Single Technology Appraisal

Talazoparib for treating HER2-negative locally advanced or metastatic breast cancer with germline BRCA1/2-mutations [ID1342]
Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Talazoparib for treating HER2-negative locally advanced or metastatic breast cancer with germline BRCA1/2-mutations [ID1342]

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 Pfizer:**
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**

3. **Patient group, professional group, and NHS organisation submissions** from:
   a. Breast Cancer Now
   b. METUP UK
   c. NCRI-ACP-RCP-RCR

4. **External Assessment Report** prepared by Liverpool Reviews and Implementation Group

5. **External Assessment Report – factual accuracy check**

6. **Technical engagement response from company**

7. **Technical engagement responses and statements from experts:**
   a. Professor Andrew Tutt - Clinical Expert, nominated by Pfizer
   b. Dr Jennifer Glendenning – Clinical Expert, nominated by NCRI-ACP-RCP-RCR
   c. Helen Stewart - Patient Expert, nominated by MET UP UK

8. **External Assessment Group critique of company response to technical engagement** prepared by Liverpool Reviews and Implementation Group

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Talazoparib for treating HER2-negative locally advanced or metastatic breast cancer with germline *BRCA*1/2 -mutations (ID1342)

Document B

Company evidence submission

9th January 2023

File name	Version	Contains confidential information	Date
ID1342_Talazoparib_Document B_09Jan23 (ACiC)	**FINAL**	**Yes**	**9th January 2023**

Tables and figures

Abbreviations

Abbreviation	Definition
1L	first-line
2L	second-line
3L	third-line
4L	fourth-line
aBC	advanced breast cancer
AE	adverse event
AIC	Akaike Information Criteria
BIC	Bayesian Information Criteria
BNF	British National Formulary
BC	breast cancer
*BRCA*1/2	BReast CAncer susceptibility gene 1 or 2
*BRCA*wt	BReast CAncer gene wild type
BSA	body surface area
CBR24	Clinical benefit rate at 24 weeks
CCG	Clinical Commissioning Group
CDK4/6	cyclin-dependent kinase 4 and 6
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CR	complete response
CSR	clinical study report
CT	computerised tomography
DDR	damage response
DOR	duration of response
DSU	Decision Support Unit
DNA	deoxyribonucleic acid
DSBs	double-strand breaks
eCRF	electronic case report form
ECOG	Eastern Cooperative Oncology Group
EMC	electronic medicines compendium
eMIT	electronic market information tool
EPAR	European Public Assessment Report
ER	oestrogen receptor
EORTC QLQ-BR23	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Breast Cancer Module
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30

ERG	Evidence Review Group
ESMO	European Society of Medical Oncology
ESO-ESMO	European School of Oncology-European Society of Medical Oncology
ET	endocrine therapy
g*BRCA1/2*m	germline breast cancer susceptibility gene 1 or 2 mutation
g*BRCA*m	germline breast cancer susceptibility gene mutation
GHS	global health status
HER2	human epidermal growth factor receptor 2
HER2-	human epidermal growth factor receptor 2 negative
HR	hazard ratio
HR+	hormone receptor positive
HRP	homologous recombination pathway
HRQoL	health related quality of life
HTA	health technology assessment
ICER	incremental cost-effectiveness ratio
IPD	individual patient data
ITC	indirect treatment comparison
IQR	interquartile range
ITT	intent-to-treat
IRF	independent radiology facility
IV	intravenous
KM	Kaplan-Meier
LABC	locally advanced breast cancer
LSLV	last subject last visit
LY	life years
mBC	metastatic breast cancer
MHRA	Medicines and Healthcare products Regulatory Agency
MIMS	Monthly Index of Medical Specialties
mo	Month
MRU	medical resource use
MoA	mechanism of action
NCRAS	National Cancer Registration and Analysis Service
NHB	net health benefit
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
ONS	Office for National Statistics
ORR	objective response rate
OS	overall survival

PARP-1	poly (ADP-ribose) polymerase-1
PARPi	poly (ADP-ribose) polymerase inhibitor
PARP	poly (ADP-ribose) polymerase
PCT	physician's choice treatment
PD-L1	programmed cell death ligand 1
PDX	patient-derived xenograft
PF	progression-free
PFS	progression-free survival
PK	pharmacokinetics
PP	post-progression
PPS	post-progression survival
PR	partial response
PRO	patient reported outcomes
PSA	probabilistic sensitivity analysis
PSM	partitioned-survival model
PSSRU	Personal Social Services Research Unit
pts	patients
QALY	quality-adjusted life years
QoL	quality of life
RCT	randomised control trial
SAE	serious adverse events
SD	stable disease
SEER	Surveillance, Epidemiology, and End Results
STD	standard deviation
SLR	systematic literature review
SmPC	summary of product characteristics
SSBs	single-strand breaks
TA	technology appraisal
TALA	talazoparib
TEAE	treatment-emergent adverse event
TN	triple negative
TNBC	triple negative breast cancer
ToT	time on treatment
TTD	Time to Treatment Discontinuation
TTF	time-to-treatment failure
γH2AX	phosphorylated histone H2AX

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

B.1.1. Decision problem

The submission covers the technology's full marketing authorisation for this indication. The decision problem that this submission addresses is outlined in Table 1.

Table 1. The decision problem

	Final scope issued by NICE[1]	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with human epidermal growth factor 2 receptor negative (HER2-) locally advanced or metastatic breast cancer (mBC) with germline BReast CAncer gene (BRCA)1/2-mutations that has previously been treated with an anthracycline and/or a taxane in the (neo)adjuvant, locally advanced or metastatic setting or for whom these treatments would not be suitable.	Adult patients with germline *BRCA1/2*-mutations, who have HER2-negative 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 (HR)-positive breast cancer (BC) should have been treated with a prior endocrine-based therapy, or be considered unsuitable for endocrine-based therapy.	As NICE scope
Intervention	Talazoparib	Talazoparib	As NICE scope
Comparator(s)	• Vinorelbine • Capecitabine • Eribulin (after at least 2 chemotherapy regimens)	• Physician's choice treatment (PCT) (capecitabine, eribulin or vinorelbine)	Talazoparib was compared with PCT (capecitabine, eribulin, gemcitabine, and vinorelbine) in the clinical pivotal trial, EMBRACA. It was assumed that the four individual treatments (capecitabine, eribulin, gemcitabine, and vinorelbine) have comparable efficacy, thus a pooled efficacy of PCT combined was derived from EMBRACA and was applied in the model. The proportion of patients receiving each treatment was re-weighted to remove gemcitabine, reflecting the final

			scope issued by NICE and UK clinical practice.
Outcomes	The outcome measures to be considered include: • overall survival • progression free survival • response rate • adverse effects of treatment • health-related quality of life	The outcome measures to be considered include: • overall survival • progression free survival • response rate • adverse effects of treatment • health-related quality of life	As NICE scope
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year (QALY). The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability and cost of biosimilar and generic products should be taken into account.	The cost associated with *BRCA* diagnostic testing is excluded from the analysis.	Individuals in UK clinical practice will receive *BRCA* testing before BC is diagnosed, due to family history of *BRCA* positive breast or ovarian cancer.[2] Furthermore, NICE recommends that genetic testing is offered to women under 50 years with triple-negative breast cancer (TNBC), including those with no family history of breast or ovarian cancer.[3] Eligible patients for talazoparib are expected to be identified by the current guidelines, therefore the cost of BRCA testing was not included in the analysis.

	The use of talazoparib is conditional on the presence of g*BRCA1/2*m. The economic modelling should include the cost associated with diagnostic testing in people with *BRCA* 1 or 2 mutated mBC who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test.		

B.1.2. Description of the technology being evaluated

Talazoparib (TALZENNA®) is an orally administered poly (ADP-ribose) polymerase (PARP) inhibitor indicated as a monotherapy for the treatment of adult patients with germline BReast CAncer gene (*BRCA)1/2*-mutations, who have human epidermal growth factor 2 receptor negative (HER2-) locally advanced breast cancer (LABC) or metastatic breast cancer (mBC). The scope of this submission is patients with HER2- breast cancer which comprises two subtypes: patients with hormone receptor-positive (HR+) / HER2- BC, and patients with triple negative BC (TNBC) locally advanced or metastatic disease with a germline breast cancer susceptibility gene 1 or 2 mutation (g*BRCA1/2*m).

Details of the technology being appraised in this submission are summarised in Table 2. The summary of product characteristics and the European Public Assessment Report (EPAR) are provided in Appendix C.

Table 2. Technology being evaluated

UK approved name and brand name	Talazoparib (Talzenna®)
Mechanism of action	Talazoparib is an inhibitor of PARP enzymes, PARP1, and PARP2. PARP enzymes are involved in cellular DNA damage response signalling pathways such as DNA repair, gene transcription, and cell death. PARP inhibitors (PARPi) exert cytotoxic effects on cancer cells by two mechanisms, inhibition of PARP catalytic activity and by PARP trapping, whereby PARP protein bound to a PARPi does not readily dissociate from a DNA lesion, thus preventing DNA repair, replication, and transcription, thereby resulting in apoptosis and/or cell death. Treatment of cancer cell lines that are harbouring defects in DNA repair genes with talazoparib single agent leads to increased levels of γH2AX, a marker of double stranded DNA breaks, and results in decreased cell proliferation and increased apoptosis. Talazoparib anti-tumour activity was also observed in a patient-derived xenograft (PDX) *BRCA* mutant breast cancer model where the patient was previously treated with a platinum-based regimen. In this PDX model talazoparib decreased tumour growth and increased γH2AX level and apoptosis in the tumours.[4]
Marketing authorisation/CE mark status	MHRA marketing authorisation was received on 20 June 2019.[4]

Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Talazoparib is indicated as monotherapy for the treatment of adult patients with germline *BRCA1/2*-mutations, who have HER2- LABC or mBC. 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 HR+ breast cancer should have been treated with a prior endocrine-based therapy, or be considered unsuitable for endocrine-based therapy.[4]
Method of administration and dosage	The recommended dose is a 1 mg talazoparib capsule taken orally once daily, with or without food. The 0.25 mg capsule is available for dose reduction. Patients should be treated until disease progression or unacceptable toxicity occurs. The hard capsules should be swallowed whole and must not be opened or dissolved. If the patient vomits or misses a dose, an additional dose should not be taken. The next prescribed dose should be taken at the usual time.[4]
Additional tests or investigations	Patients should be selected for the treatment of breast cancer with talazoparib based on the presence of deleterious or suspected deleterious germline *BRCA* mutations determined by an experienced laboratory using a validated test method.[4]
List price and average cost of a course of treatment	The current list price within the BNF, as used in the economic model, is as follows: [5] 30 x 1 mg tablets: £4,965.00 90 x 0.75 mg tablets: £4,965.00 60 x 0.5 mg tablets: £3,310.00 30 x 0.25 mg tablets: £1,655.00 Average cost/dose: £165.50
Patient access scheme (if applicable)	A [redacted] PAS has been submitted to NHS England. The net price of talazoparib with the PAS applied is [redacted] for 30 x 1 mg tablets.

BNF: British National Formulary; *BRCA*: BReast CAncer gene; DNA: deoxyribonucleic acid; HER2-: human epidermal growth factor receptor 2 negative; HR: hormone receptor; LABC: locally advanced breast cancer; mBC: metastatic breast cancer; MHRA: Medicines and Healthcare products Regulatory Agency; NHS: National Health Service; PARP: poly (ADP-ribose) polymerase; PARP1: poly (ADP-ribose) polymerase 1; PARP2: poly (ADP-ribose) polymerase 2; PARPi: poly (ADP-ribose) polymerase inhibitor; PAS: patient access scheme; PDX: patient-derived xenograft; SmPC: summary of product characteristics; γH2AX: phosphorylated histone H2AX

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

Summary

- Breast cancer (BC) is a highly heterogeneous disease, and prognosis and treatment approach are dependent on disease stage, histologic and molecular subtype, and the presence or absence of identifiable genetic mutations, particularly those in the *BRCA1* and *BRCA2* susceptibility genes.[6-8]
- Inherited g*BRCA1/2*m increases the risk of BC and/or ovarian cancer; 72% of women with the g*BRCA1*m and 69% with the g*BRCA2*m will develop BC by the age of 80.[9]
- The presence of *gBRCA1/2*m often results in the development of BC at a younger age than those without the mutation.[9,10] Internationally, the median age of diagnosis for invasive BC is 40 years in the presence of the *BRCA1*m and 43 years with *BRCA2*m.[11]
- Furthermore TNBC, which is the most common subtype in patients with *BRCA1*m, disproportionately affects younger patients, with a 5 year survival of only 12%,[12] and median overall survival in the region of 12 months for advanced TNBC.[13]
- Given the limited overall survival (OS), short median progression-free survival (PFS), and adverse events (AEs) associated with current treatment options, there is a significant unmet need for targeted therapies with: proven efficacy, the ability to maintain or prolong stable disease, improved safety and tolerability, and the potential to improve quality of life (QoL) for patients and their families.
- Currently in England there are no reimbursed targeted treatments for gBRCAm HER2- aBC. Talazoparib represents a new oral targeted treatment option for patients with g*BRCA*1/2m, who currently have limited alternatives.

B.1.3.1. Disease overview

Breast cancer (BC) is the most common type of cancer both worldwide and in the UK, with 2.26 million new cases recorded globally in 2020 alone,[14,15] and is the leading cause of death amongst women.[16] In the UK, almost 56,000 cases of BC are diagnosed each year, the equivalent of over 150 people per day.[17] Furthermore, 15% of all newly diagnosed cancers are attributed to BC.[15] BC is the 4th most common cause of cancer related death in the UK, with 7% of all cancer deaths attributed to BC between 2017 and 2019.[17] Each year, in the UK, almost 11,500 lives are lost to BC.[17] BC is more prevalent in women than men with 1 in 7 women developing BC in their lifetime.[15] Nevertheless, around 370 men are diagnosed with BC each year.[15]

There are an estimated 871 cases of g*BRCA*m HER2- LABC or mBC per year, as depicted in Table 3.

Table 3. Eligible population for talazoparib

Population		%	Figure	Source
New cases of BC per year – England and Wales		-	55,900	Cancer Research UK[6]
BC first diagnosed in stage 1		44%	24,596	Public Health England. NCRAS. Stage breakdown by CCG 2016[18]
BC first diagnosed in stage 2		41%	22,919	
BC first diagnosed in stage 3		9%	5,031	
BC first diagnosed in stage 4 (de novo metastatic)		5%	2,795	
New cases of early and LABC per year (BC first diagnosed in stage 1-3)		95%	52,546	NICE CG81 Costing template[1]
Recurred early BC cases that become advanced or metastatic each year		30%	15,764	O'Shaugnessy 2005[19]
New cases of advanced and metastatic BC per year		-	18,559	Calculation (2,795 + 15,764)
Advanced / metastatic setting: De novo				
HR+ HER2- LABC or mBC	De novo cases of ER+ HER2- aBC per year	68%	1,901	SEER Cancer Statistics[20]
	Patients eligible for CDK4/6 inhibitor	95%	1,806	Assumption: 5% die before progression
	Progressing to 2L treatment and *BRCA*m positive	5%	90	Armstrong (2019)[21]
	Number of patients who are eligible for talazoparib after anthracycline/taxane	95%	**86**	Assumption: 5% lost to death/compliance
TN LABC or mBC	De novo cases of TN advanced and metastatic BC per year	15%	419	Cancer Research UK[17]
	Number of patients *BRCA*m positive	10%	42	Cancer Research UK[17]
	Number of patients who are eligible for talazoparib after anthracycline/taxane	95%	**40**	Assumption: 5% lost to death/compliance
Advanced / metastatic setting: Recurrent				
HR+ HER2- LABC or mBC	Recurrent cases of ER+ HER2- aBC per year	68%	10,719	SEER Cancer Statistics[20]
	Pts eligible for CDK4/6 inhibitor	95%	10,183	Assumption: 5% die before progression
	Progressing to 2L treatment and *BRCA*m positive	5%	**509**	Assumption: 5% lost to death/compliance
TN LABC or mBC	Recurrent cases of TN aBC per year	15%	2,365	Cancer Research UK[17]
	Number of patients *BRCA*m positive	10%	**236**	Cancer Research UK[17]
Total number			**871**	Calculation (86 + 40 + 509 + 236)

2L: second-line; aBC: advanced breast cancer; BC: breast cancer; *BRCA*m: breast cancer susceptibility gene mutation; CCG: Clinical Commissioning Group; ER+: oestrogen receptor positive; HER2: human epidermal growth factor receptor negative; HR+: hormone receptor positive; LABC: locally advanced breast cancer; mBC: metastatic breast cancer; NCRAS: National Cancer Registration and Analysis Service; pts: patients; SEER: Surveillance, Epidemiology, and End Results; TN: triple negative

BC is a highly heterogeneous disease, and prognosis and treatment approach are dependent on disease stage, histologic and molecular subtype, and the presence or absence of identifiable genetic mutations, particularly those in the *BRCA1* and *BRCA*2 susceptibility genes.[6-8]

B.1.3.1.1. Advanced breast cancer

Advanced BC (aBC) includes locally advanced BC (LABC) (stage 3) and metastatic BC (mBC) (stage 4).[22,23] The stage of BC at diagnosis influences survival rates, where disease progression negatively impacts survival. In England, 5-year survival is 72% in patients diagnosed with LABC, though this substantially decreases to around 26% in patients diagnosed at mBC stage. TNBC is the most common subtype in patients with *BRCA1*m, disproportionately affecting younger patients. The prognosis for TNBC patients is poor, with the American Cancer Society reporting a 5-year survival rate of 65% for locally advanced TNBC patients and only 12% in advanced TNBC patients.[12] Additionally, median overall survival is reported to be in the region of 12 months for advanced TNBC.[13]

B.1.3.1.2. HER2- subtype

Molecular subtypes of BC are routinely differentiated for prognostic and treatment purposes using the cell-surface density of HER2 receptor or the presence of extra copies of the HER2 gene.[6] Tumours that do not express HER2 are described as HER2− and can be further subdivided by the presence or absence of receptors for the hormones oestrogen and progesterone.[6] The presence of either oestrogen receptors or progestogen receptors warrants classification of the tumour as hormone receptorpositive- (HR+)/HER2− BC, whereas TNBC is defined by the absence of oestrogen receptors, progesterone receptors and HER2 receptors.[6] A large proportion of BC patients are HER2- (HR+/HER2− or TN);[24-26] in England approximately 70% of all BC are HR+/HER2- and 15% are TN.[27] Presenting symptoms of HR+/HER2- or TNBC are consistent with other BC types.[28] These can include the development of a new lump, an alteration in the size or shape of the breast, a lump or swelling in the armpit, a change in appearance or texture of the skin or nipple, bleeding or discharge from the nipple, and/or a rash or redness

around the nipple area.[28,29] Patients can also present de novo with metastatic disease.

B.1.3.1.3. gBRCAm subtype

While there are several factors which can increase the risk of BC, a family history of BC and therefore inheritance of a gene mutation can increase BC risk.[30] It is estimated that inherited gene mutations cause 5-10 of BC cases out of every 100.[30] The prevalence of g*BRCA*m, is approximately 3-5% in all BC patients and 9.4%-18.2% in TNBC.[31,32] In addition, the g*BRCA*m is also prevalent in male BC, in particular the g*BRCA2*m.[33] Among women in the general population, approximately 13% will develop BC in their lifetime.[9] However, inherited g*BRCA1/2*m increases the risk of BC and/or ovarian cancer; 72% of women with the g*BRCA1*m and 69% with the g*BRCA2*m will develop BC by the age of 80.[9]

Most BCs occur in women over 50 years of age,[23] however, the presence of g*BRCA1/2*m often results in the development of BC at a younger age than those without the mutation.[9,10] Internationally, the median age of diagnosis for invasive BC is 40 years in the presence of the *BRCA1*m and 43 years with *BRCA2*m.[11]

B.1.3.1.4. Impact of gBRCAm status on LABC and mBC outcomes

A large number of studies have been conducted to address the association between BRCA mutation status and outcomes. However it is difficult to conclude as study results are inconsistent due to differences in study design, size and populations.[34] Nevertheless, a significant disease burden exists for patients with g*BRCA*m aBC, where patients with *BRCA1*m are at a higher risk of TNBC, high grade and greater tumour burden,[35] and *BRCA2* tumours are typically higher grade in comparison to sporadic tumours.[36] Furthermore TNBC patients with g*BRCA* mutation are younger at diagnosis compared to non-mutation carriers.[37] Studies have suggested that *BRCA1* carriers have worse OS than *BRCA* negative BC cases. Furthermore among Ashkenazi Jewish BC patients, *BRCA* mutation carriers have a higher risk of death compared to *BRCA* negative patients.[36] Additionally patients harboring g*BRCA* mutations have a predilection for brain metastasis which is a poor prognostic marker.[38]

Patient reported outcomes (PROs) in g*BRCA*m HER2- aBC patients are significantly worse,[39] which are exacerbated by disease progression.[40,41] Greater anxiety and depression as well as pain and discomfort is reported by patients with g*BRCA*m compared to those without;[39] this trend was also shown for worsening dyspnoea and functioning scores.[42] The QoL of patients is impacted in both LABC and mBC; although disease progression has a greater impact on QoL.[43] The extent of metastasis impacts additional symptoms experienced by patients with aBC;[44] pain, emotional health and fatigue are correlated with a reduced QoL in LABC and mBC.[45] Additionally, treatment-related side effects can also have a negative impact on patient QoL.[46,47]

Work productivity is affected by the large symptomatic burden experienced by aBC patients.[45] Work impairment is increased in patients with *BRCA*m.[39] Approximately 20% more HER2- *BRCA*m aBC patients experience work impairment in comparison to patients with HER2- wild-type *BRCA*(wt).[39] Furthermore, more than 40% of HER2- *BRCA*m aBC patients report work time missed, compared to just 20% in HER2- aBC patients with *BRCA*wt.[39]

As patients with g*BRCA*m often develop BC at a younger age in comparison to patients without the mutation,[9,10] BC impact on QoL and work productivity in the younger population is prominent.[10,48] There is also a substantial impact on family members who need to take leave from work to care for a relative. Periods of absence from work lead to a loss in work productivity and consequently may lead to wage loss.[49]

Medical resource use (MRU) is significant amongst g*BRCA*m HER2- mBC patients;[50] the number of treatment visits per year is high, especially in TNBC patients. One US study reported mean number of visits per patient per year of 21.9 for TNBC and 17.0 for HR+/HER2– patients.[50] Resultantly, a burden exists in terms of MRU to both patients and the healthcare system.

B.1.3.1.5. gBRCAm testing

The National Institute for Health and Care Excellence (NICE) NG101 guideline recommends *BRCA1/2*m testing for women under 50 years with TNBC, regardless of BC or ovarian cancer family history.[3]

In order to be eligible for genetic testing through National Health Service (NHS) England, an individual with breast or ovarian cancer with or without a family history must meet one of the following NHS England inherited BC testing criteria:[51]

- BC (age < 40 years, excluding grade 1 breast cancers)
- Bilateral BC (age < 50 years)
- TNBC (age < 60 years)
- Male BC (any age)
- BC (age < 45 years) and a first degree relative with BC (age < 45 years)
- Pathology-adjusted Manchester score ≥ 15 or CanRisk score ≥ 10%
- Ashkenazi Jewish ancestry and BC at any age

B.1.3.2. **Treatment pathway**

The European School of Oncology-European Society of Medical Oncology (ESO-ESMO) aBC 5 guidelines state the need for early genetic testing of aBC patients due to its influence on treatment choice.[52] The ESMO aBC 5 guidelines further state that "appropriate counselling should be provided to patients and their families if a pathogenic germline mutation is found. At present, only germline mutations in BRCA1/2 have proven clinical utility and therapeutic impact".[52]

The treatment pathway for aBC is dependent on a number of factors including; hormone status (HR+/HER2- or TN),[3] treatment status (treatment naïve or previously treated), and the presence of pathogenic variants such as g*BRCA1/2*m. The scope of this submission is patients with HER2- (comprises two subtypes: patients with HR+/HER2- BC, and patients with TNBC) locally advanced or metastatic disease with a g*BRCA1/2*m. The current treatment pathways for aBC patients in England are outlined below and summarised in Figure 1 to Figure 3. Relevant treatment guidelines are summarised in Table 4.

HR+/HER- aBC

The treatment pathway for newly diagnosed HR+/HER- aBC and for previously treated HR+/HER- aBC patients, is shown in Figure 1.

For the majority of HR+/HER- aBC patients, cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor and endocrine therapy are recommended first line.[1,52] Nevertheless, some patients may require first-line chemotherapy depending on disease severity.[1] Upon progression, second-line treatment options include chemotherapy,[3] further endocrine therapy,[1] or for certain populations targeted therapy is available, as detailed below.

Alpelisib plus fulvestrant has recently been recommended for the treatment of adults with HR+/HER2-, PIK3CAm locally advanced or mBC after an endocrine-based therapy with a CDK4/6 inhibitor plus an aromatase inhibitor (TA816).[53] However, alpelisib has only recently been approved and is not considered a relevant comparator in the current decision problem, as there is insufficient data to inform cost-effectiveness and budget impact models.

