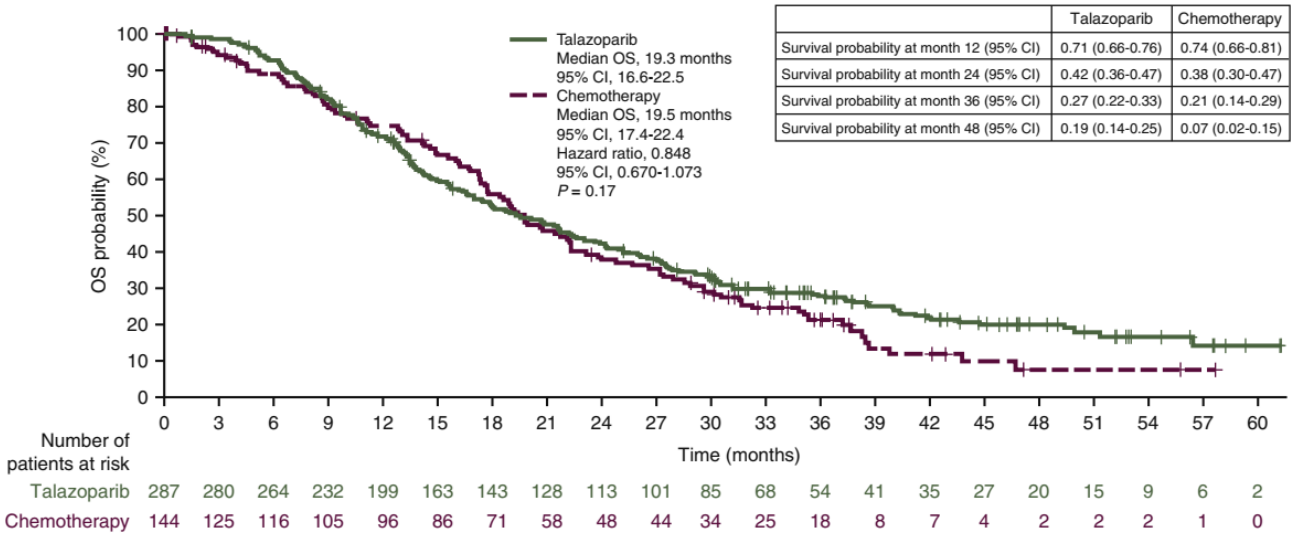
Figure 4: OS in OlympiAD trial of olaparib vs. TPC



Abbreviations: CI: confidence interval: OS: overall survival; HR: hazard ratio; TPC; treatment of physician's choice.

Source: Robson *et al.*[10], data cut-off Sept 2017

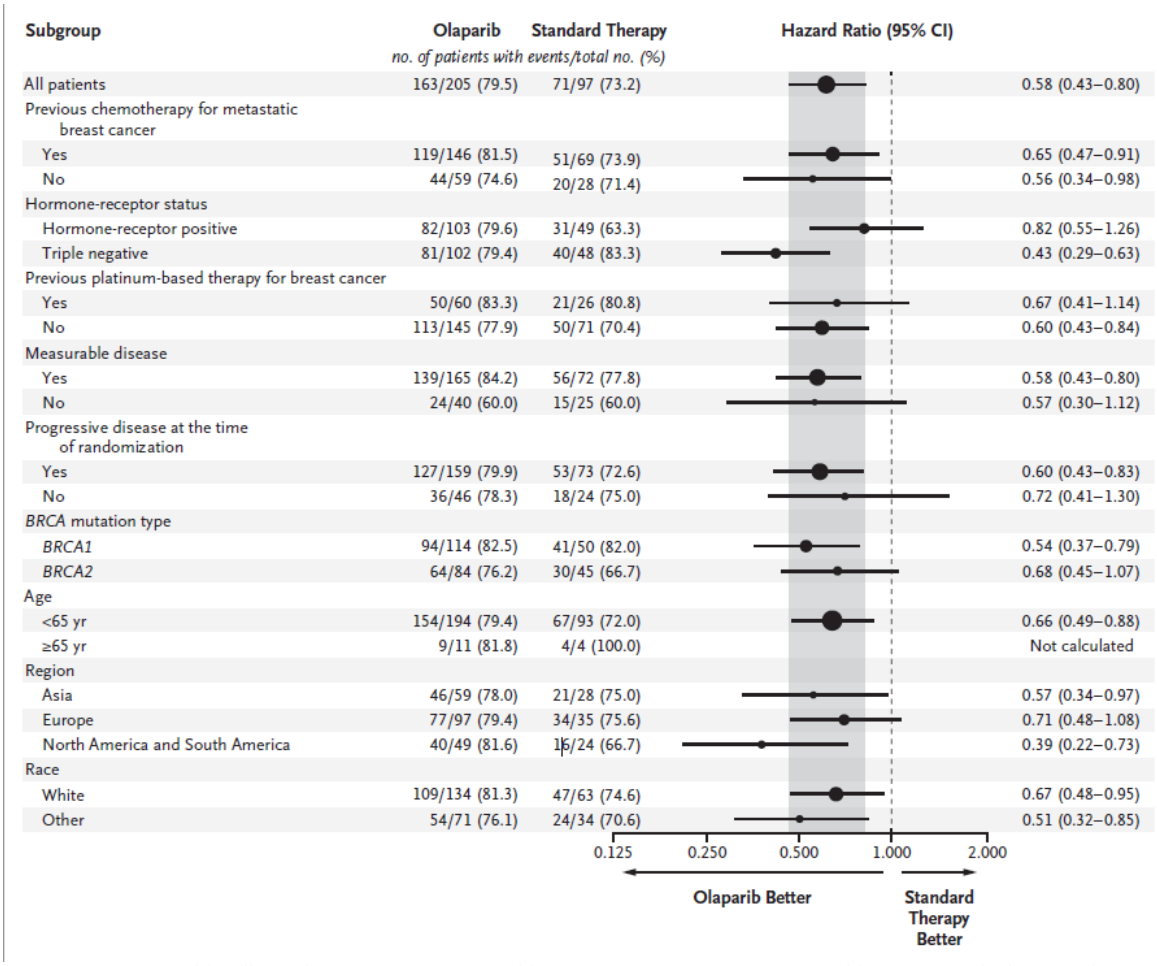
Figure 5: OS in EMBRACA trial of talazoparib vs. TPC