For postmenopausal women without symptomatic visceral disease after recurrence or progression following a non-steroidal aromatase inhibitor, everolimus plus exemestane may be used in the second-line.[54] Beyond this, subsequent systemic chemotherapy is recommended.[1]

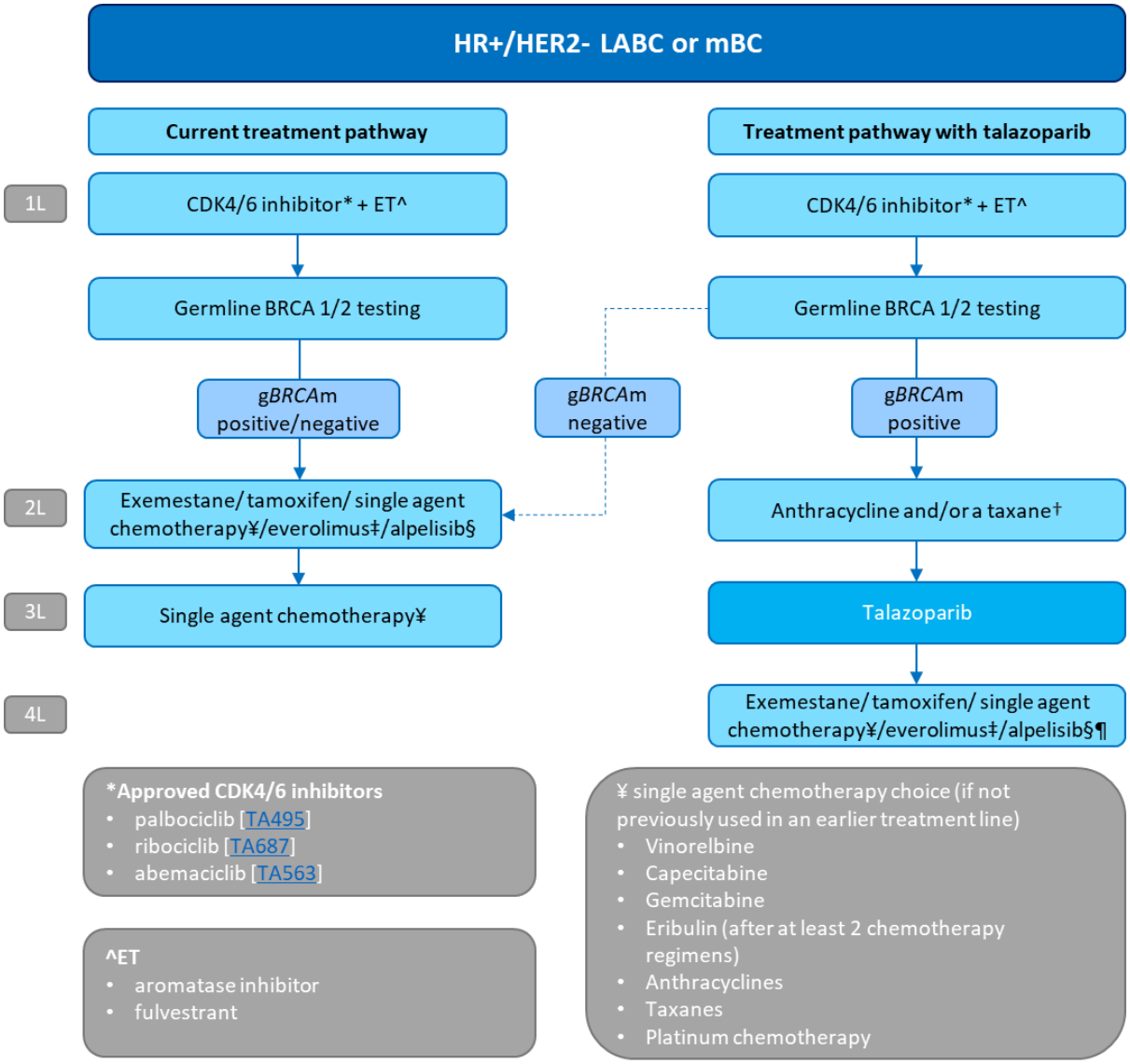


Figure 1. De novo and recurrent HR+/HER2- aBC current treatment pathway and treatment pathway with talazoparib

§ In combination with fulvestrant, in PIK3CA positive patients only

† If not previously treated with anthracycline and/or a taxane in early setting

¶ based on assumption that alpelisib can be used in the 2L plus setting

1L: first-line; 2L: second-line; 3L: third-line; 4L: fourth-line; *BRCA*: BReast CAncer gene; CDK4/6: cyclin-dependent kinase 4 and 6; ET: endocrine therapy; g*BRCA*m: germline *BRCA* mutation; HER2-: human epidermal growth factor receptor 2 negative; HR+: hormone receptor positive; LABC: locally advanced breast cancer; mBC: metastatic breast cancer

Adapted from: NICE Guidelines CG81[1] and NG101,[3] and ESMO guidelines,[52] with additional input from UK clinical experts.

TNBC

For patients with TNBC, genetic testing is recommended for inherited BCs for patients below the age of 60.[3,51,52]

For newly diagnosed g*BRCA*m positive, programmed cell death ligand 1 (PD-L1) negative advanced TNBC patients, first-line treatment with chemotherapy, including anthracycline, taxane or platinum chemotherapy (preferred), is recommended.[3] In g*BRCA*m positive, PD-L1 positive TN patients, immunotherapy (atezolizumab or pembrolizumab plus chemotherapy) is the recommended first-line treatment.[1,52]

Upon progression, second-line treatment with single agent chemotherapy, followed by sacituzumab govitecan at third-line is recommended, regardless of PD-L1 status.[53] The treatment pathway for TNBC newly diagnosed patients is shown in Figure 2.

For previously treated/ recurrent patients, given the recent NICE approval of pembrolizumab in the early setting, it is likely that the patient would have already been treated with pembrolizumab. It is unknown whether re-challenge with immunotherapy will be permitted in the advanced setting. Based on clinical expert opinion, the pathway shown in Figure 3 assumes re-challenge with immunotherapy is not permitted.[52]

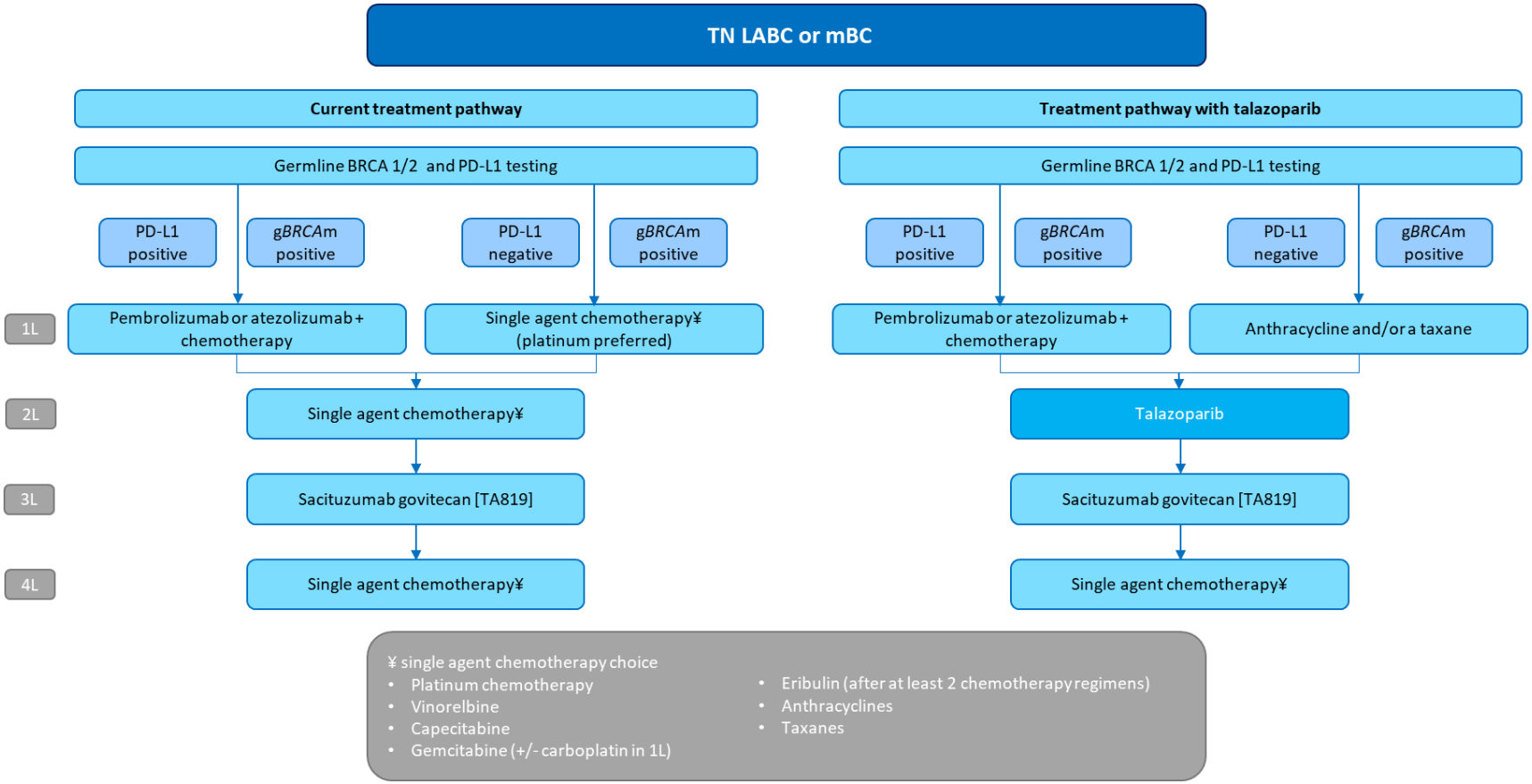


Figure 2. Newly diagnosed/de novo advanced TNBC current treatment pathway and treatment pathway with talazoparib (patients diagnosed at advanced stage, naïve to treatment)

1L: first-line; 2L: second-line; 3L: third-line; 4L: fourth-line; *BRCA*: BReast CAncer gene; g*BRCA*m: germline BRCA mutation; HER2-: human epidermal growth factor receptor 2 negative; LABC: locally advanced breast cancer; mBC: metastatic breast cancer; PD-L1: programmed cell death ligand 1; TN: triple negative

Adapted from: NICE Guideline NG101;[3] TA819,[53] TA639[55] and TA801[56] guidance; and ESMO guidelines,[52] with additional input from UK clinical experts

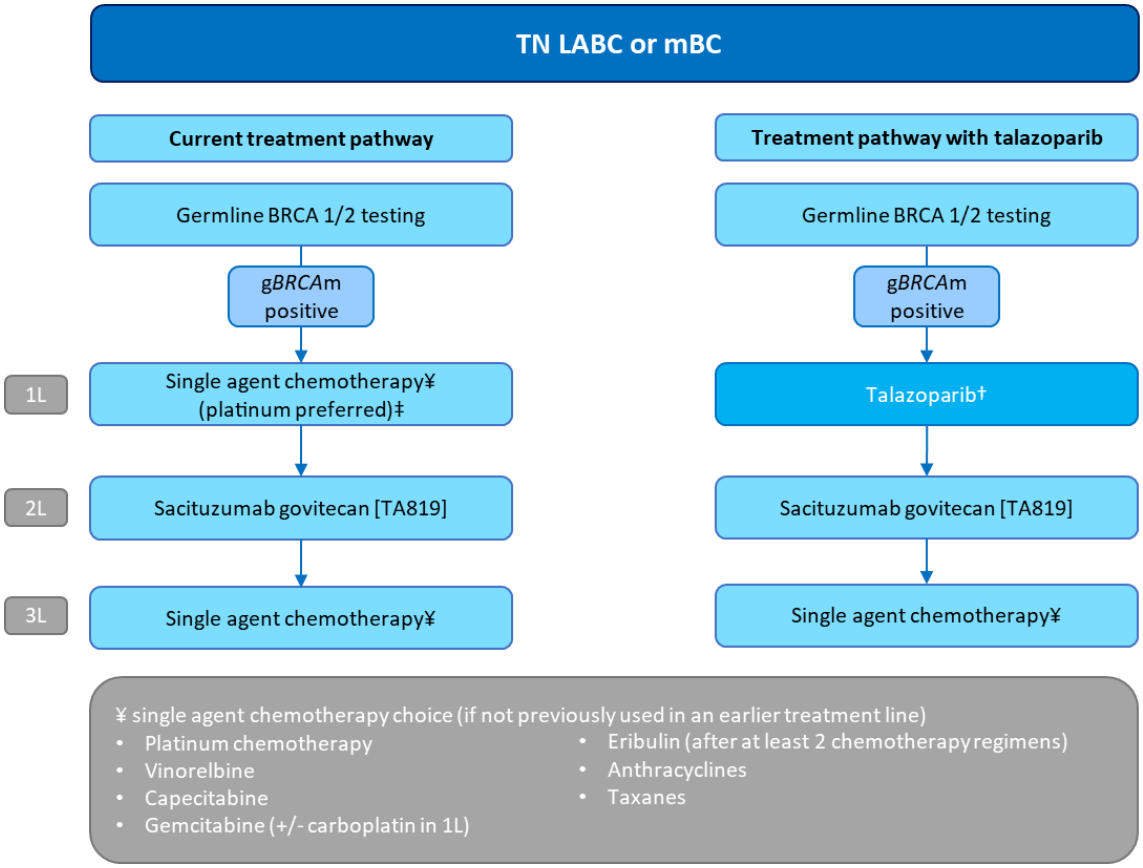


Figure 3. Previously treated/recurrence advanced TNBC current treatment pathway and treatment pathway with talazoparib (patients diagnosed at early stage).

Note: This pathway is based on the assumption that the patient has received pembrolizumab in the early setting and rechallenge with immunotherapy in aBC is not permitted.

†Previously treated with anthracycline and/or a taxane in early setting

‡ platinum preferred if not given in the (neo)adjuvant setting

1L: first-line; 2L: second-line; 3L: third-line; *BRCA*: BReast CAncer gene; g*BRCA*m: germline *BRCA* mutation; HER2-: human epidermal growth factor receptor 2 negative; LABC: locally advanced breast cancer; mBC: metastatic breast cancer; PD-L1: programmed cell death ligand 1; TN: triple negative

Adapted from: NICE Guideline CG81;[1] TA819,[53] TA639[55] and TA801[56] guidance; and ESMO guidelines,[52] with additional input from UK clinical experts

Summary of treatment guidelines in aBC

A summary of the relevant treatment guidelines for aBC is provided in Table 4 below.

Table 4. Summary of relevant treatment guidelines and guidance in aBC

Guideline	Recommendation
NICE guideline CG81: Advanced breast cancer: diagnosis and treatment[1]	
ER-positive aBC ; systemic disease modifying therapy	Offer endocrine therapy first-line for the majority of patients with ER-positive aBC. Offer chemotherapy as first-line treatment for patients whose disease is imminently life-threatening or requires early relief of symptoms. For patients who have been treated with chemotherapy as their first-line treatment, offer endocrine therapy upon completion. Upon disease progression, offer systemic sequential therapy to the majority of patients who have decided to be treated with chemotherapy.
NICE guideline NG101: Early and locally advanced breast cancer: diagnosis and management[3]	
Genetic testing for *BRCA1/2* mutations	Offer genetic testing for *BRCA1* and *BRCA2* mutations to women under 50 years with TNBC, with no family history of breast or ovarian cancer.
Adjuvant endocrine therapy for invasive breast cancer	Offer tamoxifen initially for men and premenopausal women with ER-positive invasive BC. Offer an aromatase inhibitor for postmenopausal women with ER-positive invasive BC who are at medium or high risk of disease recurrence. Offer tamoxifen to women who are at low risk of disease recurrence, or if aromatase inhibitors are not tolerated or are contraindicated.
Extended endocrine therapy	Offer extended therapy (total duration of endocrine therapy > 5 years) with an aromatase inhibitor for postmenopausal women with ER-positive invasive BC who are at medium or high/ low risk of disease recurrence and who have been taking tamoxifen for 2 to 5 years. Consider extending the duration of tamoxifen therapy for longer than 5 years for both premenopausal and postmenopausal women with ER-positive invasive BC.
Adjuvant chemotherapy for invasive breast cancer	For people with BC of sufficient risk that chemotherapy is indicated, offer a regimen that contains both a taxane and an anthracycline.
Neoadjuvant chemotherapy regimens	Consider neoadjuvant chemotherapy for people with ER-positive invasive BC to reduce tumour size if chemotherapy is indicated. For people with TN invasive BC, consider a neoadjuvant chemotherapy regimen that contains a platinum and an anthracycline.
Neoadjuvant endocrine therapy	Consider neoadjuvant endocrine therapy for postmenopausal women with ER-positive invasive BC as an option to reduce tumour size if there is no definite indication for chemotherapy.
NICE TA819: Sacituzumab govitecan for treating unresectable triple-negative advanced breast cancer after 2 or more therapies[53]	
Triple-negative advanced or mBC	First-line therapies are paclitaxel, docetaxel, nab-paclitaxel, anthracycline-based chemotherapy, gemcitabine with or without

	carboplatin, or atezolizumab plus nab-paclitaxel for PD-L1-positive disease. Second-line therapies are single-agent vinorelbine or capecitabine. Third-line therapies are eribulin or single-agent vinorelbine or capecitabine (whichever was not used previously). Sacituzumab govitecan is recommended as an option for treating unresectable triple-negative locally advanced or mBC in adults after 2 or more systemic therapies, at least 1 of which was for advanced disease.
5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5)[52]	
Genetic testing	For aBC patients, results from germline genetic testing have therapeutic implications and should therefore be performed as early as possible.
ER-positive/HER2- (luminal-like) aBC	ET is the preferred option for HR-positive disease, even in the presence of visceral disease, unless there is visceral crisis. A CDK4/6 inhibitor combined with ET is the standard of care for patients with ER-positive/HER2- aBC. Options for treatment of ER-positive disease beyond second line include single agents not previously used (NSAI, SAI, tamoxifen, fulvestrant, megestrol acetate, low-dose oestrogen) and single-agent abemaciclib. In ER-positive g*BRCA*-associated aBC, treatment with ET with or without a CDK4/6 inhibitor is recommended prior to a PARPi.
Triple-negative aBC	For patients previously treated with an anthracycline with/or without a taxane (in the adjuvant and/or metastatic setting), a platinum chemotherapy is the preferred, if not previously administered. For patients with a g*BRCA*m, single-agent PARPi is a preferred treatment option. Atezolizumab and nab-paclitaxel is an option for first-line therapy for PD-L1-positive TN aBC, either de novo or at least 12 months since (neo)adjuvant chemotherapy.
aBC: advanced breast cancer; BC: breast cancer; *BRCA*: BReast CAncer gene; CDK4/6: cyclin-dependent kinase 4 and 6; ER: oestrogen receptor; ET: endocrine therapy; HER2-: human epidermal growth factor receptor 2 negative; mBC: metastatic breast cancer; PARPi: poly (ADP-ribose) polymerase PD-L1: programmed cell death ligand 1; TNBC: triple negative breast cancer	

B.1.3.2.1. Unmet need with current therapy

Need for targeted treatments for g*BRCA1/2* mutations

Currently, in England there are no reimbursed targeted treatments indicated for g*BRCA*m HER2- aBC (LABC or mBC). Some targeted treatment options are licensed for aBC which cover specific subpopulations: TN aBC after two lines of therapy,[53] and first-line treatment of PD-L1-positive TN aBC patients.[22,56]

The only other treatment options for g*BRCA*m HER2− aBC patients are non-targeted treatments, as detailed in Section 0 above. Hence, the majority of g*BRCA*m HER2−

aBC patients receive non-targeted treatments in the form of chemotherapy as standard of care, aligning with the comparators listed in the decision problem (Section B.1.1).

A patient advocacy group voiced that it is extremely difficult for patients to be diagnosed with BRCA 1/2 mutation positive advanced breast cancer and can cause considerable anxiety and fear for them as well as their family and friends. They also raise the significant unmet need in this population and welcome the possibility of a targeted treatment option for BRCA 1/2 mutation positive advanced breast cancer patients.

Limited short median PFS and limited OS with current treatments

Current chemotherapy regimens for patients with g*BRCA*m HER2− aBC are associated with short median PFS and limited OS, as summarised in Table 5.

The OlympiAD trial; a multinational (including UK study sites), randomised, controlled, open-label, phase 3 clinical trial in patients with HER2− mBC and confirmed or suspected g*BRCA*m (N=302), reported median PFS of only 4.2 months in the standard therapy arm (capecitabine, eribulin or vinorelbine),[57] and median OS of 17.1 months.[58]

Data available for current licensed chemotherapy treatments in the US, including first-line therapies such as capecitabine and carboplatin/gemcitabine for patients with *BRCA*m mBC (N=114) reported median PFS ranging from just 6.1 months (95% CI: 4.2, 9.4) for TN mBC patients to 12.1 months (95% CI: 7.1, 14.5) for HR+/HER2- mBC patients, and median OS of 23.4 months (95% CI: 15.4, 26.4) and 38.4 months (95% CI: 28.9, 67.4), respectively.[59] Note, the study did not define type of *BRCA*m; patients may have had somatic or germline mutation.

Table 5. Summary of median OS and PFS with comparator treatments

Study	Study type	Population	Treatment	Median PFS	Median OS
OlympiAD[57,58]	Phase III RCT	HER2− mBC and confirmed or suspected g*BRCA*m	Standard therapy arm (capecitabine, eribulin or vinorelbine)	4.2 months	17.1 months
Vector Oncology Data Warehouse (Houts et al. 2019)[59]	Retrospective observational study	TN mBC	capecitabine and carboplatin/gemcitabine	6.1 months (95% CI: 4.2, 9.4)	23.4 months (95% CI: 15.4, 26.4)
Vector Oncology Data Warehouse (Houts et al. 2019)[59]	Retrospective observational study	HR+/HER2- mBC patients	capecitabine and carboplatin/gemcitabine	12.1 months (95% CI: 7.1, 14.5)	38.4 months (95% CI: 28.9, 67.4)

CI: confidence interval; g*BRCA*m: germline breast cancer susceptibility gene mutation; HER2-: human epidermal growth factor receptor 2 negative; HR+: hormone receptor positive; mBC: metastatic breast cancer; OS: overall survival; PFS: progression-free survival; TN: triple negative

Whilst US PFS data may not reflect UK PFS outcomes, as the UK is reported to have poorer survival outcomes for aBC compared to other high-income countries,[60,61] it does demonstrate poorer PFS outcomes seen in TNBC versus HR+/HER2- patients.[59]

mBC patients with g*BRCAm* and history of CNS metastases have a poor prognosis with current treatments

In the OlympiAD trial, patients with g*BRCA*m HER2− mBC and a history of central nervous system (CNS) metastases treated with chemotherapy (n=8) had a lower medium PFS of 2.8 months compared with 4.2 months for all patients treated with chemotherapy.[62,63] Lower median PFS was also observed in EMBRACA for g*BRCA*m HER2− aBC patients with a history of CNS metastasis treated with physician's choice treatment (PCT) (n=20) compared with all patients treated with PCT (n=144), PFS 1.6 months vs 5.6 months, respectively.[64]

Safety of current treatments

In addition, substantial toxicity associated with current treatment options leading to negative impact on patient QoL further highlights the need for additional, more targeted, well-tolerated therapies for these patients.

Real-world data on the toxicity of chemotherapy regimens in patients with g*BRCA*m HER2− aBC are sparse. Nevertheless, it is clear from clinical trial data in this population that chemotherapy regimens are associated with a high toxicity burden.[57] A safety analysis was conducted in the standard chemotherapy arm of the OlympiAD trial in patients with g*BRCA*m HER2− mBC. The incidence of Grade 3 AEs and above was substantially higher in the standard chemotherapy group (50.5%) than the PARPi group (36.6%).[57] AEs that occurred more frequently in patients receiving standard therapy were neutropenia (including grade 3 neutropenia in 26% patients), decreased white-cell count, palmar-plantar erythrodysesthesia, and increases in the liver enzymes alanine aminotransferase and aspartate aminotransferase.[57]

In addition, a study using Adelphi Disease Specific Program data, collected in 2015 and 2017 in the US and EU5 (France, Germany, Italy, Spain, and the UK), AEs were assessed and rates were calculated for adult women with HER2− aBC *BRCA*m or *BRCA*wt.[65] Patients with g*BRCA*m HER2− aBC were reported to experience more AEs (61%) than *BRCA*wt aBC patients (39%), when treated with current chemotherapy regimens.[65]

Data on the real-world impact of chemotherapy on PROs in patients with g*BRCA*m HER2− aBC are sparse. However, data from clinical trials in HER2− g*BRCA*m aBC patients indicate that chemotherapy leads to a deterioration in PROs, worsening patient QoL functioning and symptom burden.[66,67]

Resource use of current treatments

As an orally administered treatment, talazoparib shifts patients from day units to outpatient setting, easing the administrative service burden on the NHS. Patients receiving existing chemotherapies have a high burden of receiving treatment in

terms of time spent in the inpatient setting to receive infusions, and post-infusion monitoring, as confirmed by clinical opinion.

Given the limited OS, short median PFS, and AEs associated with current treatment options, there is a significant unmet need for targeted therapies with: proven efficacy, the ability to maintain or prolong stable disease, improved safety and tolerability, and the potential to improve QoL for patients and their families. Talazoparib represents a new oral targeted treatment option for patients with g*BRCA1/2*m, who currently have limited alternatives.

B.1.3.3. Talazoparib in the treatment of gBRCAm HER2- aBC

B.1.3.3.1. Mechanism of action

Talazoparib is one of a class of small molecules that functionally inhibit members of the poly (ADP-ribose) polymerase (PARP) family of proteins. To control neoplastic growth, PARPis exploit the concept of synthetic lethality, which describes the phenomenon of cell death resulting from the cumulative action of two genetic mutations, when either mutation alone would permit cellular viability.[68-70]

Poly (ADP-ribose) polymerase 1 (PARP1) is the most well-characterised of the PARP proteins and is known to play a role in the cellular deoxyribonucleic acid (DNA) damage response (DDR) via the repair of single-strand breaks (SSBs).[70] Inhibition of PARP1 is proposed to result in the persistence of SSBs (pathway 1 in Figure 4) and/or trapping of PARP on DNA lesions (pathway 2), both of which could conceivably stall and collapse DNA replication forks.[70] Collapse of the DNA replication fork promotes the formation of potentially lethal double-strand breaks (DSBs).[71] In normal cells, DSBs can be repaired by a process known as homologous recombination.[70] The homologous recombination pathway (HRP) is heavily reliant on the function of proteins encoded by the genes *BRCA1* and *BRCA2*.[70] In cells with deleterious mutations in *BRCA1* or *BRCA2* in each chromosome, inhibition of PARP results in synthetic lethality.[70] Therefore, PARPis are capable of moderating carcinogenesis in *BRCA*m tumour cells while leaving cells with normal homologous recombination function largely intact.[69] Talazoparib is a particularly potent member of

this class of agents (Figure 5), achieving high levels of catalytic inhibition and PARP trapping in assays conducted in vitro.[72-74]

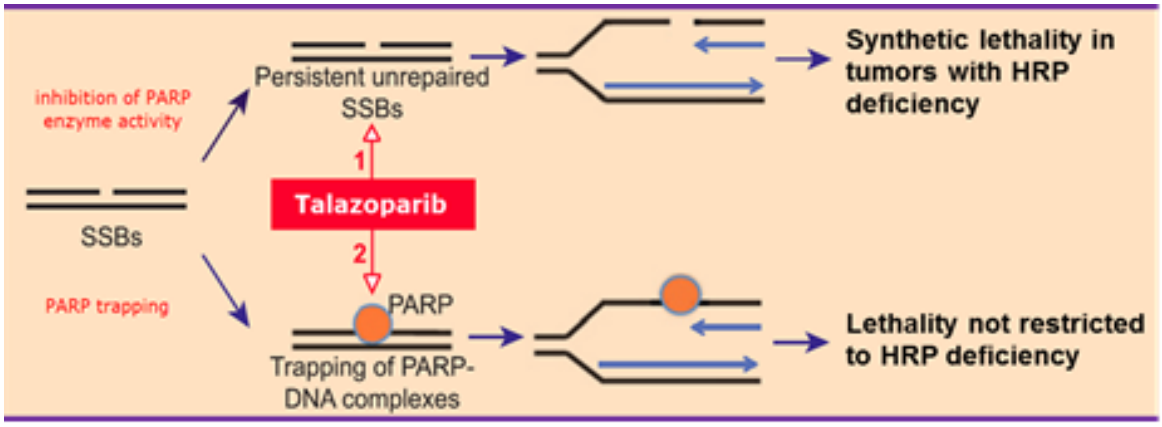


Figure 4. Talazoparib Dual Mechanism of Action.

DNA: deoxyribonucleic acid; HRP: homologous recombination pathway; MoA: mechanism of action; PARPi: poly (ADP-ribose) polymerase inhibitor; SSB: single-strand break.
Source: Turner, 2017[75]

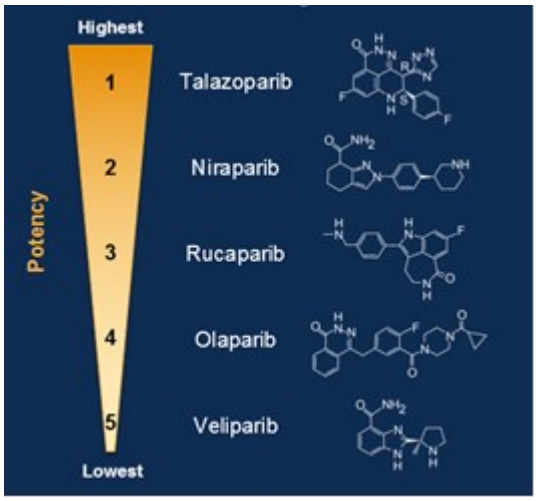


Figure 5. Relative potencies of PARP inhibitors

Source: Turner, 2017[75]

B.1.3.3.2. Place of talazoparib in aBC therapy

The positioning of talazoparib within the aBC treatment pathway is dependent on when in the treatment pathway g*BRCA* testing has occurred, as well as if or when a patient has received anthracycline and/or taxane treatment. This is due to talazoparib only being licensed for the treatment of patients with germline *BRCA1/2*-

mutations, who have HER2- LABC or mBC after prior treatment with an anthracycline and/or taxane, unless patients were not suitable for these treatments.[4] In addition to outlining the current treatment pathways, Figure 1 to Figure 3 above also depict the anticipated position of talazoparib in the treatment pathways in the UK, in line with the scope of the NICE appraisal, and are summarised below.

HR+/HER2- aBC

Newly diagnosed

For newly diagnosed HR+/HER2- aBC patients, talazoparib would be a third-line treatment option following g*BRCA1/2*m testing and treatment with an anthracycline and/or taxane. Talazoparib would be used in place of chemotherapy in the current treatment pathway, see Figure 1 for detail.

Previously treated

The positioning of talazoparib in the treatment pathway would vary depending on prior treatment with an anthracycline and/or taxane in the (neo)adjuvant setting to adhere to licensing. For aBC patients previously treated with an anthracycline and/or taxane, talazoparib is a second-line treatment option. This is in line with ESMO guidelines which recommend targeted therapy of PARP inhibitors such a talazoparib, which is approved in Europe,[4] in the second-line following a positive g*BRCA*m result.[52] In the absence of prior anthracycline and/or taxane treatment, talazoparib is positioned at third-line, see Figure 1 for detail.

TNBC

Newly diagnosed

Talazoparib would be positioned at second-line for newly diagnosed TN g*BRCA*m positive, PD-L1 negative aBC patients after first-line anthracycline and/or taxane, in comparison to second-line chemotherapy in the current treatment pathway. For TN g*BRCA*m positive, PD-L1 positive aBC, talazoparib would be a second-line treatment after pembrolizumab or atezolizumab plus chemotherapy, as the chemotherapy part will include a taxane. See Figure 2 for detail.

Previously treated

Given the recent NICE approval of pembrolizumab in the early setting,[56] it is likely most recurrent patients would have been treated already with pembrolizumab. It is currently unknown whether re-challenge with immunotherapy would be allowed in the advanced setting. With clinical expert input, for the proposed pathway in Figure 3, an assumption was made that re-challenge would not be permitted. With this assumption, talazoparib would be first line treatment for recurrent TN patients with positive g*BRCA*m.

Overall, talazoparib would be the first PARPi for g*BRCA1/2*m HER2- aBC patients in England, providing a much-needed targeted treatment option, with a dual cytotoxic mechanism. Furthermore, talazoparib offers a convenient oral once-daily dosing strategy, which would reduce treatment administration burden to patients and healthcare professionals, as well as potentially reducing MRU costs. Talazoparib represents a highly potent and novel treatment option for those with *BRCA1/2*m, who currently have limited alternatives.

B.1.4. Equality considerations

It is well known that g*BRCA* mutations are more common in certain ethnicities and population groups due to the founder effect. Therefore, it is important to raise awareness of this and strive so that all eligible patients from all ethnic backgrounds have equal access to genetic testing and subsequent treatment.

B.2 Clinical effectiveness

The phase III randomised-controlled trial (RCT), EMBRACA, represents the pivotal source of clinical evidence for talazoparib in germline *BRCA1/2*-mutated HER2-aBC.

Key evidence

- In the EMBRACA trial, patients treated with talazoparib had significantly longer median PFS than those treated with PCT (8.6 months vs 5.6 months); HR: 0.54 (95% confidence interval (CI): 0.41-0.71); $P < 0.001$.
- After 12 months, compared with PCT, talazoparib treatment was associated with consistently higher OS estimates at 24, 36 and 48 months, with survival probabilities at 48 months of 19% for talazoparib vs 7% for PCT.
- Talazoparib was generally well tolerated, with improvements in PROs indicating that talazoparib had a manageable AE profile.
- Talazoparib treatment improved QoL compared with PCT, as measured by European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and EORTC QLQ-BR23 BC module.

Other supporting evidence

- The results of from the ABRAZO phase II trial, evaluating the safety and efficacy of talazoparib, presented in Appendix M and used in the regulatory application, further support the efficacy of talazoparib.
- Additional real-world clinical effectiveness evidence for talazoparib, from the US, France, Turkey and Russia, further support the findings of the EMBRACA study.

B.2.1. Identification and selection of relevant studies

A systematic literature review (SLR) was undertaken to identify the clinical effectiveness evidence (efficacy and safety) of interventions for the treatment of adults with g*BRCA1/2*m, HER2- LABC or mBC that have previously been treated

with a taxane and/or an anthracycline. Full details of the process and methods to identify and select the relevant clinical evidence are summarised in Appendix D.

Searches were conducted using MEDLINE®, Embase (via Ovid), the Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews (CDSR), the International Network of Agencies for Health Technology Assessment (INAHTA), ClinicalTrials.gov and the International Clinical Trials Registry Platform (ICTRP) from database inception to 15 August 2022.

In total, the SLR identified 19 publications reporting on 5 studies which met the eligibility criteria for inclusion.

B.2.2. List of relevant clinical effectiveness evidence

Evidence to support the clinical effectiveness of talazoparib for the treatment of g*BRCA1/2*m, HER2- LABC or mBC in patients previously treated with a taxane and/or an anthracycline, the licensed indication,[4] is derived primarily from the EMBRACA trial (NCT01945775)[76] shown in Table 6.

In addition, the results from the ABRAZO trial (NCT02034916),[77] presented in Appendix M, support the efficacy of talazoparib and were used to support the regulatory application.[78] ABRAZO was not included in the economic model because it is a small phase II trial evaluating the safety and efficacy of talazoparib, and does not provide any data comparing talazoparib to its comparators.

Table 6. EMBRACA: Clinical effectiveness evidence

Study	EMBRACA
Study design	Phase III, multicentre, randomised, parallel, 2-arm, open-label study
Population	Patients aged ≥18 years with g*BRCA*1/2m, HER2- LABC or mBC that received no more than three previous cytotoxic regimens for aBC and been previously treated with a taxane and/or anthracycline, unless this treatment was contraindicated.
Intervention(s)	Talazoparib at a dose of 1 mg/day administered orally (with or without food) continuously.
Comparator(s)	Physicians' choice of: • Capecitabine • Eribulin mesylate • Gemcitabine • Vinorelbine For continuous 21-day cycles (see section B.2.4 for regimen details).
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	Yes
Rationale if study not used in model	Not applicable
Reported outcomes specified in the decision problem	**Overall survival** **Progression-free survival** **Objective response rate** **Adverse events** **HRQoL (EORTC QLQ-C30/EORTC QLQ-BR23 QOL measures)**
All other reported outcomes	Duration of response Pharmacokinetics of talazoparib Time to end of first post-study therapy Change in clinical laboratory tests Change in vital signs Concomitant medication use Research assessments related to blood and tumour sampling that included characterisation of tumour sensitivity and resistance to talazoparib

aBC: advanced breast cancer; EORTC QLQ-BR23: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Breast Cancer Module; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30; g*BRCA*1/2m: germline breast cancer gene 1/2 mutation; HER2-: human epidermal growth factor negative; HRQoL: health-related quality of life; IV: intravenous; LABC: locally advanced breast cancer; mBC: metastatic breast cancer.

Source: Committee for Medicinal Products for Human Use (CHMP), 2019[78]; Full Clinical Study Report (CSR) EMBRACA, 2018[79]

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

A summary of methodology for EMBRACA is provided in Table 7 and detailed below (Sections B.2.3.1 to B.2.4.9), along with detail of patient disposition and baseline patient characteristics in B.2.4.10.

Table 7. EMBRACA: Summary of trial methodology

Trial	EMBRACA[79,64]
Location	US, Europe (Belgium, France, Germany, Ireland, Italy, Poland, Spain, UK, Russia, Ukraine, and Israel), Australia, Brazil, South Korea, and Taiwan
Trial design	Phase III, multicentre, randomised, parallel, 2-arm, open-label study
Eligibility criteria for participants	Patients aged ≥18 years with histologically or cytologically confirmed LABC (not amenable to curative radiation or surgical cure) and/or mBC (appropriate for systemic single cytotoxic chemotherapy) with g*BRCA*1/2m, HER2- status and have received no more than three previous cytotoxic regimens for aBC and have been previously treated with a taxane and/or anthracycline, unless this treatment was contraindicated.
Settings and locations where data were collected	The study was conducted at 145 sites in the US, Europe (Belgium, France, Germany, Ireland, Italy, Poland, Spain, UK, Israel, Russia, and Ukraine), Brazil, South Korea, Australia, and Taiwan.
Trial drugs	Talazoparib (n = 287): Patients received talazoparib at 1 mg/day orally Physician's choice treatment (n = 144): Patients received either capecitabine (1250 mg/m^2 orally twice daily on Days 1 to 14 of each 21-day cycle) or eribulin mesylate (1.4 mg/m^2 IV infusion on Days 1 and 8 of each 21-day cycle) or gemcitabine (1250 mg/m^2 on Days 1 and 8 of each 21-day cycle) or vinorelbine (30 mg/m2, IV infusion on Days 1, 8, and 15 of each 21-day cycle).
Primary outcomes	Radiologic progression–free survival
Other outcomes used in the economic model/specified in the scope	Overall survival, objective response rate, adverse events, HRQoL
Pre-planned subgroups†	Triple-negative status (yes vs no) derived from eCRF Prior regimens of cytotoxic chemotherapy for aBC (0, 1, or 2+) History of CNS metastasis (yes vs no) derived from eCRF

†For the full list of pre-planned subgroups see Section 9.7.1.5.1. of the EMBRACA full CSR, 2018[79]

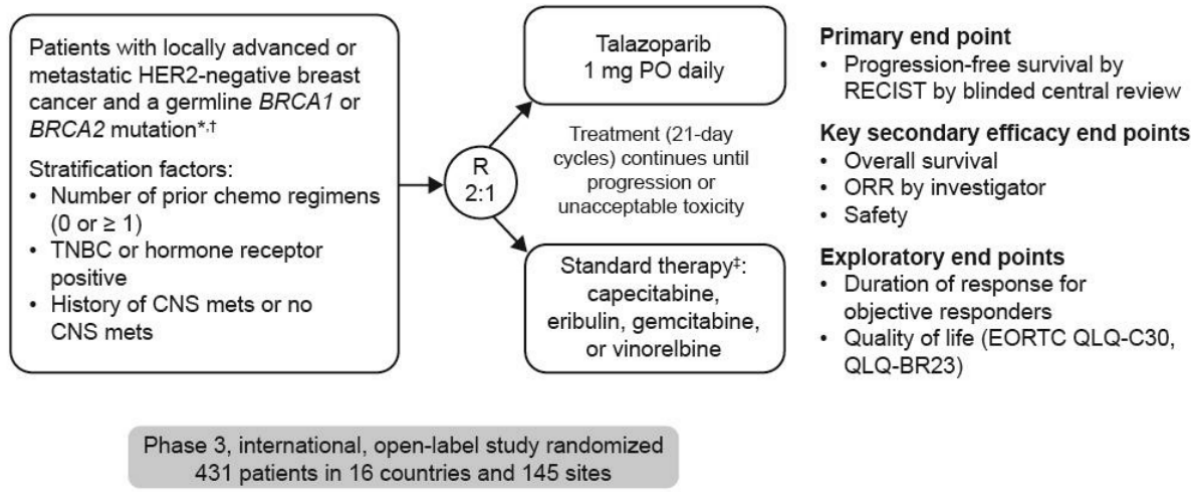
aBC: advanced breast cancer; eCRF: electronic case report form; g*BRCA*1/2m: germline breast cancer gene 1/2 mutation; HER2-: human epidermal growth factor receptor 2 negative; HRQoL: health-related quality of life; PCT: physician's choice treatment; HRQoL: health-related quality of life; RECIST 1.1: Response Evaluation Criteria in Solid Tumours 1.1

B.2.3.1. Study design

The EMBRACA study is a phase III, open-label, multicentre, randomised, parallel, 2-arm trial sponsored by Medivation, Inc to support the filing of talazoparib with the regulatory authorities across the US, UK and Asia (Clinical Trials Identifier NCT01945775).[76] The objective of the study was to evaluate the efficacy and safety of talazoparib in patients with g*BRCA*1/2m who received no more than 3 prior cytotoxic chemotherapy regimens for LABC or mBC. The trial was initiated in October 2013 and was conducted across sites in the US, Europe (Belgium, France, Germany, Ireland, Italy, Poland, Spain, UK, Israel, Russia, and Ukraine), Brazil, South Korea, Australia, and Taiwan.[78]

Patients were randomised in a 2:1 ratio to treatment with talazoparib (1 mg/day) or to the physician's choice treatment group (PCT; capecitabine, eribulin, gemcitabine or vinorelbine in continuous 21-day cycles; see Section B.2.4 for regimens).[64,76] Randomisation was central and stratified by the number of prior cytotoxic chemotherapy regimens for LABC or mBC (0 vs 1, 2, or 3); TNBC status (ER-negative, PR-negative, or HER2-) based on the most recent biopsy (yes vs no); and history of CNS metastases (yes vs no).[64] The study design for EMBRACA is provided in Figure 6.

Figure 6. EMBRACA: Study design



*Additional inclusion criteria included ≤ 3 prior cytotoxic chemotherapy regimens for locally advanced or metastatic disease, prior treatment with a taxane and/or anthracycline unless medically contraindicated.

†Patients with HER2-positive disease are excluded.

‡Physician's choice of therapy must be determined prior to randomisation.

Abbreviations: CNS: central nervous system; EORTC-QLQ: European Organisation for Research and Treatment of Cancer quality of life questionnaire; PO: orally (per os); R: randomized; RECIST: Response Evaluation Criteria in Solid Tumours version 1.1; TNBC: triple-negative breast cancer.

Source: Litton, 2018[64]

B.2.3.2. Eligibility criteria

Patients aged ≥18 years with histologically or cytologically confirmed LABC and/or mBC with g*BRCA1/2*m, HER2- status who had received ≤ 3 previous cytotoxic regimens and had been previously treated with a taxane and/or anthracycline were enrolled. The key eligibility criteria for EMBRACA are listed in Table 8; a full list is available in the study protocol.[64]

Table 8. EMBRACA: Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
• Histologically or cytologically confirmed carcinoma of the breast. • LABC 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 *BRCA*1 or *BRCA*2 mutation. • No more than 3 prior chemotherapy-inclusive regimens for locally advanced and/or metastatic disease. • Prior treatment with a taxane and/or anthracycline in the neoadjuvant, adjuvant, locally advanced, or metastatic setting unless medically contraindicated. • 18 years of age or older. • Have measurable or non-measurable, evaluable disease by revised RECIST 1.1. • ECOG ≤ 2. • Adequate organ function.	• First-line locally advanced and/or mBC with no prior adjuvant chemotherapy unless the investigator determined that 1 of the 4 cytotoxic chemotherapy agents in the control arm would be otherwise offered to the patient. • Prior treatment with a PARP inhibitor (not including iniparib). • Not a candidate for treatment with at least 1 of the treatments of protocol specified PCTs (i.e., capecitabine, eribulin, gemcitabine, vinorelbine). • Patients who had objective disease progression while receiving platinum chemotherapy administered for locally advanced or metastatic disease; patients who received low-dose platinum therapy administered in combination with radiation therapy were not excluded. • Patients who received platinum in the adjuvant or neoadjuvant setting were eligible; however, patients may not have relapsed within 6 months of the last dose of prior platinum therapy. • Cytotoxic chemotherapy within 14 days before randomization. • HER2-positive breast cancer. • CNS metastases (with exceptions). • Known to have been HIV positive and/or active hepatitis C virus or known active hepatitis B virus. • Major surgery within 14 days before randomization. • Myocardial infarction within 6 months before randomization, symptomatic congestive heart failure, unstable angina, or unstable cardiac arrhythmia requiring medication. • Concurrent disease or condition that would interfere with study participation or safety. • Known hypersensitivity to any of the components of talazoparib.

*BRCA*1/2: breast cancer susceptibility gene 1 or 2; CNS: central nervous system; ECOG: Eastern Cooperative Oncology Group; HER2: human epidermal growth factor receptor 2; HIV: human immunodeficiency virus; LABC: locally advanced breast cancer; mBC: metastatic breast cancer; PARP: poly ADP-ribose polymerase; PCT: physician's choice treatment; RECIST 1.1: Response Evaluation Criteria in Solid Tumours 1.1;

See Section 9.3 of the CSR[79] for full detail of the inclusion and exclusion criteria

Source: Litton, 2018[64], Full CSR EMBRACA, 2018[79]

B.2.3.3. Settings and locations where the data were collected

Patients from 145 study sites across 16 countries were randomised between study arms.[64] Of the 145 study sites, there were [redacted] study sites in the US, [redacted] study sites in Europe (Belgium, France, Germany, Ireland, Italy, Poland, Spain, UK, Russia, Ukraine, and Israel), and [redacted] study sites in other countries (Australia, Brazil, South Korea, and Taiwan). At least [redacted] enrolled at each study site with 156 patients (36.2%) enrolled in the US,[78,79] 190 patients (44.1%) in Europe,[78] including [redacted] UK patients, and 85 patients (19.7%) elsewhere in the world.[78,79]

B.2.4. Clinical effectiveness results of the relevant studies

Evidence for the clinical efficacy of talazoparib is derived from the EMBRACA study, a phase III randomized, open-label, study. Additional clinical effectiveness evidence from the ABRAZO study is provided in Appendix M.

The 15 September 2017 EMBRACA data cut was used for the primary PFS analysis and interim OS analysis,[64] and the 30 September 2019 data cut was used for final OS analysis.[80] The median follow up for PFS was 11.2 months[64] ([redacted]),[79] and for final OS was 44.9 months (95% CI: 37.9-47.0) and 36.8 months (95% CI: 34.3-43.0) for patients treated with talazoparib and PCT, respectively.[80]

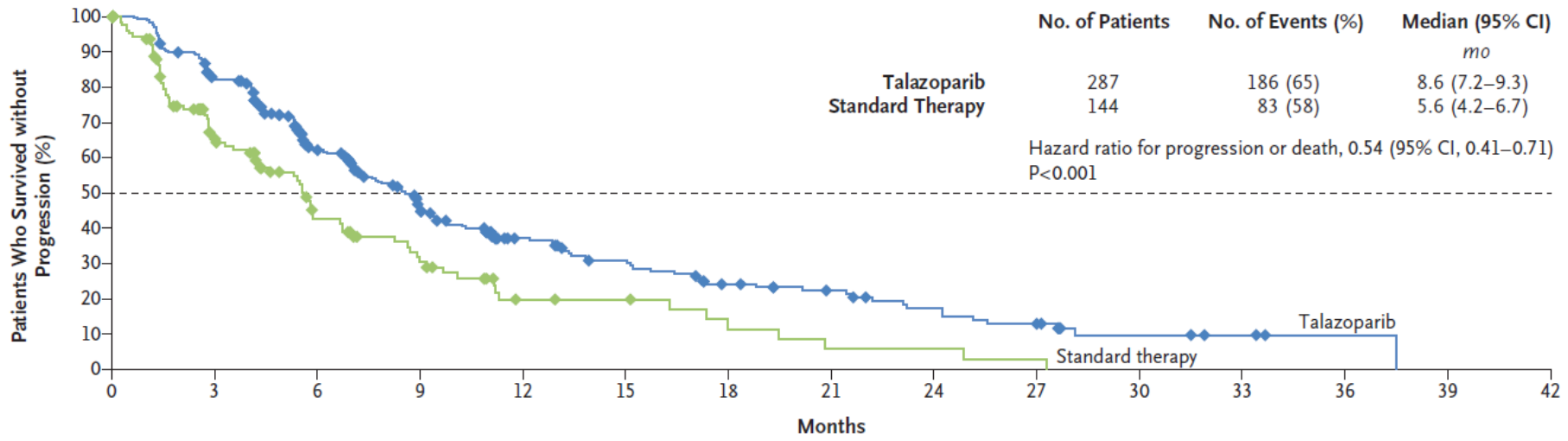
B.2.4.1. Primary endpoint: Progression-free survival by blinded independent clinical review (ITT population)

Patients treated with talazoparib had significantly longer median PFS than those treated with PCT, 8.6 months (95% CI: 7.2-9.3) vs 5.6 months (95% CI: 4.2-6.7), HR: 0.54 (95% CI: 0.41-0.71; $P < 0.001$), an increase of 3 months as shown in Table 9. The estimated 1 year PFS rate was 37% for patients treated with talazoparib in comparison to 20% of PCT patients (Figure 7).[64] Sensitivity analyses of PFS supported the primary analysis; the hazard ratio (HR) by stratified Cox regression analysis was 0.538 (95% CI: 0.420, 0.689; $P < 0.0001$).

Table 9. EMBRACA: Progression free survival (primary endpoint)

Endpoint	Talazoparib	Overall PCT
PFS[a]		
Evaluable patients	287	144
Median, months (95% CI)	8.6 (7.2, 9.3)	5.6 (4.2, 6.7)
Hazard Ratio (95% CI)	0.542 (0.41, 0.71)	
Number of events, n (%)	186 (65%)	83 (58%)

The data cut-off date for PFS, response and clinical benefit rate was 15 September 2017.
a. by independent radiology facility
CI: confidence interval; PFS: progression-free survival
Source: Litton, 2018[64]



No. at Risk (events/cumulative events)

Talazoparib	287 (0/0)	229 (50/50)	148 (53/103)	91 (34/137)	55 (17/154)	42 (9/163)	29 (9/172)	23 (2/174)	16 (5/179)	12 (4/183)	5 (2/185)	3 (0/185)	1 (0/185)	0 (1/186)	0 (0/186)
Standard therapy	144 (0/0)	68 (41/41)	34 (20/61)	22 (8/69)	9 (7/76)	8 (0/76)	4 (3/79)	2 (2/81)	2 (0/81)	1 (1/82)	0 (1/83)	0 (0/83)	0 (0/83)	0 (0/83)	0 (0/83)

Figure 7. EMBRACA: PFS of patients treated with talazoparib and PCT

Source: Litton, 2018[64]

CI: confidence interval, mo: month; No: number

The data cut-off date was 15 September 2017.

B.2.4.2. Secondary endpoint: Overall survival (ITT population)

As of the 15 September 2017 data cut-off, median interim OS for patients treated talazoparib was 22.3 months (95% CI: 18.1-26.2) vs 19.5 months (95% CI: 16.3-22.4) for patients treated with PCT. The interim median HR for death was 0.76 (95% CI: 0.55-1.06; *P* = 0.11 [57% of projected events]).[64] See Figure 8 for detail.