Abbreviations: CI: confidence interval: OS: overall survival.
Source: Litton *et al.*[12], data cut-off Sept 2019

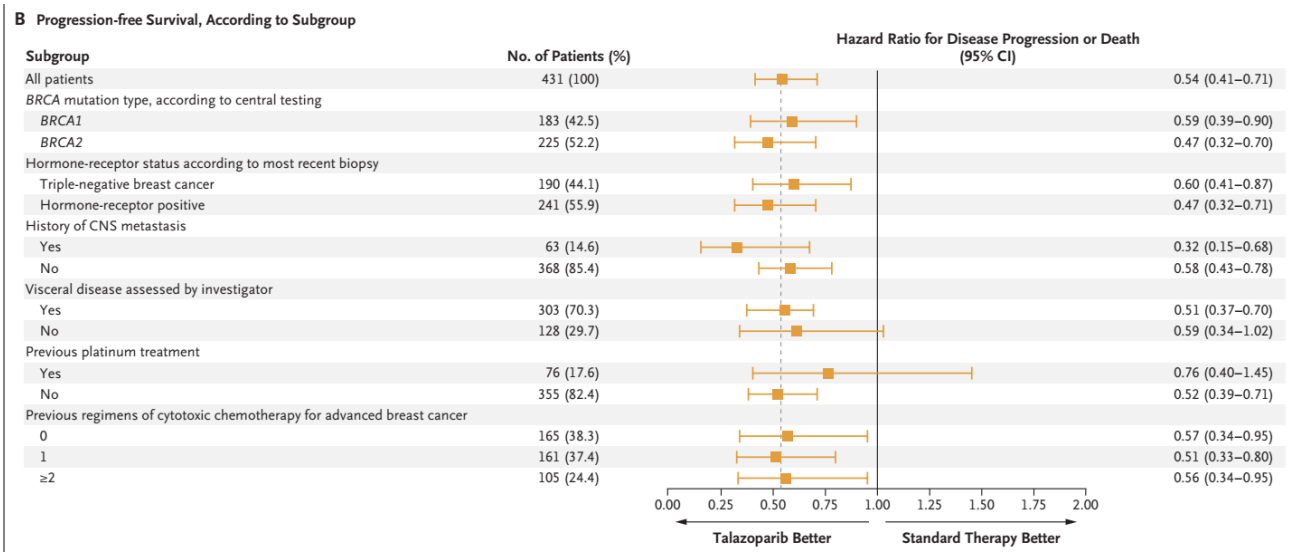
Appendix 4: Subgroup analyses of PFS and OS in OlympiAD and EMBRACA

Figure 6: Subgroup analyses of PFS in OlympiAD



Hormone receptor positive disease is oestrogen receptor positive (ER+), progesterone receptor positive (PgR+) or both. TNBC is HER2 negative, ER negative, and PR negative.
Abbreviations: CI: confidence interval; HER2: human epidermal growth factor receptor type 2; PFS: progression-free survival; TNBC: triple negative breast cancer.
Source: CS; Robson *et al.*[9]

Figure 7: Subgroup analyses of PFS in EMBRACA



Abbreviations: CI: confidence interval; PFS: progression-free survival.
Source: Litton *et al.*[11]

Single Technology Appraisal

Olaparib for treating BRCA mutation-positive HER2-negative advanced breast cancer after chemotherapy (Review of TA762) [ID6336]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by the end of **6 August 2024** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as [redacted] should be highlighted in turquoise and all information submitted as 'depersonalised data' in pink.

Issue 1 Description of olaparib discount

Description of problem	Description of proposed amendment	Justification for amendment
[redacted]	[redacted]	[redacted]