As of the final OS analysis (data cut-off 30 September 2019), there was no statistically significant difference in the OS between the talazoparib and PCT arms (HR: 0.848; 95% CI: 0.670-1.073; *P* = 0.17).[80] The median OS were 19.3 months (95% CI: 16.6-22.5) and 19.5 months (95% CI: 17.4-22.4) for talazoparib and PCT, respectively (Table 10).[80] Unlike the 12 month Kaplan-Meier (KM) survival probabilities, which were similar between talazoparib and PCT (71% [95% CI: 0.66-0.76] vs 74% [95% CI: 0.66-0.81], respectively), survival probabilities were consistently higher for talazoparib treated patients at 24, 36 and 48 months, compared to PCT (Figure 9).[80] Survival probability at 48 months were 19% (95% CI: 14-25) for talazoparib vs 7% (95% CI: 2-15) for PCT.[80,81]

Two analyses using the rank-preserving structural failure time model (RPSFTM) method were carried out to estimate the treatment effect on OS adjusting for subsequent treatment with a PARP inhibitor.[82,83] Most patients received subsequent treatments: in the talazoparib and PCT arm, 4.5% and 32.6% received a PARPi, respectively. When adjusting for subsequent PARPi use, the HR for OS was 0.820 (95% CI: 0.617-1.047) (Figure 10).[80] Adjusting for subsequent PARP inhibitor and/or platinum chemotherapy use, the HR for OS was 0.756 (95% CI: 0.503-1.029).[80]

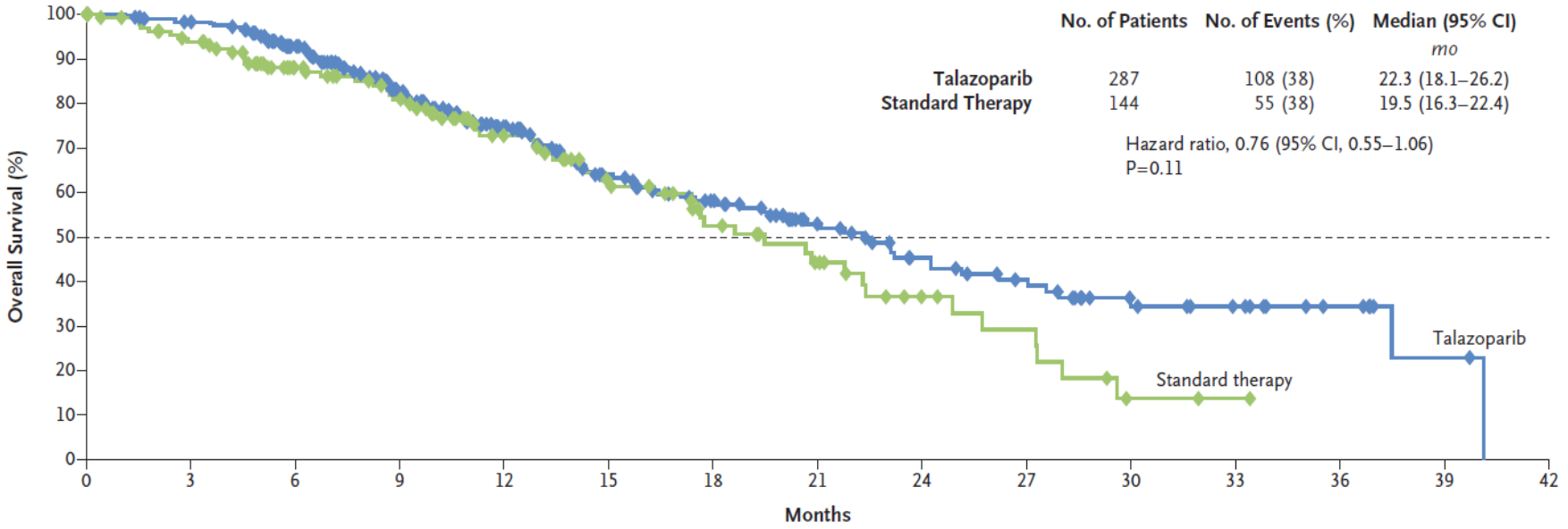
Table 10. EMBRACA: Final OS

Endpoint	Talazoparib	Overall PCT
Evaluable patients	287	144
Median, months (95% CI)	19.3 (16.6-22.5)	19.5 (17.4-22.4)
HR (95% CI)	0.848 (0.670-1.073)	
Number of events (%)	216 (75.3)	108 (75.0)
Survival probability at month 12 (95% CI)	0.71 (0.66-0.76)	0.74 (0.66-0.81)
Survival probability at month 24 (95% CI)	0.42 (0.36-0.47)	0.38 (0.30-0.47)
Survival probability at month 36 (95% CI)	0.27 (0.22-0.33)	0.21 (0.14-0.29)
Survival probability at month 48 (95% CI)	0.19 (0.14-0.25)	0.07 (0.02-0.15)

The data cut-off date for OS was 30 September 2019.

a. by independent radiology facility

CI: confidence interval; HR: hazard ration; PCT: physician's choice treatment Source: Litton, 2020[80]



No. at Risk (events/cumulative events)

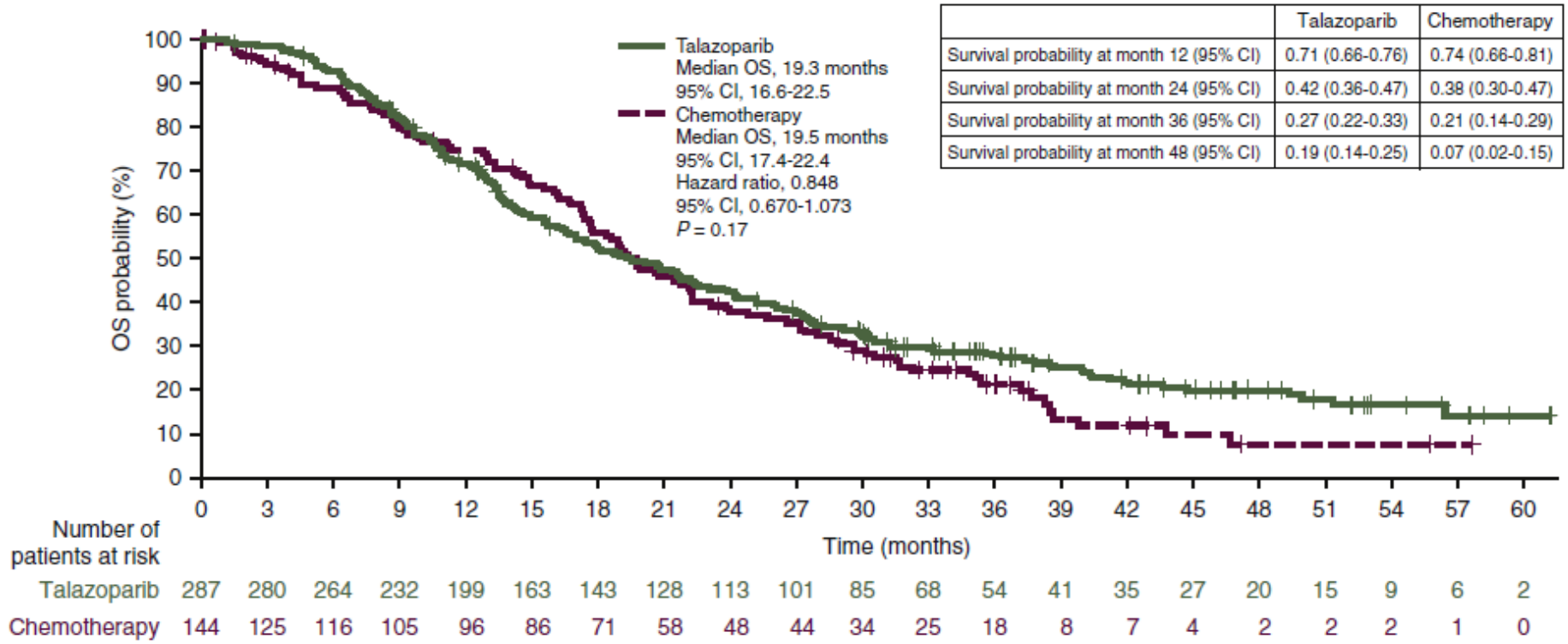
Talazoparib	287 (0/0)	278 (5/5)	236 (15/20)	179 (24/44)	132 (16/60)	91 (17/77)	74 (8/85)	52 (6/91)	38 (7/98)	30 (4/102)	18 (4/106)	14 (0/106)	8 (0/106)	2 (1/107)	0 (1/108)
Standard therapy	144 (0/0)	119 (8/8)	92 (7/15)	78 (7/22)	55 (7/29)	41 (7/36)	28 (6/42)	20 (4/46)	11 (3/49)	8 (2/51)	2 (4/55)	1 (0/55)	0 (0/55)	0 (0/55)	0 (0/55)

Figure 8. EMBRACA: Interim OS of patients treated with talazoparib and PCT

Source: Litton, 2018[64]

CI: confidence interval; mo; months; No.; number

Data cut-off date 15 September 2017.



	Talazoparib	Chemotherapy
Survival probability at month 12 (95% CI)	0.71 (0.66-0.76)	0.74 (0.66-0.81)
Survival probability at month 24 (95% CI)	0.42 (0.36-0.47)	0.38 (0.30-0.47)
Survival probability at month 36 (95% CI)	0.27 (0.22-0.33)	0.21 (0.14-0.29)
Survival probability at month 48 (95% CI)	0.19 (0.14-0.25)	0.07 (0.02-0.15)

Figure 9. EMBRACA: Final OS of patients treated with talazoparib and PCT

Source: Litton, 2020[80]

CI: confidence interval; OS: overall survival

Data cut-off date 30 September 2019.

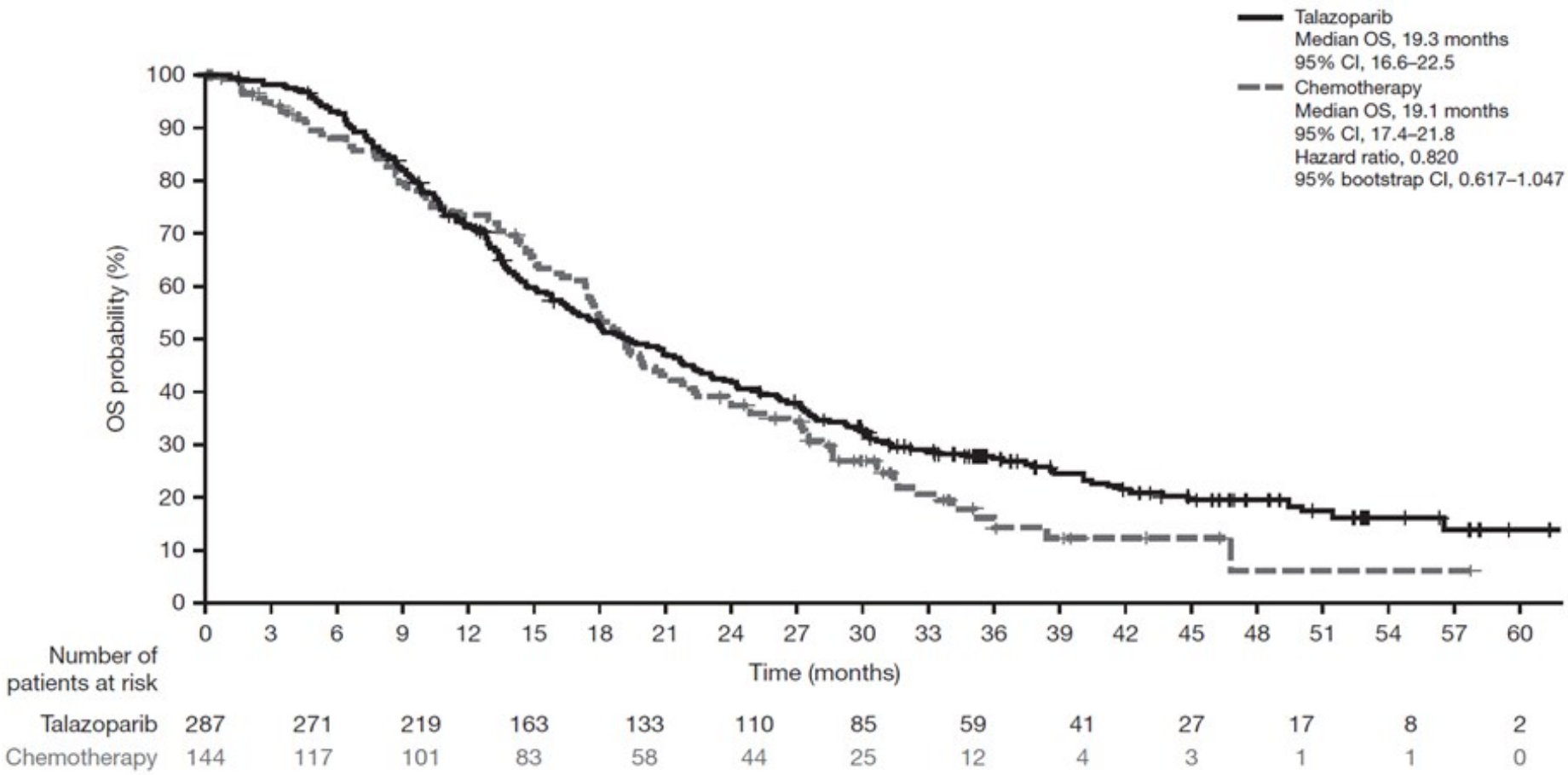


Figure 10. EMBRACA: Final OS adjusting for subsequent PARP inhibitor only

Source: Litton, 2020[80]

CI: confidence interval; ITT: intent-to-treat; OS: overall survival; PARP: poly(ADP-ribose) polymerase

Data cut-off date 30 September 2019.

B.2.4.3. Secondary endpoint: Objective response rate (ITT with measurable disease population)

Objective response rate (ORR) was higher in patients that received talazoparib treatment compared to PCT, an increase of 35.4% (62.6% [95% CI: 55.8-69.0] vs 27.2% [95% CI: 19.3- 36.3]). A complete response (CR) and partial response (PR occurred in a greater proportion of patients treated with talazoparib in comparison to PCT, 5.5% and 0.0% and 57.1% and 27.2% respectively (Table 11).[64]

Table 11. EMBRACA: Objective response rate

Endpoint	Talazoparib	Overall PCT
Responses*		
Evaluable patients	219	114
ORR, n (%) [95% CI]	62.6 (55.8–69.0)	27.2 (19.3–36.3)
CR, n (%)	12 (5.5)	0
PR, n (%)	125 (57.1)	31 (27.2)
SD, n (%)	46 (21.0)	36 (31.6)
Could not be evaluated, n (%)	4 (1.8)	19 (16.7)

The data cut-off date was 15 September 2017.

* According to Response Evaluation Criteria in Solid Tumours, version 1.1, confirmation of complete response or partial response was not required

CI: confidence interval; CR: complete response; ORR: Objective response rate; PR: partial response; SD: stable disease

Source: Litton, 2018[64]

B.2.4.4. Exploratory endpoints: Duration of response (responders); Clinical benefit rate (ITT population)

Median duration of response was 5.4 months in patients who received talazoparib and 3.1 months in those who received PCT (Table 12). Additionally, the clinical benefit rate at 24 weeks (CBR24) for patients treated with talazoparib was almost double that of patients treated with PCT, 68.6% (95% CI: 62.9-74.0) and 36.1% (95% CI: 28.3-44.5).[64]

Table 12. EMBRACA: Clinical benefit rate and duration of response

Endpoint	Talazoparib	Overall PCT
Clinical benefit rate at 24 weeks		
Evaluable patients	287	144
Patients with clinical benefit, n (%) [95% CI]	197 (68.6) [62.9–74.0]	52 (36.1) [28.3–44.5]
Duration of response		
Evaluable patients	137	31
Median, months (IQR)	5.4 (2.8–11.2)	3.1 (2.4–6.7)

The data cut-off date was 15 September 2017
CI: confidence interval; IQR: interquartile range; PCT: physicians choice treatment
Source: Litton, 2018[64]

B.2.4.5. Exploratory endpoint: Time to the end of first post-study therapy (ITT population)

Time to the end of first post-study therapy was defined as the time from randomisation to the end date of the first post-study antineoplastic therapy after the first documented disease progression by investigator assessment while on a study drug (talazoparib or PCT). A total of 178 patients (62.0%) in the talazoparib arm and 98 patients (68.1%) in the PCT arm received antineoplastic therapies after study drug discontinuation.[64] Median time to the end of the first post-study therapy was 11.9 versus 10.1 months for talazoparib and PCT, respectively; the HR (as stratified by Cox regression analysis) was 0.68 (95% CI: 0.505-0.912; P = 0.0096.85).

B.2.4.6. Exploratory endpoint: Patient reported outcomes (PRO-evaluable population)

QoL was improved with talazoparib treatment in comparison to PCT according to PROs. PROs were evaluated through use of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and the EORTC QLQ-BR23 BC module. These were conducted at baseline (day 1), the start of each treatment cycle (every 3 weeks), and at treatment termination.[67]

B.2.4.6.1. EORTC QLQ-C30

EORTC QLQ-C30 is made up of subscales; a global health status (GHS)/QoL subscale, five multi-item functional scales, three multi-item symptom scales and six single item symptom scales which measure other disease and/or treatment-related symptoms.

GHS/QoL

Patients treated with talazoparib had a significantly better GHS/QoL score, with a difference between talazoparib and PCT treatments arms of 8.4 (95% CI: 4.6-12.3; *P* < 0.0001) (Figure 11A); a statistically significant improvement in overall change from baseline was also seen with talazoparib treatment (3.0; 95% CI: 1.2-4.8).[67]

Functional QLQ-C30 scales

For all five functional scales of EORTC QLQ-C30, a statistically significant difference in favour of talazoparib was determined (Figure 11A). Overall change from baseline showed significant improvement in physical functioning (92.9 [95% CI: 0.9, 4.9]) and emotional functioning (6.1 [95% CI: 3.8, 8.4]) for talazoparib (Figure 11A).[67].

Symptom QLQ-C30 scales

With talazoparib treatment, a statistically significant difference was found for fatigue, pain, insomnia, and appetite loss (Figure 11B). Additionally, there was a significant improvement in fatigue (-3.9; 95% CI: -6.2, -1.6), pain (-7.5: 95% CI: -10.0, -5.1), insomnia (-7.1; 95% CI:-9.5, -4.7), appetite loss (-5.1: 95% CI: -7.9, -2.4), and constipation (-3.3: 95% CI: -5.9, -0.8) with talazoparib treatment.[67]

B.2.4.6.2. EORTC QLQ-BR23

EORTC QLQ-BR23 consists of four functional scales and four symptom scales.

Functional QLQ-BR23 scales

For body image, a greater statistically significant overall change from baseline was detected for talazoparib as shown in Figure 11A. Talazoparib treatment showed overall improvement from baseline for body image (3.9; 95% CI: 1.6, 6.3), while

future perspective was improved in both treatment arms with a greater improvement seen with talazoparib treatment: talazoparib (15.3: 95% CI: 12.3, 18.3) and PCT (9.1: 95% CI: 3.7, 14.5).[67]

Symptom QLQ-BR23 scales

Talazoparib showed a statistically significant greater overall change from baseline in comparison to PCT for breast symptoms, arm symptoms and systemic therapy side-effects Figure 11A). Furthermore, breast symptoms (-5.1: 95% CI: -6.7, -3.5) and arm symptoms (-4.6: 95% CI: -6.5, -2.8) both improved significantly with talazoparib treatment.[67]

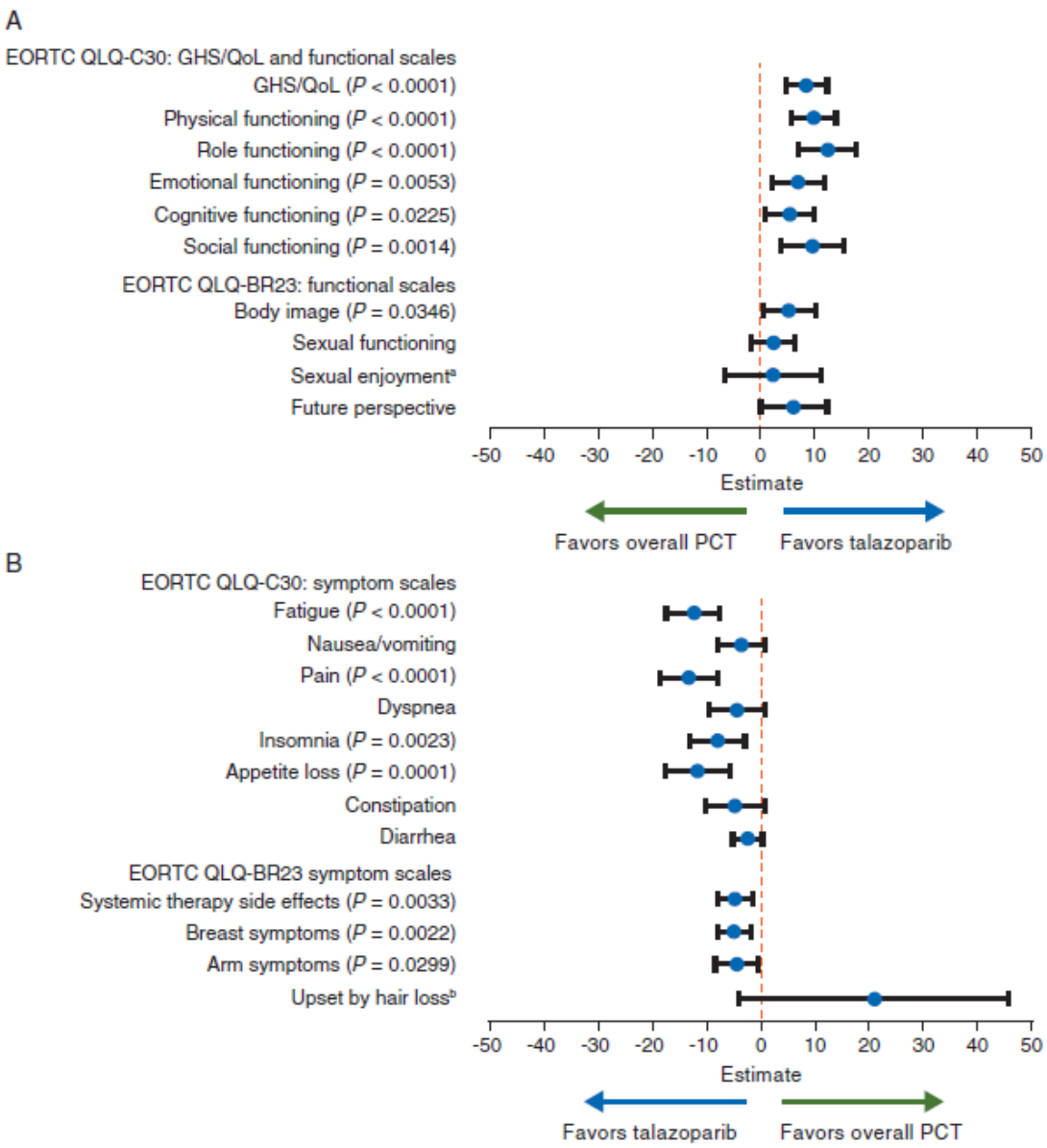


Figure 11. EMBRACA: Forest plot model of estimated difference (talazoparib and overall PCT) in overall change from baseline (repeated-measures mixed-effect model) in PRO-evaluable population (P values are shown only if significant between-arm differences, *P* < 0.05, were observed).

(A) EORTC QLQ-C30: GHS/QoL and functional scales; EORTC QLQ-BR23: functional scales. (B) EORTC QLQ-C30: symptom scales; EORTC QLQBR23 symptom scales. aThe sample sizes for the 'sexual enjoyment' functional scale were smaller than other functional scales because patients were asked to respond to this question only if they responded that they were sexually active in a previous question. bThe sample sizes for the 'upset by hair loss' symptom scale were smaller than other symptom scales because patients were asked to respond to this question only if they responded that they were experiencing hair loss in a previous question. EORTC, European Organisation for Research and Treatment of Cancer; GHS, global health status; PCT, physician's choice of therapy; PRO, patient-reported

Source: Ettl, 2018[67]

B.2.4.7. Real-world evidence

Talazoparib has been approved in the US since 16 October 2018 and the EU since 20 June 2019. Evidence from real-world clinical practice from these regions, as well as Russia and Turkey, provides additional evidence for the clinical effectiveness of talazoparib and supports the findings of the EMBRACA study.

A recent US retrospective chart review assessed the real-world clinical outcomes of g*BRCA*m HER2- LABC or mBC patients treated with talazoparib (N=84), with a median follow-up from the initiation of talazoparib treatment of 8.2 months.[84] Among all patients, the median PFS for talazoparib was 8.7 months (95% CI: 8.0-9.9), the median time-to-treatment failure (TTF) of talazoparib was 8.6 months (95% CI: 8.0-9.7; Figure 12) and, the objective response rate (ORR) during talazoparib treatment was 63% (95% CI: 52%-74%); however, OS data were immature. For patients with HR+/HER2- and TNBC subtypes, TTF, PFS and overall tumour response were similar.[84]

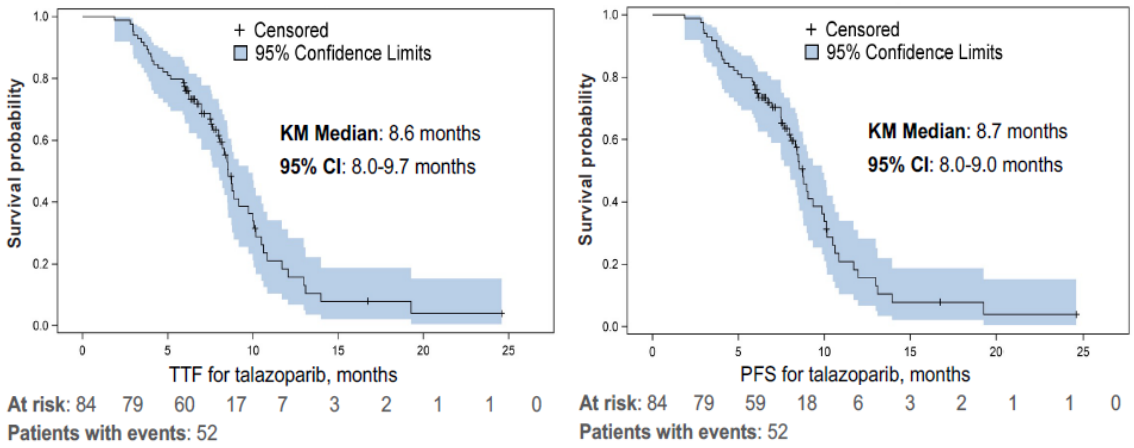


Figure 12. TTF and PFS of patients with g*BRCA*m HER2- LABC/mBC treated with talazoparib in the US

TTF (left): Time from talazoparib initiation to discontinuation for any reason. Patients still on therapy at last encounter were censored at last encounter date.

PFS (right): Time from initiation of talazoparib to charted disease progression based on radiographic imaging or death from any cause, whichever occurred first. Patients who discontinued talazoparib for a reason other than progression or death were censored at talazoparib discontinuation date. Patients still receiving talazoparib at last encounter were censored on date of last encounter.

CI: confidence interval; g*BRCA*m: germline breast cancer susceptibility gene mutated; HER2-: human epidermal growth factor receptor 2 negative; KM: Kaplan-Meier; LA/mBC: locally advanced or metastatic breast cancer; PFS: progression-free survival, TTF: time-to-treatment failure.

Source: Mahtani, 2022[84]

This study demonstrates the real-world clinical benefits of talazoparib for the treatment of g*BRCA*m HER2- LABC and mBC patients in the US consistent with EMBRACA, as well as real-world evidence reported for talazoparib in other countries, including France, Turkey and Russia described below.[84-87]

The objective of a French ambispective phase IV study, ViTAL, was to examine the effectiveness and safety of talazoparib in *BRCA*m HER2- LABC or mBC patients in a real-world setting. With a median follow-up of 17.8 months (95% CI: 15.7-21.0), of 86 treated patients 69 patients (80%) discontinued talazoparib due to: progressive disease (87%), toxicity (7%), cancer-related death (3%), or other reasons (3%). Median Time to Treatment Discontinuation (TTD) for talazoparib was 8.6 months (95% CI: 6.0-10.9). No difference was observed in relation to HR status. OS data were not yet mature; however, 82% of patients were still alive at 24 months. Treatment-related adverse events occurred in 10% of patients, overall, at least 1 AE was recorded for 71% of patients. Outcomes and safety results were consistent with those reported in EMBRACA.[85]

A retrospective real-world study in Turkey investigated talazoparib treatment in aBC *BRCA*1/2 patients in a heavily pre-treated population (51.1% of the patients had received talazoparib as fourth line or beyond). After a median follow up period of 13.6 months (6.5-21.5 months), the overall PFS was 6.5 months (5.0-8.1 months, 95% CI) and the median PFS for the patient subgroup who received talazoparib in the first, second or third line was 9.9 months (4.4-15.5 months, 95% CI), which are reflective of the EMBRACA trial.[86]

Additionally, a multicentre compassionate use program in Russia concluded talazoparib to be an effective targeted therapy for g*BRCA*m HER2- mBC patients. In this study population, 75% were TNBC and 25% were HR+/HER2-. The overall median PFS was 6.5 months (3-10 months, 95% CI). However on subgroup analysis, the median PFS for HR+/HER2- was 9 months and for TNBC it was 5 months (HR 0.705, 95% CI 0.231-2.147, p value: 0.5208).[87]

B.2.4.8. Study medications

Patients were randomised in a 2:1 ratio to treatment with talazoparib (1 mg/day) or to the PCT group (capecitabine, eribulin, gemcitabine or vinorelbine).[64,76] Following randomisation, patients in the talazoparib arm received talazoparib treatment 1 mg/day (orally),[64] and those in the PCT arm received one of the following interventions:

- Capecitabine 1250 mg/m^2 orally twice daily on Days 1 to 14 of each 21-day cycle, 30 minutes after food.[78]
- Eribulin mesylate 1.4 mg/m^2 (equivalent to eribulin 1.23 mg/m^2), 2- to 5-minute intravenous (IV) infusion on Days 1 and 8 of each 21-day cycle.[78]
- Gemcitabine 1250 mg/m^2, 30-minute IV infusion on Days 1 and 8 of each 21-day cycle.[78]
- Vinorelbine 30 mg/m^2, 6- to 10-minute IV infusion weekly on Days 1, 8, and 15 of each 21-day cycle.[78]

Treatment continued until disease progression, unacceptable toxicity, consent withdrawal, or if the treatment was ended by the physician.[64]

B.2.4.9. Study endpoints and assessments

The primary, secondary and exploratory endpoints of EMBRACA are summarised in Table 13. The primary endpoint was determined by independent central review, as per RECIST version 1.1.[64]

Table 13. EMBRACA: Study endpoints

Endpoint	Definition
Primary endpoint	**Radiographic progression-free survival (PFS)** defined as the time from randomization 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.
Secondary and exploratory endpoints	**Objective response rate (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 **Overall survival (OS)** defined as the time from randomization to death due to any cause **Safety** The incidence of adverse events, including serious adverse events Change in clinical laboratory tests (serum chemistry and haematology) Change in vital signs Concomitant medication use **Pharmacokinetics (PK) of talazoparib** A population PK modelling approach was used to estimate individual values of apparent clearance (CL/F) and central volume of distribution (Vc/F). Individual CL/F estimates were used to estimate individual area under the concentration time curve over a dosing interval. **Duration of response (DOR)** defined as the time from first radiographic documentation of objective response (CR or PR) until radiographic disease progression by RECIST 1.1 based on investigator assessment, or to death due to any cause, whichever occurred first. **Time to End of First Poststudy Therapy** defined as the time from randomization to the end date of the first post-study antineoplastic therapy after the first documented disease progression by investigator assessment while on study treatment (talazoparib or PCT). **QoL (EORTC QLQ-C30/EORTC QLQ-BR23)** Patient-reported outcomes (PRO) were assessed as an exploratory efficacy endpoint using the EORTC QLQ-C30 and EORTC QLQ-BR23 at baseline, Day 1 of each cycle, and at the end of treatment. **Research assessments related to blood and tumour sampling that includes characterisation of tumour sensitivity and resistance to talazoparib**

CL/F: apparent clearance; CR: complete response; DOR: duration of response; EORTC QLQ-BR23: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Breast Cancer Module; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30; IRF: independent radiology facility; ITT: intent-to-treat; ORR: objective response rate; OS: overall survival; PCT: physician's choice treatment; PFS: progression free survival; PK: pharmacokinetic(s); PR: partial response; PRO: patient reported outcomes; QoL: quality of life; RECIST: Response Evaluation Criteria in Solid Tumours; Vc/F: central volume of distribution

Source: Committee for Medicinal Products for Human Use (CHMP), 2019[78]

B.2.4.10. Patient disposition and baseline patient characteristics

B.2.4.10.1. Patient disposition

A total of 995 patients were screened for the EMBRACA study and 431 patients were subsequently enrolled in the intent-to-treat (ITT) population from October 2013-April 2017.[78] Of those enrolled, 287 patients were randomised to receive talazoparib and 144 were randomised to receive PCT.[64] Nineteen patients (one in the talazoparib arm and 18 in the PCT arm) were randomised but did not receive treatment.[64] Of the remaining 126 patients that received PCT, 55 received capecitabine, 50 received eribulin, 12 received gemcitabine and 9 received vinorelbine.[64]

As of the data cut-off date (15 September 2017) for the full clinical study report (CSR), 64 patients (22.3%) in the talazoparib arm and 7 patients (4.9%) in the PCT arm had ongoing treatment. Disease progression accounted for the majority of permanent discontinuations across both arms (284 patients [65.9%]). A total of 166 patients (57.8%) in the talazoparib arm and 65 patients (45.1%) in the PCT arm were in long-term follow-up.[78]

Final OS analysis was carried out when 321 deaths had occurred, which took place by 30 September 2019.[80] As of the supplemental OS CSR data cut-off (30 September 2019), 17 (5.9%) patients in the talazoparib group and 1 (0.7%) patient in the PCT group were receiving ongoing treatment.[80] Disease progression accounted for the majority of permanent discontinuations across both arms (329 [76.3%]),[88] followed by patient withdrawal (34 patients [7.9%]), and physician decision (26 patients [6.0%]).[79-81] A summary of the patient disposition at 30 September 2019 data cut-off is provided in Figure 13. Following the OS supplemental CSR, updated safety analysis as of the last subject last visit (LSLV) (05 March 2021) reported no patients were receiving treatment or participating in the study.[88,89]

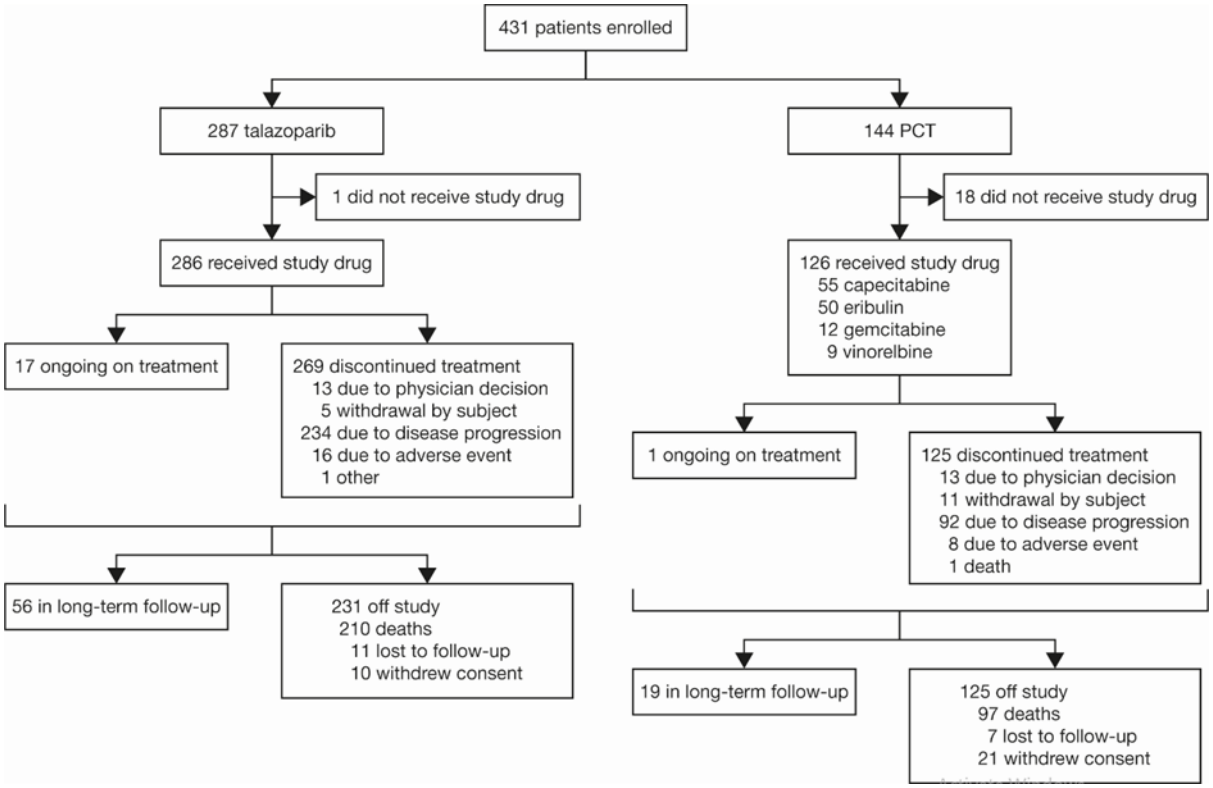


Figure 13. EMBRACA: Patient disposition flow chart at final data cut-off (ITT Population)

Source: Litton, 2020[80]

B.2.4.10.2. Baseline patient characteristics

Baseline characteristics of patients enrolled in the EMBRACA trial are summarised in Table 14.

In the EMBRACA trial, 431 patients were enrolled in the ITT population. The median age in the talazoparib and PCT groups were 45.0 (range: 27.0-84.0) and 50.0 (range: 24.0-88.0),[80] respectively. Of patients in the talazoparib arm, 63.4% were aged < 50 years and 46.5% in the PCT arm.[64] Almost all of the patients enrolled in both treatment arms were female (98.6% in talazoparib arm; 97.9% in PCT arm).[64] Additionally, most patients had mBC (94.4% in talazoparib arm; 93.8% in PCT arm).[64] In regards to *BRCA* status, a total of 133 patients (46.3%) were *BRCA*1-positive and 154 patients (53.7%) were *BRCA*2-positive in the talazoparib arm, whilst 63 patients (43.8%) were *BRCA*1-positive and 81 patients (56.2%) were *BRCA*2-positive in the PCT arm.[64]

Table 14. EMBRACA: Characteristics of participants in the studies across treatment groups

Baseline characteristic		EMBRACA (ITT population)[64,78,79]	
		Talazoparib	Overall PCT
Cohort size		287	144
Age	Median (range), years	45.0 (27.0 - 84.0)	50.0 (24.0 - 88.0)
	Mean (STD), years	47.5 (11.61)	49.4 (12.12)
Age category (years), n (%)	<50	182 (63.4)	67 (46.5)
	50 to <65	78 (27.2)	67 (46.5)
	≥65	27 (9.4)	10 (6.9)
Gender	Female	283 (98.6)	141 (97.9)
	Male	4 (1.4)	3 (2.1)
Height (cm)	Mean (STD)	163.2 (7.03)	162.4 (6.82)
	Median (range)	162.5 (142.0-188.0)	161.0 (147.0-180.0)
Weight (kg)	Mean (STD)	69.8 (17.24)	68.9 (16.36)
	Median (range)	65.6 (42.3-141.2)	66.0 (41.7-157.8)
BMI (kg/m^2)	Mean (STD)	26.1 (6.03)	26.1 (5.95)
	Median (range)	24.5 (17.2-49.6)	25.3 (17.3-56.2)
Race, n (%)	Asian	31 (10.8)	16 (11.1)
	Black or African American	12 (4.2)	1 (0.7)
	White	192 (66.9)	108 (75.0)
	Other	5 (1.7)	1 (0.7)
	Not reported	47 (16.4)	18 (12.5)
Ethnicity, n (%)	Not Hispanic or Latino	210 (73.2)	111 (77.1)
	Hispanic or Latino	31 (10.8)	15 (10.4)
	Not reported	46 (16.0)	18 (12.5)
ECOG performance status, n (%)	0	153 (53.3)	84 (58.3)
	1	127 (44.3)	57 (39.6)
	2	6 (2.1)	2 (1.4)
	Missing	1 (0.3)	1 (0.7)
Hormone receptor status, n (%)	Triple-negative	130 (45.3)	60 (41.7)
	HR-positive	157 (54.7)	84 (58.3)
BRCA status, n (%)	*BRCA*1-positive	133 (46.3)	63 (43.8)

Baseline characteristic		EMBRACA (ITT population)[64,78,79]	
		Talazoparib	Overall PCT
	*BRCA*2-negative	154 (53.7)	81 (56.2)
BC stage, n (%)	Locally advanced	15 (5.2)	9 (6.2)
	Metastatic	271 (94.4)	135 (93.8)
History of CNS metastasis, n (%)	Yes	43 (15.0)	20 (13.9)
Visceral disease, n (%)	Yes	200 (69.7)	103 (71.5)
Previous cytotoxic regimens for aBC, n (%)	0	111 (38.7)	54 (37.5)
	1	107 (37.3)	54 (37.5)
	1-2	NR	NR
	2	57 (19.9)	28 (19.4)
	3	12 (4.2)	8 (5.6)
	3-4	NR	NR
	≥ 5	NR	NR
Patients with ≥ 1 prior antineoplastic therapy for aBC		[redacted]	[redacted]

aBC: advanced breast cancer; BC: breast cancer; CNS: central nervous system: ECOG: Eastern Cooperative Oncology Group; ITT: intent-to-treat; kg: kilogram; m: meter; n: number of patients included in summary statistics; NR: not reported; PCT: physician's choice treatment; STD: standard deviation

B.2.5. Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

A summary of the statistical analysis of EMBRACA is provided in Table 15.

Table 15. EMBRACA: Summary of statistical analyses

	EMBRACA[90]
Hypothesis objective	The hypothesis was that treatment with talazoparib will improve PFS compared with physician's choice, in all randomised patients with germline *BRCA* mutations with locally advanced and/or mBC who had received prior chemotherapy regimens.
Analysis populations	Unless otherwise specified, efficacy analyses were performed in all randomised patient, defined as the intention-to-treat population. Unless otherwise specified, safety analyses were performed in all patients who had received either treatment (talazoparib or physician's choice), defined as the safety population.
Interim analysis	If the primary PFS analysis was statistically significant, a detailed interim analysis of OS of the ITT population at a 0.0001 significance level using Haybittle-Peto boundary was planned.
Statistical analysis of primary endpoints	Analysis of the primary endpoint, PFS was performed in the ITT population. Statistical significance of PFS was based on a stratified 2-sided log-rank test at a 0.05 significance level. The Kaplan-Meier (KM) method was used to estimate median PFS. A stratified Cox regression model was used to estimate the HR and the 95% CI.
Statistical analysis of secondary endpoints: OS, ORR, CBR24	Final OS analysis was conducted using a stratified 2-sided log-rank test in the ITT population. Median OS were estimated for each treatment group using the KM method and the 95% CIs were calculated. The HR was estimated using a stratified Cox regression model with treatment group as the only main effect. For ORR hypothesis testing, a stratified Cochran-Mantel-Haenszel method at a 0.05 significance level was used by the investigator to compare both treatment arms. Clinical benefit rate at 24 weeks (CBR24) by investigator assessment were compared between the 2 treatment arms for all patients in the ITT population. Patients who do not have any postbaseline tumour assessments were be considered responders. A point estimate of CBR24 weeks and the exact 95% CI are provided.
Statistical analysis of safety endpoints	All safety analyses will use the safety population, summarised by the actual treatment received. Descriptive statistics of safety are presented using MedDRA v18.0 and National Cancer Institute Common Terminology Criteria for Adverse Events (v.4.03).

Sample size, power calculation	The planned sample size of up to 429 patients considers the ability to verify comparisons of the primary endpoint (PFS) and key secondary endpoint (OS) between the treatment arms (talazoparib vs PCT). An exponential distribution was assumed for PFS and OS. Using a 2:1 randomization allocation ratio (talazoparib:PCT), the total number of PFS events needed to provide 90% power for a 2-sided log-rank test at a 0.05 significance level and hazard ratio (HR) of 0.67 was predicted to be 288.7 This equates to an increase in median PFS from 4.6 months in PCT arm to 6.9 months in talazoparib arm. In regard to OS, the total number of events needed to provide 80% power for a 2-sided log-tank test at a 0.05 significance level and HR of 0.72 is approximately 321. This equates to an increase in median OS from 20 months in PCT arm to 27.8 months in talazoparib arm.
Data management, patient withdrawals	Unless otherwise specified, missing data will not be imputed. Missing dates or partially missing dates were imputed conservatively for adverse events and prior/concomitant medications/procedures.
Censoring methods	If a patient meets the criteria for more than 1 censoring rule (see Table 2 in statistical analysis plan) PFS will be censored at the earliest censoring date.
CBR24: clinical benefit rate at 24 weeks; HR: hazard ratio; KM: Kaplan-Meier; mBC: metastatic breast cancer; ORR: objective response rate; OS: overall survival; PCT: physician's choice treatment; PFS: progression-free survival	

B.2.6. Critical appraisal of the relevant clinical effectiveness evidence

Quality assessment of the pivotal EMBRACA trial was conducted using the Centre for Reviews and Dissemination risk of bias question set, as recommended by NICE (Table 16).

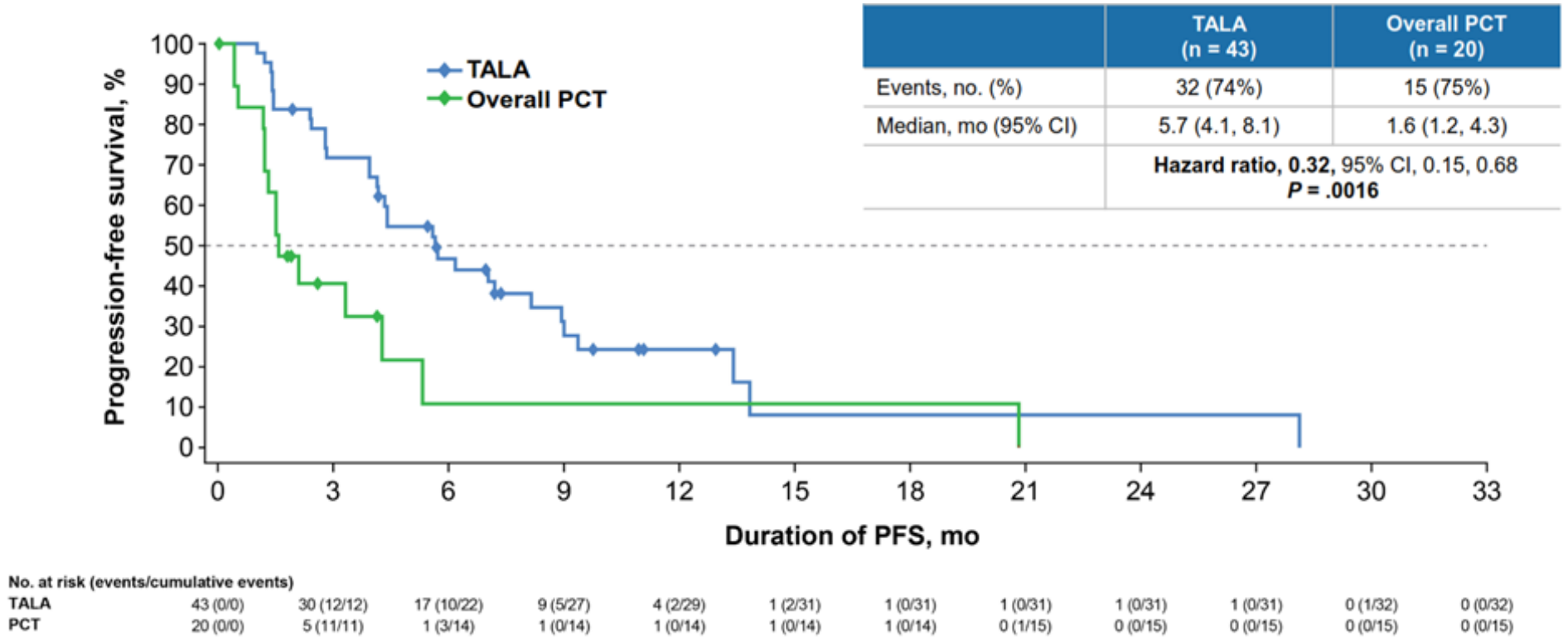
The complete quality assessments are shown in Appendix D.

Table 16. Quality assessment of the EMBRACA trial using Centre for Reviews and Dissemination risk of bias question set

Checklist questions	Trial (NCT number) Main publication (Author (year))
	EMBRACA (NCT01945775) Litton 2018[64]
Was the randomization method adequate?	Not clear
Was the allocation adequately concealed?	Yes
Were the groups similar at the outset of the study in terms of prognostic factors, for example severity of disease?	Not clear
Were the care providers, participants and outcome assessors blind to treatment? If any of these people were not blind to treatment allocation, what might be the likely impact on the risk of bias (for each outcome)?	No
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	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
Did the authors of the study publication declare any conflicts of interest?	Yes

B.2.7. Subgroup analysis

The results of subgroup analyses for the primary endpoint of median PFS are presented in Figure 15. The observed PFS benefit with talazoparib was consistent across prespecified and clinically relevant subgroups including HR+ status (TNBC or HR+), *BRCA*m (*BRCA1* or *BRCA2*), prior chemotherapy, and history of CNS metastases. In the CNS metastases subgroup, median PFS was 5.7 months (95% CI: 4.1, 8.1) vs 1.6 months (95% CI: 1.2, 4.3) in the talazoparib and PCT groups respectively (HR 0.32 (95% CI: 0.15, 0.68, *P* = 0.0016) (Figure 14).[91] OS subgroups results generally favoured talazoparib as shown in Figure 16.



	TALA (n = 43)	Overall PCT (n = 20)
Events, no. (%)	32 (74%)	15 (75%)
Median, mo (95% CI)	5.7 (4.1, 8.1)	1.6 (1.2, 4.3)
	Hazard ratio, 0.32, 95% CI, 0.15, 0.68 ***P* = .0016**	

Figure 14. EMBRACA: PFS history of CNS metastases subgroup

CI: confidence interval; CNS: central nervous system; mo: months; PCT: physician's choice of therapy; PFS: progression-free survival; TALA: talazoparib

Source: Litton, 2017[92]

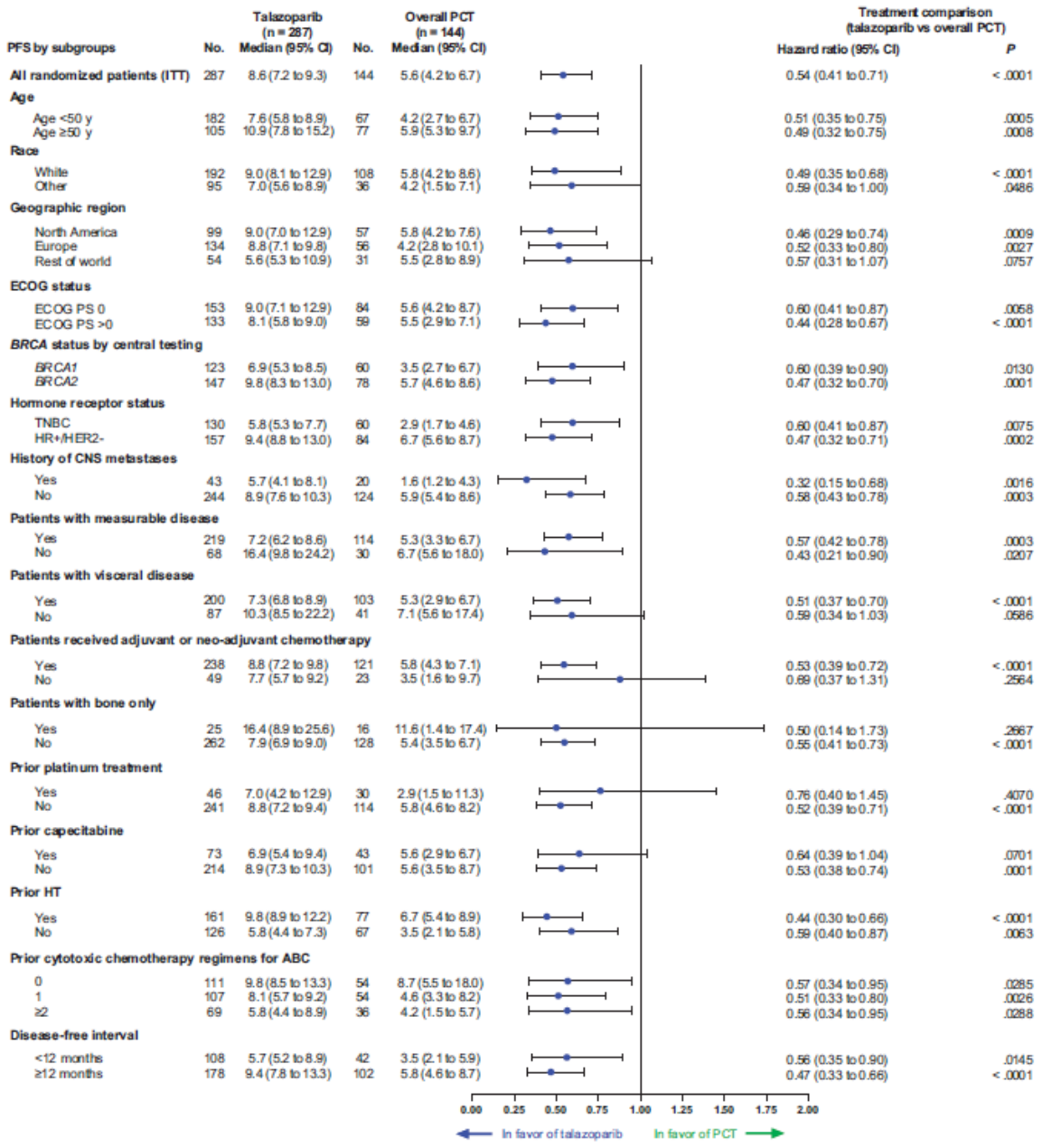


Figure 15. EMBRACA: Subgroup analysis for PFS

aBC: advanced breast cancer; *BRCA*1/*BRCA*2: breast cancer susceptibility gene 1 or 2; CI: confidence interval; CNS: central nervous system; ECOG PS: Eastern Cooperative Oncology Group performance status; HER2-: human epidermal growth factor receptor 2-negative; HR+: hormone receptor-positive; HT: hormone therapy; ITT: intent-to-treat; PFS: progression-free survival; TNBC: triple-negative breast cancer

Source: Rugo, 2020[91]

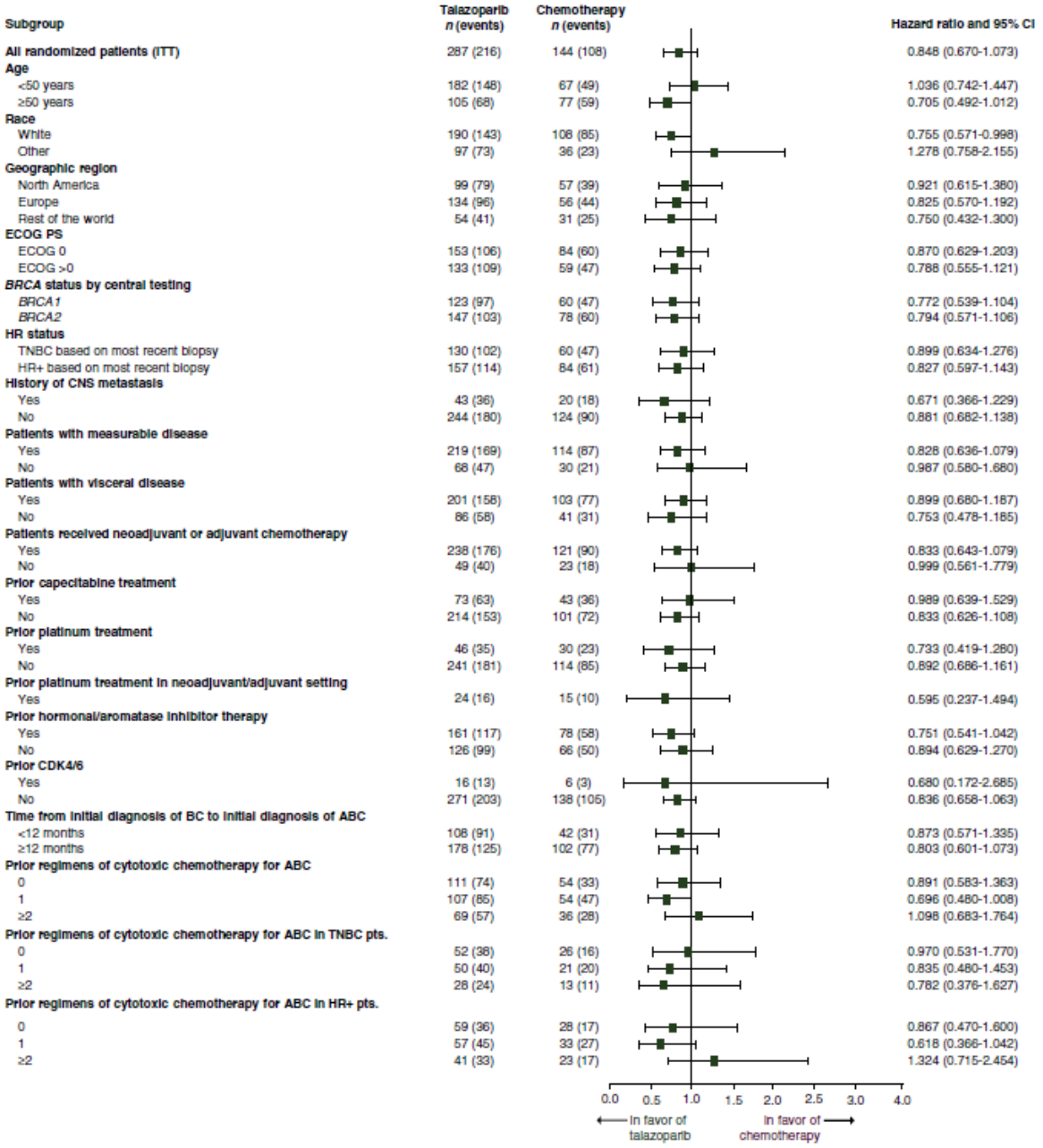


Figure 16. EMBRACA: Subgroup analysis for OS

The *BRCA* subgroup analysis included patients evaluated by a central test only; patients evaluated by local testing were excluded (n = 23)

aBC: advanced breast cancer; *BRCA*: breast cancer susceptibility gene; CDK: cyclin-dependent kinase; CI: confidence interval; CNS: central nervous system; ECOG: Eastern Cooperative Oncology Group; HR+: hormone-receptor positive; ITT: intent-to-treat; OS: overall survival; PS: performance status; pts: patients; TNBC: triple-negative breast cancer

Source: Litton, 2020[80]

B.2.8. Adverse reactions

Summary of safety evidence

- In the EMBRACA trial, AEs were reported in a similar proportion of patients, 98.6% in the talazoparib arm and 97.6% in the PCT arm. However, the proportion of patients reporting serious AEs (SAE) and grade 3 or 4 AE were higher in the talazoparib arm vs PCT, 36.0% and 31.0%, and 70.3% and 64.3% respectively.[88]
- The most frequent treatment-emergent AEs (TEAEs) (≥ 30%) for patients treated with talazoparib were anaemia (54.2%), fatigue (51.4%), nausea (49.7%), and headache (33.9%); in comparison to nausea (47.6%), fatigue (42.9%) and neutropenia (30.2%) for patients who received PCT.[88]
- The median duration of talazoparib treatment was 6.1 months (range, 0.03-36.9) compared with 3.9 months (range, 0.2-18.1) for the overall PCT arm.
- Overall, talazoparib was generally well tolerated with a consistent safety profile to that of the previous data cuts, the ABRAZO trial and real world evidence. Furthermore, the majority of frequently reported AEs in the talazoparib arm were consistent with other PARP inhibitors.

EMBRACA safety data is available as of the LSLV which occurred 05 March 2021 (database lock 22 March 2021) since the last data cut off on 30 September 2019.[88,89]

B.2.8.1. Extent of exposure

The study drug was received by 412 patients; 286 patients received talazoparib, and 126 patients received PCT which consisted of capecitabine ([redacted] patients), followed by eribulin ([redacted] patients), gemcitabine ([redacted] patients), and vinorelbine ([redacted] patients).[88,89] The median duration of exposure to talazoparib was [redacted] (range: [redacted]) and [redacted] months (range: [redacted] months) for patents in the PCT arm, respectively.[89] For patients receiving talazoparib, [redacted] than in patients treated with PCT. At 6 months, [redacted], [redacted] and [redacted], respectively.[89] The median of the relative dose intensity, was [redacted] (range: [redacted]) for the talazoparib arm compared with [redacted] (range: [redacted]) for capecitabine, [redacted] (range: [redacted]) for eribulin, [redacted] (range: [redacted]) for

gemcitabine, and [redacted] (range: [redacted]) for vinorelbine.[89] Duration of treatment and dose intensity for both treatment arms are summarised in Table 17.

Table 17. EMBRACA: Extent of talazoparib exposure

	Talazoparib (N=286)	Overall PCT (N=126)	Capecitabine (N=55)	Eribulin (N=50)	Gemcitabine (N=12)	Vinorelbine (N=9)
Study drug exposure (months) [1]						
n	286	126	[redacted]	[redacted]	[redacted]	[redacted]
Mean (STD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Min, Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Actual dose intensity (mg/day for Talazoparib and Capecitabine; mg/m^2/day for IV PCT) [2]						
n	286	NR	[redacted]	[redacted]	[redacted]	[redacted]
Mean (STD)	[redacted]	NR	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	NR	[redacted]	[redacted]	[redacted]	[redacted]
Min; Max	[redacted]	NR	[redacted]	[redacted]	[redacted]	[redacted]
Relative dose intensity (%) (mg/day for Talazoparib and Capecitabine; mg/m^2/day for IV PCT) [3]						
n	286	NR	[redacted]	[redacted]	[redacted]	[redacted]
Mean (STD)	[redacted]	NR	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	NR	[redacted]	[redacted]	[redacted]	[redacted]
Min; Max	[redacted]	NR	[redacted]	[redacted]	[redacted]	[redacted]

The date of database lock is 22 March 2021

N: Number of patients in the treatment group; NR: Not reported; PCT: Physician's Choice Therapies; IV: Intravenous; STD: standard deviation

[1]Study drug exposure is defined as (last dose date - first dose date +1) for talazoparib, (last dose date - first dose date +8) for capecitabine, (last dose date - first dose date +7) for vinorelbine, and (last dose date - first dose date +14) for eribulin and gemcitabine. For patients who were still on treatment, data analysis cut-off date is used as the last dose date of study drug if start date of last dose record before data cut-off date is available but stop date of this record is missing.

[2]Actual dose intensity is defined as the cumulative dose divided by study drug exposure.

[3]Relative dose intensity is defined as actual dose intensity divided by planned dose intensity. The planned dose (Cycle 1 Day 1) for capecitabine will be based on actual dose (in milligram), as the planned dose must be adjusted to account for capecitabine's fixed capsule strengths. Other agents will use the planned dose for this analysis.

Source: Supplemental LSLV CSR EMBRACA, 2021[89]

B.2.8.2. Overall adverse events

Overall, talazoparib was generally well tolerated with a consistent safety profile to that of the prior data cuts.[80,89]

AEs were reported in 98.6% (282 patients) in the talazoparib arm and 97.6% (123 patients) in the PCT arm (Table 18).[80,88,89] Drug-related AEs were reported by 89.5%

(256 patients) and 88.9% (112 patients) of patients in the talazoparib and PCT, respectively.[80,88,89] Serious AEs (SAE) were reported in 36.0% (103 patients) in the talazoparib arm and 31.0% (39 patients) in the PCT arm, while 10.8% (31 patients) and 8.7% (11 patients) drug-related SAEs were reported in the talazoparib and PCT arm.[80,88,89] Of patients in the talazoparib arm, 70.3% (201 patients) experienced a grade 3 or 4 AE (Table 20 and the supplemental LSLV EMBRACA CSR).[80,88,89] Further AE's are summarised in Table 19.

The most frequent treatment-emergent AEs (TEAEs) (≥30%) for patients treated with talazoparib was [redacted], [redacted], [redacted], and [redacted]; in comparison to [redacted], [redacted] and [redacted] for patients who received PCT as shown in Table 19 and the supplemental LSLV EMBRACA CSR.[80,88,89]

Table 18. EMBRACA: Summary of adverse events

Number of Patients Reporting at Least 1 TEAE	Talazoparib (N=286) (%)	Overall PCT (N=126) (%)
Any	282 (98.6)	123 (97.6)
Grade 3 or 4	201 (70.3)	81 (64.3)
Related to study drug	256 (89.5)	112 (88.9)
Leading to death	6 (2.1)	4 (3.2)
Serious	103 (36.0)	39 (31.0)
Serious and related to study drug	31 (10.8)	11 (8.7)
Grade 3 or 4 serious	83 (29.0)	34 (27.0)
Grade 3 or 4 related to study drug	167 (58.4)	62 (49.2)
Leading to study dose modification [1]	197 (68.9)	76 (60.3)
AEs as primary reason for permanent discontinuation [2]	15 (5.2)	7 (5.6)

The date of database lock is 22 March 2021
For all percentages, the denominator was the number of patients in each treatment group within the safety population.
Adverse event grades are evaluated based on NCI-CTCAE (version 4.03).
Related TEAEs are TEAEs that were judged by the investigators as possibly, probably, or definitely related to study drug.
Derived from AE CRF, Action taken.
Derived from the Treatment Discontinuation CRF.
N: Number of patients in the treatment group; PCT: physicians treatment choice; TRAE: treatment-related adverse events
Source: Supplemental LSLV CSR EMBRACA, 2021[89]; Supplemental full CSR EMBRACA, 2018[88]

Table 19. EMBRACA: TEAEs in ≥10% of patients in any treatment arm by decreasing frequency of preferred term

	Talazoparib (N=286) (%)	Overall PCT (N=126) (%)
Number of patients with at least 1 TEAE	282 (98.6)	123 (97.6)
Anaemia	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]
Palmar-plantar erythrodysaesthesia syndrome	[redacted]	[redacted]

The date of database lock is 22 March 2021

For all percentages, the denominator was the number of patients in each treatment group within the safety population.

Patients with multiple events for a given preferred term were counted once only for each preferred term. Events are sorted by decreasing frequency of preferred term in the talazoparib group.

MedDRA Version: 20.0

N: Number of patients in the treatment group; PCT: physicians treatment choice; TEAE: Treatment-Emergent Adverse Event

Full details are available in Section 12.2.2.1 Supplemental LSLV CSR EMBRACA, 2021[89]

Source: Supplemental LSLV CSR EMBRACA, 2021[89]

Table 20. EMBRACA: Grade 3 or 4 TEAEs in ≥ 2% of patients in either treatment arm by decreasing frequency of preferred term

	Talazoparib (N=286) (%)			Overall PCT (N=126) (%)		
	Grade 3	Grade 4	Total Grade 3/4	Grade 3	Grade 4	Total Grade 3/4
Patients with at least one Grade 3 or 4 TEAE	[redacted]	[redacted]	201 (70.3)	[redacted]	[redacted]	81 (64.3)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]*
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The date of database lock is 22 March 2021

For all percentages, the denominator was the number of patients in each treatment group within the safety population. Patients with multiple events grade 3 or 4 were counted once for each preferred term and overall under each column. For each preferred term, patients were only counted at highest TEAE grade. Events are sorted by decreasing frequency of preferred term in the Total Grade 3/4 talazoparib group. Adverse event grades are evaluated based on NCI-CTCAE (version 4.03). MedDRA Version: 20.0

*Note: 1 death, not specified as neutropenic sepsis

N: Number of patients in the treatment group; PCT: physicians treatment choice; TEAE: Treatment-Emergent Adverse Event

Full details are available in Section 12.2.2.1 Supplemental LSLV CSR EMBRACA, 2021[89]

Source: Supplemental LSLV CSR EMBRACA, 2021[89]; Supplemental full CSR EMBRACA, 2018[88]

B.2.8.3. Discontinuation due to adverse events

AEs as the primary reason for permanent discontinuation of talazoparib occurred in 5.2% (15 patients) of patients and 5.6% (7 patients) in the PCT arm as reported in Table 18.[88]

B.2.8.4. Deaths

As of the LSLV data cut-off, a total of 320 patients (77.7%) had died, 220 patients (76.9%) in the talazoparib arm and 100 patients (79.4%) in the PCT arm. Since the data cut-off date of the OS supplemental CSR, 5 additional deaths in the talazoparib arm and 1 additional death in the PCT arm were reported. In both arms, the majority

of deaths were attributed to disease progression, 91.8% in the talazoparib arm and 94.0% in the PCT arm.[88] A summary of deaths is provided in Appendix M.

B.2.8.5. Serious adverse events

SAEs were reported for [redacted] in the talazoparib arm and [redacted] in the PCT arm. Three additional SAEs were reported since the data cut-off date of the OS supplemental CSR, cellulitis in 1 patient, and pancytopenia and myelodysplastic syndrome in another patient who was subsequently diagnosed with AML after the safety reporting period of 30 days after last dose. The most frequently reported SAE in the talazoparib arm was [redacted], and [redacted] was the most frequently reported SAE in the PCT arm [redacted]. Serious TEAEs are summarised in Table 21. Study drug-related SAEs were reported in 10.8% (31 patients) of patients in the talazoparib arm and 8.7% (11 patients) in the PCT arm.[88]

Table 21. EMBRACA: Serious TEAEs in ≥ 2% of patients in any treatment arm by decreasing frequency of preferred term

	Talazoparib (N=286) (%)	Overall PCT (N=126) (%)
Number of patients with at least 1 serious TEAE	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

The date of database lock is 22 March 2021

For all percentages, the denominator was the number of patients in each treatment group within the safety population.

Patients with multiple events for a given preferred term were counted once only for each preferred term. Events are sorted by decreasing frequency of preferred term in the Talazoparib group.

N: Number of patients in the treatment group; PCT: physicians treatment choice; TEAE: Treatment-Emergent Adverse Event

Source: Supplemental LSLV CSR EMBRACA, 2021[89]

B.2.9. Ongoing studies

Additional evidence will become available from two of the real-world evidence studies described in Section B.2.4.7, the US retrospective chart study and the French phase IV ViTAL study.

B.2.10. Interpretation of clinical effectiveness and safety evidence

B.2.10.1. Principal findings from the clinical evidence

The clinical evidence supporting the use of talazoparib for the treatment of adult patients with g*BRCA1/2*m, who have HER2- LABC or mBC was derived from the EMBRACA and ABRAZO studies. Primary clinical evidence was obtained from the randomised controlled trial EMBRACA and supportive evidence is available from ABRAZO.

EMBRACA is a is a phase III, open-label, multicentre, randomised, parallel, 2-arm trial which demonstrated the benefits of talazoparib over PCT (standard therapies: capecitabine, eribulin, gemcitabine or vinorelbine) in terms of PFS, as described in Section B.2.4, as well as a significant impact on health related quality of life (HRQoL).

- Talazoparib treated patients had a 46% reduction in the risk of disease progression or death (HR: 0.542; 95% CI: 0.413, 0.711; $P < 0.0001$), almost doubling the 1-year PFS rate vs PCT (37% vs 20%).
- PFS sensitivity analyses supported the robustness of the primary analysis, and subgroup analyses were consistent with the primary PFS outcome.
- Analysis of ORR supported the primary analysis PFS benefit observed, with ORR by investigator assessment more than double with talazoparib vs PCT (62.6% vs 27.3%). Most notably, 12 patients (5.5%) in the talazoparib arm had complete response (CR) vs none in the PCT arm. A favourable treatment effect with talazoparib for ORR was also observed in relevant clinical subgroups, supporting the robustness of the results.
- Sustained responses were observed with talazoparib, as the median duration of response (DOR) for talazoparib was 5.4 months (interquartile range [IQR]: 2.8, 11.2 months) compared to 3.1 months (IQR: 2.4, 6.7 months) for PCT. At 1 year,

the probability of achieving a sustained response with talazoparib was 23% vs 0% with PCT.

- At the time of the final median OS analysis the estimated HR was 0.85 (95% CI: 0.67, 1.07; *P* = 0.169). The survival probability at 48 months was greater in the talazoparib group vs PCT (0.19 (95% CI: 0.14,0.25) vs 0.07 (95% CI: 0.02,0.15) respectively. Moreover, primary OS analysis is impacted by subsequent treatments, when adjusting for subsequent PARPi use, the HR for OS was 0.820 (95% CI: 0.617-1.047).[80] Therefore, the OS in the talazoparib arm may be underestimated.
- Furthermore, in all time-to-event analyses (PFS by independent radiology facility (IRF), PFS by investigator assessment, OS, and DOR), a subset of patients experienced a substantially longer duration of treatment effect, supporting the impression of sustained, long-term benefit with talazoparib.
- With respect to PROs, talazoparib treatment was associated with a statistically significant delay in time to clinically meaningful deterioration on the Global Health Status (GHS)/QoL and breast symptoms scale compared to PCT. There were also significant overall improvements in GHS/QoL and breast symptoms for patients treated with talazoparib compared to PCT.
- Talazoparib (1 mg/day) was generally well tolerated, and a low proportion of patients (7.7%) experienced an AE associated with permanent discontinuation of talazoparib. When needed, AEs were manageable through dosing interruption, dose reduction, and/or standard supportive medical therapy. The majority of frequently reported AEs in the talazoparib arm were consistent with what is commonly observed with other PARP inhibitors.

Together these data demonstrate the favourable risk-benefit assessment of talazoparib.

B.2.10.2. Strengths and limitations of the clinical evidence base

The main strengths of the clinical evidence base are set out in Section B.2.10.2.1 while limitations of the evidence are outlined in Section B.2.10.2.2. However, these limitations should be viewed within the context of the study strengths and the high unmet need in this patient population.

B.2.10.2.1. Strengths of the clinical evidence

Study population

Overall, the clinical evidence available provides an appropriate base to inform the assessment of clinical effectiveness and cost-effectiveness of talazoparib vs PCT, which is standard of care and recommended by ESMO guideline for g*BRCA*m patients previously treated with a taxane and/or anthracycline.

EMBRACA is a well-designed, phase III, randomised controlled trial which provided direct comparative evidence on the clinical efficacy of talazoparib vs PCT. Demographic characteristics were generally similar, however, a number of differences are noted and are detailed in Section B.2.10.2.2. Overall, the 431 patients randomised in EMBRACA were considered representative of patients with gBRCAm aBC. Generalisability to clinical practice in England is discussed in Section B.2.10.3.

The majority of the patients (44.1%) were enrolled in Europe (including [redacted]% in the UK) and 36.2% in the US,[78] therefore the study represents a Western population well.

PFS benefit and delayed progression

Talazoparib was associated with a significantly longer PFS than PCT (8.6 months vs 5.6 months), with an almost 50% reduction in the risk of disease progression or death, and almost double the 1-year PFS rate compared with PCT, further detailed in Section B.2.10.1. The results from ABRAZO further support the efficacy of talazoparib; treatment with talazoparib was associated with positive efficacy outcomes in heavily pre-treated HER2− aBC patients with g*BRCA1/2*m.[75]

PFS may be considered the most relevant endpoint in this setting, as once a patient has progression, subsequent therapies are likely to be a significant confounder for the assessment of OS. For example, 32.6% of patients in the PCT arm received subsequent PARPi compared to 4.5% in the talazoparib group and 14.6% in the PCT group received a PARPi and platinum compared to 2.4% in the talazoparib group. In contrast, PFS gives a clear picture of agent's efficacy in the treatment of g*BRCA*m

aBC after treatment with a taxane and/or anthracycline, regardless of subsequent treatment.

Furthermore, study publication Litton et al. (2020) highlights that there is continued justification for PFS as a surrogate for OS, with significant associations found between PFS and OS in patients with HER2- mBC.[80,93,94] This is further supported by meta-analyses in mBC and HR+ HER2- mBC patients, reporting significant correlations between PFS/time to progression and OS.[95,96]

The sustained responses observed with talazoparib compared to PCT (DOR: 5.4 months vs 3.1 months) are also very important to aBC patients, since delaying progression could slow the deterioration of QoL, discussed below.

HRQoL benefit

Maintaining QoL in patients with aBC is crucial. As part of the EMBRACA trial the EORTC QLQ-C30 questionnaire, a widely used and well validated instrument specifically designed to measure the QoL of people with cancer,[97] and the EORTC QLQ-BR23 breast cancer-specific questionnaire were used to measure PROs. These instruments record on domains relevant to g*BRCA1/2*m HER2- locally advanced or mBC patients, and in EMBRACA represent the first-ever detailed cancer-related and breast cancer-specific PROs regarding talazoparib in this patient population.[67]

The PRO results demonstrated that patients who received talazoparib had significant overall improvements and significant delay in time to deterioration in multiple cancer-related and breast cancer-specific symptoms, functions, and GHS/QoL as reported in study publication, Ettl et al. (2018).[67] Thus, the extensive positive cancer-related and breast cancer-specific PROs observed in EMBRACA support the idea that improved PFS with talazoparib translates to better QoL compared with PCT in patients with g*BRCA1/2*m aBC.

A large percentage of patients with aBC and bone metastases experience significant pain;[98] results from EMBRACA showed that talazoparib was associated with

significant overall improvement and a significant delay in time to deterioration in pain symptoms compared to PCT.

Furthermore, the results from EMBRACA support the positive risk-benefit profile of talazoparib and show that talazoparib does not impose toxicities that interfere with patient QoL.

B.2.10.2.2. Limitations of the evidence base

The evidence available from EMBRACA has some limitations.

Open-label design

The EMBRACA trial is an open-label study, necessitated by the mix of oral and intravenous treatment options in the PCT group, causing a number of limitations:

- A significantly higher number of patients in the PCT arm withdrew consent before receiving the first dose of trial drug, 18 patients compared to just 1 patient in the talazoparib arm. This led to censoring of data for the primary efficacy end point. However, to ensure robustness, the primary analysis was based on blinded independent central review of data in the ITT population.[64]
- Furthermore, the patient reported outcome results may be subject to patient biases; however, there is lack of clear empirical evidence that such biases are sufficient to significantly affect results of clinical trials.[99]

Study population

Differences were noted in several patient demographics:

- A slightly higher proportion of patients in the talazoparib arm had a baseline Eastern Cooperative Oncology Group (ECOG) status of 1 or 2 (46.4%) compared to patients in the PCT arm (41.0%).
- The median time from diagnosis of BC to diagnosis of advanced disease was shorter in the talazoparib arm than in the PCT arm (1.9 vs 2.7 years, respectively).
- The proportion of patients whose BC progressed to advanced disease within 12 months of initial diagnosis was higher in the talazoparib arm (37.6%) than in the PCT arm (29.2%).

Despite these differences, the baseline characteristics suggest that patients in the talazoparib arm likely had a slightly poorer prognosis than patients in the PCT arm.

Lack of patient reported outcomes for progressed patients

Despite ≥ 81% of patients in the talazoparib arm and ≥ 73% of patients in the PCT arm completing at least one question (baseline and post baseline) in each of the EORTC questionnaires for every cycle, from baseline to Cycle 13, the PRO results may have overrepresented the patients who do well in both treatment arms, since patients who progressed no longer completed the questionnaires.[67]

Lack of statistically significant improvement in overall survival

Talazoparib did not statistically significantly improve median OS over PCT (HR: 0.848; 95% CI: 0.670-1.073; *P* = 0.17); however, most patients received subsequent treatments, 46.3% and 41.7% received platinum chemotherapy and 4.5% and 32.6% received a PARPi in the talazoparib and PCT arms, respectively. RPSFTM analysis adjusting for subsequent PARPi and/or platinum showed that the primary OS analysis was impacted by these subsequent treatments.[80] Adjusting for subsequent PARP inhibitor and/or platinum chemotherapy use, the HR for OS was 0.756 (95% CI: 0.503-1.029) and when adjusting for PARPi only, the HR for OS was 0.820 (95% CI: 0.617-1.047), suggesting that the primary OS analysis underestimates the treatment benefit of talazoparib.[80] Therefore, the influence of subsequent treatments on the post-progression survival (PPS); the time from progression to death) needs to be addressed in order to understand the effects of talazoparib in the trial.[80] Variability in PPS, influenced by subsequent treatments, can dilute the OS benefit so that the ability to detect statistical significance is minimised.[80,100]

In addition, pre-specified subgroup analysis showed generally consistent results across subgroups, as described in Section 2.7.

Nevertheless, as described in Section B.2.10.2.1, PFS may be the most relevant endpoint in this treatment setting, as extending PFS will result in patients accruing

more survival time before moving into the next treatment line and can therefore be expected to extend survival regardless of subsequent treatment outcomes.

B.2.10.3. External validity of study results to patients in routine clinical practice

Patients enrolled in EMBRACA can be considered broadly representative of UK practice, in terms of baseline characteristics, as confirmed by UK clinician opinion.

B.2.10.4. Relevance of the evidence base to the decision problem

The submission presents two studies, one of which is a randomised controlled trial evaluating the efficacy and safety of talazoparib vs PCT in patients with g*BRCA1/2*m who received no more than 3 prior cytotoxic chemotherapy regimens for LABC or mBC. This is directly relevant to the decision problem, both in terms of the population and the comparators (vinorelbine, capecitabine, eribulin). Furthermore, outcomes considered in the submission closely mirror the decision problem set out by NICE.

The evidence base presented within this submission represents the best available evidence and is directly relevant to the decision problem.

B.3 Cost effectiveness

Summary of cost-effectiveness

- A cohort partitioned-survival model (PSM) was developed to assess the cost-effectiveness of talazoparib compared with PCT combined for adults with *BRCA* 1 or 2 mutated aBC who have been treated with chemotherapy in the neoadjuvant, adjuvant, or metastatic setting (consistent with the population in the EMBRACA trial).
- Use of talazoparib will result in additional discounted quality-adjusted life years (QALYs) and life years (LYs) of [redacted] and [redacted], respectively, compared to PCT combined
- Discounted incremental costs were estimated to be [redacted] under base case assumptions and the resultant incremental cost-effectiveness ratio (ICER) was £34,644 per QALY, which is cost-effective at a willingness-to-pay threshold of £36,000 per QALY with a severity modifier of 1.2 applied.
- Uncertainty in the model was explored in probabilistic and deterministic sensitivity analysis. Results from 1,000 iterations of the model using probabilistic values shows that there is limited spread in the results from each iteration and these are predominately contained in the north-east quadrant, demonstrating cost effectiveness.
- The largest drivers of uncertainty in the deterministic sensitivity analysis are the acquisition cost of talazoparib, subsequent treatment costs and model time horizon.
- Extensive scenario analyses were undertaken, reflecting the assumptions required to undertake plausible, robust and transparent base case analysis.

B.3.1. Published cost-effectiveness studies

In line with the NICE guide to the methods of technology appraisal 2013,[2] a SLR was conducted to identify cost-effectiveness studies for the treatment of HER2- LABC or mBC. In brief, electronic database searches (MEDLINE, Embase, International health technology assessment (HTA) database, NHS Economic Evaluation

Databases and EconLit) were conducted on 31 August 2022 and were designed to capture cost-effectiveness evidence.

A total of 30 unique studies describing full economic evaluations of interventions aimed at managing HER2- LABC or mBC were identified and summarised in Appendix G. Full details and results of the cost-effectiveness SLR, including PRISMA diagrams, are also provided in Appendix G.

B.3.2. Economic analysis

The economic case presented in this submission is based on conventional cost-effectiveness analysis, assessing the use of talazoparib versus relevant comparators.

B.3.2.1. Patient population

This economic evaluation considered the use of talazoparib for the treatment of adults with deleterious or suspected deleterious g*BRCA1/2*m, HER2- LABC or mBC who have been previously treated with an anthracycline and/or a taxane in the (neo)adjuvant, locally advanced or metastatic setting. This population matches the target population as defined in the EMBRACA trial and is in line with the licensed indication as noted in Section B.1.1.[4]

In the base case analysis, baseline patient parameters are derived from the baseline characteristics of patients enrolled in EMBRACA, as detailed in Table 22.

Table 22. Baseline parameters: patient characteristics (ITT population)

Characteristic	Mean value	Source
Baseline age, years (STD)	[redacted]	EMBRACA OS supplemental CSR[81]
Baseline weight, kg (STD)	[redacted]	
Body surface area, m^2*	[redacted]	
Proportion male (%)	[redacted]	

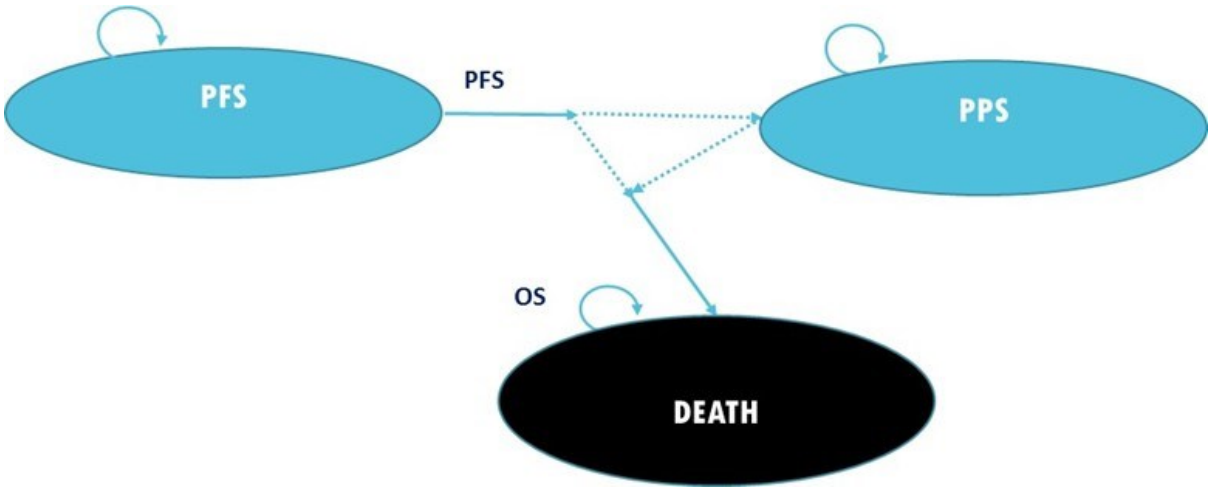
CSR: clinical study report; ITT: intention-to-treat; OS: overall survival; STD: standard deviation

* Body surface area is calculated as SQRT (height x weight/3600). The height is 162.9 cm sourced from EMBRACA OS supplemental CSR[81]

B.3.2.2. Model structure

A cohort partitioned-survival model (PSM) has been utilised for the analysis (Figure 17). This type of model is frequently used to model cancer treatments, with separate survival equations for overall survival and progression-free survival. The use of this model is in line with previous breast cancer TAs which are summarised in Table 23. The model employs a Markov cohort approach that follows patients as they transition between health states that reflect the disease progression and treatment patterns of aBC. The three health states modelled were progression-free (PF), post-progression (PP), and death. For the adequate modelling of treatment-related costs, it is necessary to keep track of treatment status within the PF state.

Figure 17. Model diagram of survival partition approach



Dotted lines represent the fact the transitions between health states are not directly tracked, but proportions of patients in each health state are calculated through the partition approach at each time point.

OS: overall survival; PFS: progression-free survival; PPS: post-progression survival

Patients who are eligible for treatment enter the model, initiate treatment, and experience an interval of PFS. Patients who experience disease progression and who do not die during the initial modelled line of treatment continue to the PP health state and may receive subsequent treatments. Patients may die at any timepoint in the model. Death is an absorbing state.

Costs were assigned to each health state, and utilities were applied according to patients' disease progression status and type of treatment received.

The analysis was performed from an NHS perspective. A cycle length of 3 weeks was used, reflecting treatment cycles for patients and the frequency of follow-up. A half-cycle correction is applied to all costs and outcomes other than first-line drug and administration costs (which were assumed to be incurred at the start of each cycle) to improve the accuracy of the results by averaging outcomes between the beginning and end of each cycle, in line with previous submissions TA639, TA816 and TA819.[53,55,101]

A lifetime horizon of 10 years was considered in the model. Discount rates of 3.5% were applied to both costs and benefits in line with the NICE methods guide. A summary of the features of the PSM is presented in Table 23.

Table 23. Features of the economic analysis

Factor	Previous evaluations					Current evaluation	
	TA423[102]	TA515[103]	TA639[55]	TA816[101]	TA819[53]	Chosen values	Rationale
Submission	Eribulin for treating locally advanced or mBC after 2 or more chemotherapy regimens	Eribulin for treating LABC or mBC after 1 chemotherapy regimen	Atezolizumab with nab-paclitaxel for untreated PD-L1-positive, LABC or mBC, TNBC	Alpelisib with fulvestrant for treating HR+, HER2-, PIK3CA-mutated aBC	Sacituzumab govitecan for treating unresectable advanced TNBC after 2 or more therapies	Talazoparib for treating HER2-LABC or mBC with g*BRCA1/2*m	-
Model approach/ structure	Three-state PSM	Three-state PSM	Three-state PSM	Three-state PSM	Three-state PSM	Three-state PSM	Appropriate for modelling disease area, consistent with previous HTA submissions for aBC.
Time horizon	5 years	5 years	15 years	Lifetime (assumed to be 40 years)	10 years	Lifetime horizon of 10 years.	NICE reference case and consistent with previous HTA submission in TA819, considered appropriate by ERG.
Cycle length	3 weeks	1 month	1 week	4 weeks	1 week	3 weeks	Cycle length reflects the treatment cycles for patients and the frequency of follow-up, minimum time during which symptoms or response can change. Consistent with previous HTA

Factor	Previous evaluations					Current evaluation	
	TA423[102]	TA515[103]	TA639[55]	TA816[101]	TA819[53]	Chosen values	Rationale
							submission in TA423 considered appropriate by ERG
Half-cycle correction	No	No	Yes	Yes	Yes	Yes	NICE reference case
Treatment waning	None	None	None	None	None	None	PFS from the EMBRACA trial was considered mature and OS data are available for 5 years. As a result, treatment waning effect was captured in the trial.
Source of clinical efficacy data	Within-trial comparison only, no ITCs used. PFS data were mature and therefore no extrapolation was applied.	Within-trial comparison only, no ITCs used	Within-trial comparison; ITC used	Within-trial comparison; Bucher ITC used	Within-trial comparison only, no ITCs used	Within-trial comparison only	NICE reference case
Source of utilities	EORTC-QLQ C30 in the Study 301 trial mapped to EQ-5D-3L via	Same utility mapping algorithm and same ERG	EQ-5D-5L mapped to EQ-5D-3L from	Utility values were estimated from EQ-5D-5L data from the SOLAR-1 trial	EORTC-QLQ C30 in the ASCENT trial mapped to EQ-5D-3L via	EORTC QLQ-C30 data from EMBRACA were mapped to EQ-5D-3L based on the algorithm described	NICE reference case

Factor	Previous evaluations					Current evaluation	
	TA423[102]	TA515[103]	TA639[55]	TA816[101]	TA819[53]	Chosen values	Rationale
	published algorithm.[104] Note: ERG considered it inappropriate as it was based on trial results from untreated LABC with good baseline health status.	comments received as in submission TA423 (third-line).	Impassion130, literature	(using the UK tariff), mapped onto the EQ-5D-3L;	published algorithm[105]	in Longworth 2014.[105]	
Source of costs	NHS reference costs; PSSRU; BNF/eMIMS; literature; expert opinion	NHS reference costs; PSSRU; BNF/eMIMS; literature; expert opinion	NHS reference costs; PSSRU; BNF/eMIMS; Published literature; Expert opinion input;	Resource use inputs were derived from NHS reference costs 2019–2020 and NICE TA687/TA593 where applicable; Drug costs were derived from the BNF and eMIT.	NHS reference costs; PSSRU; BNF/eMIT/MIMS; literature; expert opinion	2020/21 National Cost Collection data ;[106] PSSRU;[107] BNF/eMIT/MIMS;[108-110] Published literature; expert opinion	NICE reference case

aBC: advanced breast cancer; BNF: British National Formulary; eMIT: electronic market information tool; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ-5D-3L: EuroQoL 5-dimensional 3-level index; ERG: evidence review group; g*BRCA1/2*m: germline breast cancer susceptibility gene 1 or 2 mutation; HER2-: human epidermal growth factor receptor negative; HR+: hormone receptor positive; HTA: health technology assessment; ITC: indirect treatment comparison; LABC: locally advanced breast cancer; mBC: metastatic breast cancer; MIMS: Monthly Index of Medical Specialties; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; PD-L1: programmed cell death ligand 1; PFS: progression-free survival; PSM: partitioned-survival model; PSSRU: Personal Social Services Research Unit; TA: technology appraisal; TNC: triple negative breast cancer

B.3.2.2.1. Modelling approach to track progression and death

A survival partition approach was applied to track patients' progression and death using treatment-specific and -independent PFS and OS curves. A survival partition approach does not directly calculate transitions between health states but partitions the modelled population into groups. The method postulates that at any timepoint, the proportion of patients falling under the PFS curve is in the "PF" health state, the proportion of patients falling above the OS curve is in the "Dead" health state, while whoever remains must be in the "PP" health state (Table 24).

Table 24. Health state occupancy

Health state	Occupancy at time (t)
Progression free	PFS(t)
Post progression	OS(t) – PFS(t)
Death	1 – OS(t)
OS: overall survival; PFS: progression-free survival	

While in the PF state, patients can be classified further as responders or non-responders. Furthermore, while in the PF state, patients are classified as on treatment or off treatment. "On treatment" includes patients who receive active therapies, while "off treatment" includes patients who have discontinued these therapies.

B.3.2.2.2. Derivation of health state occupancy estimates

Health state occupancy is defined by treatment specific PFS and OS extrapolations, derived from available data. It is assumed that OS data implicitly include the effects of any subsequent treatment that may have been administered; hence, the benefits of subsequent treatment are captured.

In the base-case model, parametric models were fitted to PFS and OS KM data. It needs to be noted that although PFS data is considered mature, a parametric approach was chosen to smooth out the tail of the KM data for PFS but not to extrapolate over long-term. For details on selection of the most appropriate parametric models, refer to Section B.3.3.2.

B.3.2.2.3. Derivation of treatment line occupancy

Patients enter the model and receive talazoparib or a comparator treatment. Following progression, patients receive a subsequent line of therapy. As a simplifying assumption, it is assumed that patients may not discontinue this final line of therapy until death.

B.3.2.2.4. Outcome measures

The primary model output is the ICER expressed as incremental costs per QALY gained. Additionally, the model provides an overview of other outcomes, such as LYs gained and clinically relevant outcomes, such as predicted median OS and PFS.

B.3.2.2.4.1. Treatment Response

Within the PF state, a certain proportion of patients (i.e., “responders”) responded to the treatment and achieved objective responses (CR or partial response [PR]) for a certain amount of time, while the remaining patients stayed in stable disease (SD). The ORR was specified as the proportion of patients with a CR or PR as defined by the modified Response Evaluation Criteria in Solid Tumours 1.1 in the target population with measurable disease population by investigator.

DOR, defined as the time from objective response until disease progression or death, was not available for all comparators or any subgroups. Thus, a time-dependent response ratio based on DOR was not feasible; instead, a constant ratio of responders vs. non-responders was assumed throughout the PF duration. In EMBRACA, the reported median DOR was 5.4 months for talazoparib treated patients, and 3.1 months for those treated with PCT.[64]

The current base case analysis allows response criteria to impact utilities and MRU patterns.

B.3.2.2.4.2. Treatment Duration

Median treatment duration from EMBRACA was used to model treatment duration for talazoparib and PCT combined.

B.3.2.3. Intervention technology and comparators

The intervention in this submission is talazoparib and the comparator considered is PCT combined. The proportion of treatments in the PCT arm of the EMBRACA trial[64] were reweighted to exclude gemcitabine, to align with the final NICE scope, resulting in capecitabine (48%), eribulin (44%) and vinorelbine (8%).

Talazoparib was compared with PCT combined to reflect the within-trial comparison. It was assumed that the four individual treatments (capecitabine, eribulin gemcitabine, and vinorelbine) used in EMBRACA have comparable efficacy, an assumption which was validated with UK clinical input. Thus, re-weighting to exclude gemcitabine the pooled efficacy of PCT combined was considered reflective of the efficacy of the three remaining comparators and was applied in the model. Therefore, the change of composition only affects the treatment cost estimation of PCT combined.

B.3.3. Clinical parameters and variables

B.3.3.1. Evidence synthesis

Evidence to describe the effectiveness of talazoparib for g*BRCA*1/2m, HER2-, LABC or mBC patients who have been previously treated with an anthracycline and/or a taxane is primarily derived from EMBRACA, a phase III, open-label, RCT evaluating the efficacy and safety of talazoparib versus PCT in patients with g*BRCA*1/2m, HER2- LABC or mBC who have received prior chemotherapy for aBC. In the base case analysis, talazoparib efficacy was derived from the talazoparib arm of EMBRACA, while PCT combined efficacy was derived from the PCT arm. As such, there was no requirement to synthesise evidence in the base case analysis.

B.3.3.2. Survival analysis approach

As described in Section B.3.2.2.2, extrapolation of survival data from the study was required to inform long-term outcomes for PFS and OS, undertaken with reference to the guidance from the NICE Decision Support Unit (DSU)[83] and Bagust and Beale (2014).[111] The model selection algorithm was used to select a suitable model.

Further details of the methods used are provided in Appendix O.

Since the follow-up period of the EMBRACA trial was shorter than the time horizon of the model, parametric distributions were fitted to PFS and OS KM curves derived from EMBRACA individual patient data (IPD) to estimate patients in the PF and PD health states for talazoparib and PCT.

The extrapolated OS and PFS curves were compared to observed EMBRACA data visually and statistically (using Akaike Information Criteria (AIC) and Bayesian Information Criteria (BIC) goodness of fits statistics) as much as possible. This method informed selection of the most appropriate modelling approach and fits as a form of validation.

Parametric curves were fitted separately to the talazoparib and PCT arms, as it is generally considered unnecessary to rely on a proportional hazards assumption when patient-level data are available (NICE technical support document 14).[112] Curve selection was based on statistical goodness-of-fit to the observed data, visual inspection and clinical opinion.

Parametric survival functions were fitted to the extracted data using the R statistics environment, including exponential, Weibull, Gompertz, log-logistic, log-normal, and generalised Gamma distributions, undertaken with reference to the guidance from the NICE DSU.[112]

Goodness-of-fit was evaluated using the AIC and BIC; minimisation of these measures is used to indicate goodness-of-fit whilst penalising overfitting, so that a smaller value demonstrates a more appropriate fit. In addition to assessment of goodness-of-fit statistics, the appropriateness of the parametric extrapolation was by visual inspection of the fit over the observed period and consideration of the log cumulative hazard plots.

It is worth noting that while the above methods for validating the extrapolation of progression and death events are appropriate, they are also necessarily constrained by derivation from observed data, which is, as previously indicated, limited by the uncertainty in the tail of the data. Therefore, the plausibility of the extrapolation was assessed through consideration of the long-term hazard profile and the extrapolated

mean survival estimates. Additionally, clinical expert opinion was sought to ensure that the results of survival extrapolation are considered clinically plausible.

B.3.3.2.1. Progression-free survival

Clinical data on PFS to inform the base case analysis was derived from EMBRACA trial interim data cut-off of September 15, 2017.

Parametric survival curves were fitted to the KM data from EMBRACA, with goodness-of-fit (AIC and BIC) and visual inspection used to evaluate the best fit.

Figure 18 and Figure 19 present PFS extrapolations for talazoparib and PCT respectively.

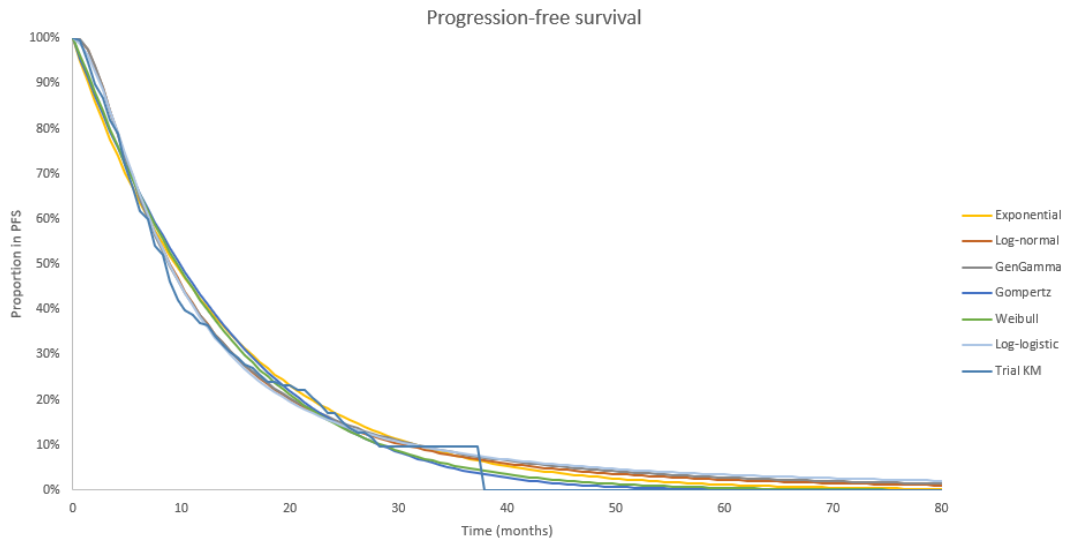


Figure 18. EMBRACA from September 2017 DBL, Talazparib: Parametric PFS models overlaid upon Kaplan-Meier curve

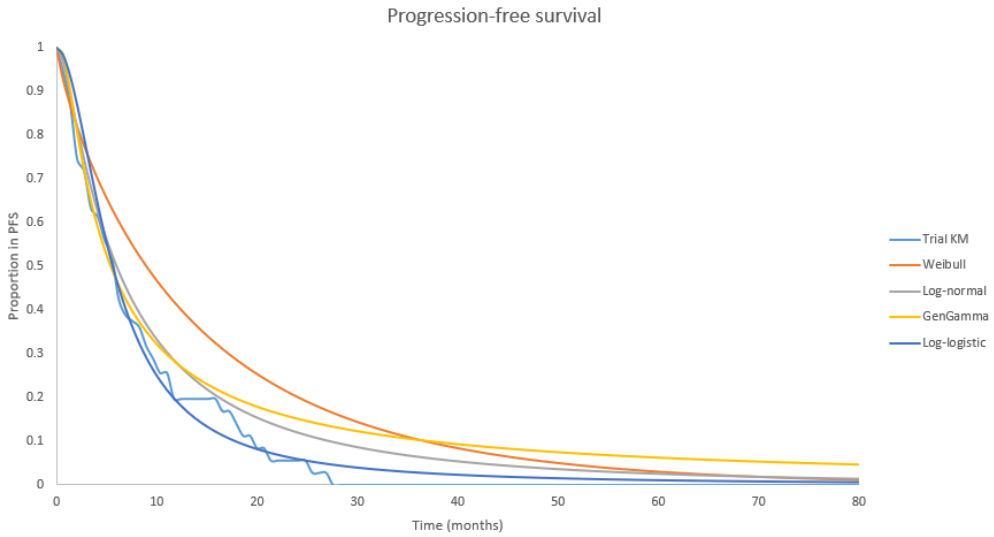


Figure 19. EMBRACA from September 2017 DBL. PCT: Parametric PFS models overlaid upon Kaplan-Meier curve

AIC and BIC for talazoparib and PCT are presented in Table 25. The log-normal and log-logistic distributions were the best fit to the talazoparib and PCT data, respectively. With the different mechanism of action of PARPi and conventional chemotherapies included in the PCT arm, fitting different distributions to the two arms is considered to be appropriate. Outcomes from alternative parametric distributions will be presented as scenario analyses (see B.3.11.3).

Table 25. AIC and BIC statistics

	Talazoparib			PCT		
	AIC	**BIC**	**PFS Mean**	**AIC**	**BIC**	**PFS Mean**
Exponential	1296.788	1300.448	14.04	N/A	N/A	N/A
Generalised gamma	1264.488	1275.466	14.97	485.3214	494.2308	14.79
Gompertz	1296.567	1303.886	13.17	N/A	N/A	N/A
Log-logistic	1267.564	1274.883	15.55	487.9142	493.8538	9.40
Log-normal	1262.668	1269.987	14.48	498.875	498.875	12.22
Weibull	1283.764	1291.083	13.26	544.6547	550.5943	15.35
AIC: Akaike Information Criteria; BIC: Bayesian Information Criteria; PCT: physican's choice treatment; progression free survuial						

Table 26. Best parametric fit used in the base case (PFS)

Population	Best parametric fit	
	Talazoparib	PCT
Overall (n=431)	Log-normal (n=287)	Log-logistic (n=144)
PCT: physician's choice therapy.		

The median PFS reported from trials and modelled for each treatment is presented in Table 27. Appendix O presents the PFS curves applied in base case for all treatment comparators for HER2- patients in all treatment lines.

Table 27. Median PFS by treatment from trial and modelled (base case)

Treatment comparator	Median PFS reported from trial (months)	Median PFS modelled (months)	Source/assumption
Talazoparib	8.6	8.6	EMBRACA IPD
PCT combined	5.6	5.6	
1L: first-line; HER2-: human epidermal growth factor receptor 2-negative; HR+: hormone receptor-positive; IPD: individual patient data; PCT: physician's choice therapy; PFS: progression-free survival; TNBC: triple-negative breast cancer. Note: PFS data was based on EMBRACA trial data cut-off date of September 15, 2017			

B.3.3.2.2. Overall survival

OS data was derived from EMBRACA data cut-off of September 30, 2019. OS KM curves derived from EMBRACA IPD were directly used to estimate patients for talazoparib and combined PCTs. Parametric fittings providing the best goodness of fits and reasonable long-term projection are presented in Table 29.

As discussed in Section B.2.4.2, 32.6% of patients in the PCT arm of EMBRACA received subsequent treatment with a PARPi compared to 4.5% in the talazoparib arm. A RPSFTM analysis adjusting for subsequent use of PARPi was carried out on EMBRACA KM data.[88] The crossover adjusted HR for OS was 0.820 (95% CI: 0.617-1.047),[80] which was applied to the unadjusted PCT OS data and included in the base-case to account for treatment switching. This was in order to provide an unbiased estimate of the treatment effect on OS as if patients in the chemotherapy arm had not received a PARPi after discontinuation of chemotherapy, leading to an adjusted median OS of 17.6 months (Table 30).

Overall, given the maturity of the data from EMBRACA, mean survival predicted by various distributions are within a reasonable range (Table 30). The KM curves and fitted curves are presented in Appendix O for talazoparib and PCT combined.

Table 28. AIC/ BIC for extrapolations of OS data by treatment

	Talazoparib			PCT		
	AIC	**BIC**	**OS mean**	**AIC**	**BIC**	**OS mean**
Exponential	1896.078	1899.723	29.8	918.786	921.727	26.0
Generalised gamma	1852.246	1863.140	32.0	905.445*	914.183*	N/A*
Gompertz	1894.653	1901.929	27.6	907.250	913.105	23.3
Log-logistic	1851.914	1859.190	33.0	910.924	916.778	31.4
Log-normal	1850.412	1857.688	31.1	919.562	925.416	29.6
Weibull	1876.446	1883.723	27.4	903.423	909.277	23.9
* Generalized gamma cannot be used in the modelling due to non-convergence for PCT arm						

Table 29. Best parametric fit used in the base case (OS)

Population	**Best parametric fit**
	Talazoparib
Overall (n=431)	Log-normal (n=287)

The median OS reported from trials and modelled for each treatment are presented in Table 30.

Table 30. Median OS by treatment from trials and modelled in base-case analysis

Treatment comparator	**Median OS reported from trial (months)**	**Median OS modelled (months)**	**Mean OS modelled (months)**	**Source/assumption**
Talazoparib	19.3	20.4	31.1	EMBRACA IPD
PCT Combined	19.5	17.6	25.3	
	IPD: individual patient data; OS: overall survival; PCT: physician's choice therapy.			

B.3.3.2.3. Clinical rationale and validation of survival extrapolation

The method of fitting observed EMBRACA data visually and statistically as much as possible informed selection of the most appropriate modelling approach and fits as a form of validation.

Additionally, it was possible to validate the survival extrapolations for the talazoparib and PCT arm against longer-term survival data from literature (see B.3.14.2 for further details).

Table 31. Survival extrapolations applied in the economic model (base-case analysis)

	Talazoparib	PCT combined
OS	Parametric; Log-normal	RPSFTM adjusted HR
PFS	Parametric; Log-normal	Parametric; Log-logistic
OS: overall survival; PFS: progression-free survival		

B.3.3.2.4. All-cause mortality

To model the death state both disease related mortality and background mortality have been incorporated in the cost-effectiveness model. The model used the baseline characteristics of age and gender from the EMBRACA RCT to include age and gender-adjusted mortality, participating based on UK lifetables.[113] These are included in every cycle in addition to the disease-related mortality values and are applied multiplicatively. It is acknowledged that there exists the possibility of some deaths occurring in the RCT that were non-cancer related, and therefore some form of double counting could occur. This possibility exists in many RCTs and as the effect applies equally to all treatments, it is likely to have a negligible impact on predicted survival (and hence cost-effectiveness).

B.3.3.3. Treatment discontinuation

As described in Section B.3.2.2.4.2, median treatment duration from EMBRACA IPD was used to model treatment duration for talazoparib and PCT in the base case.

B.3.3.4. Adverse events

Treatment-related AEs are an inevitable consequence of any intervention, and these events are applied in the economic model, affecting the costs and disutilities accrued by patients on each intervention.

The ten most frequently occurring treatment-related grade 3–4 serious AEs were included in the economic model. Each treatment has a unique AE profile, with each

AE requiring an AE-specific cost of management in the cycle in which the AE occurs. Each AE also has an AE specific utility decrement, applied additively to the health state utility values in the cycle in which the AE occurs.

These AEs were applied in the model as a one-off cost in the first cycle only upon treatment initiation. Therefore, the proportion of the cohort demonstrated in Table 32 receives the costs and utility decrements associated with that AE.

Table 32. Incidence of grade 3 and 4 AEs (%)

AE	Talazoparib (n = 286)			PCT combined (n =126)		
	n	%	SE	n	%	SE
Total patients with an event	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA
Anaemia	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA
Diarrhoea	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA
Fatigue	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA
Hand and Foot Syndrome	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA
Leukopenia	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA
Nausea	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA
Neuropathy	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA
Neutropenia	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA
Thrombocytopenia	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA
Vomiting	[redacted]	[redacted]	NA	[redacted]	[redacted]	NA

AE: adverse event; CSR: clinical study report; PCT: physician's choice treatment; SE: standard error.
Source: Supplemental LSLV CSR EMBRACA, 2021[89]

B.3.4. Measurement and valuation of health effects

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

EORTC QLQ-C30 data was collected during EMBRACA trial but not EQ-5D data. Therefore, the EORTC QLQ-C30 data from the September 2019 DBL were mapped to EQ-5D-3L based on the algorithm described in Longworth 2014.[105] Details of the mapping are described in B.3.4.2.The results were used to inform utilities for the PF health state (CR/PR and SD). The utility estimate for progressive disease was derived from the literature. A summary of all health-specific utility used is presented in Table 33.

Table 33. Health state utility values

Treatment arm	Health state		
	PFS – CR/PR (EMBRACA-based)	PFS – SD (EMBRACA-based)	Progressive disease
Talazoparib	[redacted]		[redacted]
PCT combined	[redacted]		
Source	EMBRACA IPD		Average of Lambert-Obry[114] and Huang[115] (see Appendix H)

CR: complete response; IPD: individual patient data; NICE: National Institute for Health and Care Excellence; PCT: physician's choice treatment; PFS: progression-free survival; PR: partial response; SD: stable disease

B.3.4.2. Mapping

Utility values were applied to each health state and event in the model to capture patient QoL associated with treatment and disease outcomes. Utility values were derived from analysis of EORTC QLQ-C30 data from EMBRACA trial.

EORTC QLQ-C30 data was collected in the EMBRACA trial and was mapped to EQ-5D-3L based on the algorithm described in Longworth 2014.[105] There were 371 subjects with 3,220 observations. Average baseline utility was estimated using a linear regression model because there was only one observation per subject. The analysis results show there is no difference in baseline utility between the two arms: 0.679 (95% confidence interval [CI]: 0.649 to 0.708) for talazoparib (n=259) vs 0.682 (95% CI: 0.638 to 0.725) for PCT combined (n=112).

Average utilities in the pre- and post-progression periods were estimated using a repeated measures mixed effects model that assumed a random intercept for each subject. For both arms, average PP utility increased compared to average baseline utility. An incremental utility gain of [redacted] was observed for talazoparib vs PCT combined [redacted]. As treatment-specific utilities derived from EMBRACA have already considered the impact of treatment-specific response rates, the same utility was assumed for PFS regardless of response status (CR/PR or SD). In the base case, a utility value of [redacted] for PFS was applied to patients who received talazoparib. A utility value of [redacted] was applied to patients in the PCT combined arm.

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

In line with the NICE guidelines to the methods of technology appraisal 2013, studies describing HRQoL for patients with *BRCA*1/2m aBC were identified systematically. Relevant studies were identified by searching the following databases: MEDLINE, Embase, International Network of Agencies for Health Technology Assessment (INAHTA), NHS Economic Evaluation Databases and EconLit. The database searches were executed on 16 August 2022 and identified 5,439 abstracts. Of the 1,679 publications moving to full-text screening, 18 were eligible for inclusion in the SLR. Additional supplemental searching identified 3 additional publications eligible for inclusion in the review. In total, 10 unique studies from 18 publications met the eligibility criteria for inclusion in the SLR.

The methods and results of the SLR are fully described in Appendix H.

An average of the utility value for progressed disease was chosen from the most recent publications: Lambert et al. 2018 and Huang et al. 2020 to account for the diversity of patients included in EMBRACA (Table 34).[114,115]

Table 34. Utility value for progressed disease

Published utility value for progressed disease	Reference	Average utility value used in model
0.601	Huang (2020)[124]	0.626
0.650	Lambert (2018)[123]	

B.3.4.4. Adverse reactions

AE utility decrements are shown in Table 35. Full details of selection of AEs are described in Section B.3.3.4.

Table 35. AE utility decrements applied in economic model

AE	Utility decrement	SE	Source
Anaemia	0.010	NA	TA819[53]
Diarrhoea	0.103	NA	TA819[53]
Fatigue	0.115	NA	TA819[53]
Hand and foot syndrome	0.116	NA	Lloyd 2006[116]
Leukopenia	0.003	NA	TA819[53]
Nausea	0.103	NA	TA819[53]
Neuropathy	0.014	NA	TA515[53]
Neutropenia	0.124	NA	TA819[53]
Thrombocytopenia	0.124	NA	Assumed the same as neutropenia
Vomiting	0.103	NA	Lloyd 2006[116]
AE: adverse event; SE: standard error			

B.3.4.5. Health-related quality-of-life data used in the cost-effectiveness analysis

All health-related quality-of-life data used in the cost-effectiveness analysis are presented in Table 33 and Table 35 in Section B.3.4.1 and B.3.4.4.The general population utility through which the percentage decrements will be calculated using the equation developed by Ara and Brazier, 2010.[117] The equation is characterised as a function of age and sex and is as such:

$$Utility = 0.9508566 + (0.0212126 \times male) - (0.0002587 \times age) - (0.0000332 \times age^2)$$

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

In line with the NICE guidelines to the methods of technology appraisal 2013, studies describing costs and MRU for patients with aBC were identified systematically, during the cost-effectiveness SLR. Relevant studies were identified by searching the following databases: MEDLINE, Embase, INAHTA, NHS Economic Evaluation Databases and EconLit The searches were executed on August 31, 2022, and are fully described in Appendix I.

Costs have been categorised as relating to the intervention/comparator, subsequent therapies, monitoring and management of the disease, management of AEs, and terminal care. Costs have been sourced from the relevant UK literature and NHS reference costs. Where values for standard errors (SE) are not available and could not be calculated using standard deviation, a default value of 20% of the mean has been used.

B.3.5.1. Intervention and comparator costs and resource use

The costs of each therapy are applied each cycle where treatment is continued and include drug procurement and administration costs.

Costs of the intervention and comparators comprise the unit costs of the treatment, costs according to the dose and frequency administered to patients and the administration of treatment. An overview of drug acquisition costs and administration costs is provided in Table 36 and Table 37, respectively. Administration costs were applied to intravenous (IV) drugs, which differ by the time of administration (initial versus subsequent regimen) and the duration of each infusion. Medications that are orally administered do not incur administration costs; however, in the model, a specific administration cost can be used for oral medications such as talazoparib at treatment initiation.

In the current analysis, the monthly cost of PCT combined (£1,171 including acquisition and administration) was assumed, of which the weights (capecitabine – 48%, eribulin – 44%, vinorelbine – 8%) were re-weighted from the EMBRACA trial.[79]

The dosing and costs used in the model for each treatment option are reported in Table 36, Table 37 and Table 38. Dosing information for each treatment option were drawn from the EMBRACA trial, each treatment's Summary of Product Characteristics (SmPC), or published trials. This information was used to calculate drug and administration costs.

Table 36. Drug acquisition costs

Drug	Formulation	Cost per pack	Source
Talazoparib*			
	1 mg tablets pack size 30	£4,965	BNF database[118]
	0.75 mg tablets pack size 90	£4,965	
	0.5 mg tablets pack size 60	£3,310	
	0.25 mg tablets pack size 30	£1,655	
PCT combined			
Capecitabine	150 mg tablets pack size 60	£30	BNF database[119]
Eribulin	0.88 mg solution for infusion vial pack size 1	£361	BNF database[120]
Vinorelbine	50 mg solution for infusion vial pack size 10	£159.46	eMIT database[110]

* Patient access schemes available

BNF: British National Formulary; eMIT: electronic market information tool; PCT: physician's choice therapy; UK: United Kingdom

Table 37. Administration costs

Details	Mean value	Drug	Source
Exclusively oral at initiation	£215.80	Talazoparib and PCT combined	2020/21 National Cost Collection data [106] - SB11Z
Infusion: ≤ 60 min, initial	£281.11	PCT combined	2020/21 National Cost Collection data [106] - SB12Z
Infusion: 60-120 min, initial	£258.56	-	2020/21 National Cost Collection data [106] - SB13Z
Infusion: 2+ hours, initial	£342.66	-	2020/21 National Cost Collection data [106] - SB14Z
Infusion: Subsequent regimen	£438.38	PCT combined	2020/21 National Cost Collection data [106] - SB15Z

Table 38. Drug dosing (current treatment)

Treatment	Dosing	Source
Talazoparib	1 mg once daily	EMBRACA trial[64]
Capecitabine	1250 mg/m^2 twice daily orally for 2 weeks followed by a 7-day rest period in 3-week cycles	Capecitabine SmPC[121]
Eribulin	1.23 mg/m^2 IV over 2 to 5 minutes on Days 1 and 8 of a 21-day cycle	Halaven SmPC[122]
Vinorelbine	25 mg/m^2 IV day 1, weekly	Navelbine SmPC[123]
AUC: area under curve; IV: intravenous; SmPC: Summary of Product Characteristics		

B.3.5.1.1. Subsequent treatment

In clinical practice, aBC patients who discontinue their 1L therapy are likely to receive subsequent therapy, with the possible subsequent therapies determined by the treatment they received in the 1L. Reflecting this, the economic model assumes that patients discontinuing initial treatment receive a subsequent therapy. The composition of subsequent treatment was assumed to impact costs only, and not its clinical efficacy. For details on how treatment options were specified in the model, refer to Section B.1.1.

It was assumed that both treatment arms incur the same subsequent treatment costs which are based on PCT combined because there are no sufficient clinical data to capture the cost of subsequent treatments differently.

B.3.5.2. Health-state unit costs and resource use

Monitoring and disease management costs vary by health state. These costs are associated with medical resource use. MRU costs include those incurred by recurrent routine follow-up care and by one-off procedures. The overall MRU costs were calculated by multiplying the frequencies of use (monthly use) and unit costs for each resource use item.

In the current analysis, frequencies of use were assumed based on UK clinicians' opinions (internal communication) due to lack of data; percentage of patients who used each medical resource was based on the EMBRACA trial; and unit costs for

each medical resource was sourced from the 2020/21 National Cost Collection data and PSSRU. [106,107,124] Frequencies of use differ by health state (PFS vs post-progression survival [PPS]) or response status (CR/PR vs SD vs progressive disease) and were assumed the same for all patients regardless of the treatment they receive.

Unit costs for MRU micro-costing items are presented in Table 39. Monthly utilization frequency and assumed percentage of patients using each resource are presented in Table 40.

Table 39. Medical resource use unit cost

Resource	Unit Cost
General practitioner visits	£39
Oncology consultant visits	£225
Community nurse	£44
Clinical nurse specialist	£90
CT Scan	£202
Red blood cell transfusion	£746
Platelet transfusion	£738
Immunostimulants	£92

CT: computerised tomography; NHS: National Health Service; PSSRU: Personal Social Services Research Unit
Sources: BNF, 2022;[108]2020/21 National Cost Collection data[106] PSSRU, 2021[124]

Table 40. Monthly use and percentage of patients using medical resource

Resource	Frequency per month	Percent of patients	
		Talazoparib	PCT combined
PFS (CR/PR)			
General practitioner visits	0.2	100%	100%
Oncology consultant visits	0.2	100%	100%
Community nurse	0.2	100%	100%
Clinical nurse specialist	0.8	100%	100%
CT scan	0.3	100%	100%
Red blood cell transfusion	0.8	8.3% †	6%
Platelet transfusion	0.8	3.1%	0%
Immunostimulants	24.4	9%	18%
PFS (SD)			
General practitioner visits	0.4	100%	100%
Oncology consultant visits	0.2	100%	100%
Community nurse	0.4	100%	100%
Clinical nurse specialist	1.2	100%	100%
CT scan	0.3	100%	100%
Red blood cell transfusion	1.2	8.3% †	6%
Platelet transfusion	1.2	3.1%	0%
Immunostimulants	36.5	9%	18%
Progressive Disease			
General practitioner visits	0.3	100%	100%
Oncology consultant visits	0.2	100%	100%
Community nurse	0.3	100%	100%
Clinical nurse specialist	1.0	100%	100%
CT scan	0.0	100%	100%
Social Worker	0.5	100%	100%

CR: complete response; CT: computerised tomography; PCT: physician's choice therapy; PFS: progression-free survival; PR: partial response; SD: stable disease

Source: Frequency per month, EMBRACA trial;[125] percent of patients using each resource, assumption

† Source: Mahtani 2022[84]

Whilst 38% of patients in EMBRACA received red blood cell (RBC) transfusion, this is not understood to be reflective of UK clinical practice. High transfusion rates in EMBRACA are attributed to the protocol which required haemoglobin (Hb) values recover to grade 1 or better (10g/dL) before resuming talazoparib after a dosing interruption. A protocol amendment was made updated that talazoparib could be resumed at Hb of 9g/dL or greater, leading to lower transfusion rates.[126]

A real-world study[127] in the US found that 8.3% of patients treated with talazoparib received RBC transfusion. Clinical guidelines published by the Association for the advancement of blood and biotherapies[128] state a restrictive RBC transfusion threshold in which the transfusion is not indicated until the haemoglobin level is 7 g/dL for hospitalized adult patients who are hemodynamically stable, including critically ill patients, rather than when the haemoglobin level is 10 g/dL as per EMBRACA.

The US guidelines are very similar to NICE guidelines.[129] They recommend when using a restrictive red blood cell transfusion threshold, a threshold of 70 g/litre and a haemoglobin concentration target of 70–90 g/litre after transfusion should be considered.

Thus, the transfusion guidelines for the US and UK are less stringent than EMBRACA and similar blood transfusion practice is expected to be observed in UK clinical practice aligning with the US RW study.[84]

B.3.5.2.1. Terminal care costs

Terminal care costs represent the management, monitoring and resource use for patients with aBC in the months prior to death and are applied to patients who enter the death state as a one-off cost. The terminal care cost used in the model, was calculated based on the weighted average approach used in NICE TA639, which is in line with the approach used in TA495.[55,130] Unit cost for each resource were sourced from PSSRU[124] and percentage of patients in each setting were in line with TA639,[55] which are presented in Table 41. The weighted terminal care cost in the model is £7,952.60 (2021).

Table 41. Resource use for terminal care/end of life

Resource	Unit cost	% of patients in each setting	Source
Hospital and social care (combined)	£8,777	40.00%	PSSRU;[124]
Hospice	£22,238	10.00%	PSSRU;[124]
Home	£4,436	50.00%	PSSRU;[124]
PSSRU: Personal Social Services Research Unit			

B.3.5.3. Adverse reaction unit costs and resource use

The costs of treating common grade 3 and 4 AEs were multiplied with the rates of each event to derive the total cost of treating grade 3 and 4 AEs for each treatment. These costs address the impact of differences in AE rates between treatments. The cost of treating AEs was assumed to be a one-time cost and the same for all patients, regardless of the treatment arm. Costs of per episode AEs were sourced from 2020/21 National Cost Collection data ,[106] and are presented in Table 42.

Table 42. AE management costs

AE	HRG Code	Resource use assumption	Cost	Source
Anaemia	SA04	Total HRGs, Iron deficiency anaemia with CC score 0-1, 2-5, 6-9, 10-13 and 14+	£777	2020/21 National Cost Collection data[106]
Fatigue	SA04K	Iron deficiency anemia CC score 2-5	£712	
Nausea	JA12D to JA12L	Malignant breast disorders	£867	
Thrombocytopenia	WF01A	Additional outpatient visit	£158	
Diarrhoea	WF01A	Additional outpatient visit	£158	
Neutropenia	WF01A	Additional outpatient visit	£158	
Vomiting	JA12D to JA12L	Malignant breast disorders	£867	
Neuropathy	WF01A	Additional outpatient visit	£158	
Hand-foot syndrome	WF01A	Additional outpatient visit	£158	
Febrile neutropenia	WF01A	Additional outpatient visit	£158	
Leukopenia	WF01A	Additional outpatient visit	£158	

B.3.6. Severity

The severity of a disease is an important consideration in a health technology assessment. In the cases of medicines being appraised for a severe disease, such as talazoparib for aBC, NICE considers the severity of the disease via absolute QALY shortfall (AS) and proportional QALY shortfall (PS).

Age-related general population utilities as reported by Ara and Brazier[117] were used to calculate QALYs in the age and sex matched general population.

The calculation used to determine AS was as follows:

$$Absolute\ QALY\ shortfall = QALYs\ in\ SoC - QALYs\ in\ age\ and\ sex\ matched\ general\ population$$

The calculation used to determine PS was as follows:

$$Proportional\ QALY\ shortfall = \frac{Absolute\ QALY\ shortfall}{QALYs\ in\ age\ and\ sex\ matched\ general\ population}$$

Table 43 shows sex distribution and starting age for the analysis.

Table 43. Summary features of QALY shortfall analysis

Factor	Value (reference to appropriate table or figure in submission)	Reference to section in submission
Sex distribution	98.4% female, 1.6% male (Table 22)	B.3.2.1
Starting age	48.1 years (Table 22)	

Results of the calculation are shown in Table 44Table 44. In the base case analysis, with a mean age at baseline of 48.1 and a proportion of males of 1.6%, the absolute shortfall estimate is 14.964 and the proportional shortfall is 0.934. This gives a severity modifier of 1.2. Note that the values are calculated based on discounted QALYs.

Table 44. QALY shortfall calculation results

Outcome	Total QALYs	Shortfall	
		Absolute	Proportional
General Population	16.026		
Disease Specific	1.062	14.964	0.934
QALY Multiplier		1.2	1.2
WTP Threshold		£36,000	
QALY: quality adjusted life year; WTP: willingness to pay threshold			

B.3.7. Uncertainty

Data from the EMBRACA trial represents the highest-quality evidence available quantifying the clinical efficacy of PCT in this indication but is not sufficient to inform the total time horizon of the model due to immaturity of OS data. Therefore, extrapolation of survival data from EMBRACA was required to inform long-term outcomes. Nevertheless, it was possible to validate the extrapolation for talazoparib and PCT combined against longer-term survival data from the literature, detailed in Section B.3.14.2. Since talazoparib is indicated for 2L+ treatment in aBC and limited to patients with g*BRCA*m the patient numbers are low, and therefore adding to the uncertainty of outcomes.

B.3.8. Managed access proposal

Pfizer is not submitting a managed access proposal and is committed to securing a positive routine commissioning decision for talazoparib, working with all stakeholders throughout the process.

B.3.9. Summary of base-case analysis inputs and assumptions

B.3.9.1. Summary of base-case analysis inputs

A summary of the base case analysis inputs is provided in Table 45.

Table 45. Summary of variables applied in the economic model

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Baseline parameters			
Baseline parameters	Table 22	SE (age: normal; weight: normal; BSA: normal; sex:beta)	B.3.2.1
Survival and progression functions			
PFS	Table 31	Described in B.3.3.2	B.3.3.2
OS			
Clinical parameters			
Treatment duration	Median treatment duration from EMBRACA	Described in B.3.2.2.4.2	B.3.2.2.4.2
AE prevalence	Table 32	SE (beta)	B.3.3.4
Utilities			
Health state utilities	Table 33	SE (beta)	B.3.4.1
AE Utility Decrement	Table 35	SE (normal)	B.3.4.4
Costs			
Treatment costs	Table 36 Table 37 Table 38	SE (gamma)	B.3.5.1
Subsequent treatment costs	NA	SE (gamma)	B.3.5.1.1
Health state costs	Table 40	SE (gamma)	B.3.5.2
Terminal care costs	Table 41	SE (gamma)	B.3.5.2.1
AE costs	Table 42	SE (gamma)	B.3.5.3

AE: adverse events; CI: confidence interval; OS: overall survival; PFS: progression-free survival; SE: standard error

A summary of the base case analysis assumptions is provided in Table 46.

Table 46. Assumptions applied in the economic model

Assumption	Rationale
Baseline parameters are derived from EMBRACA cohort, which is assumed to be reflective of patients seen in UK clinical practice for the anticipated MA.	Although there may be differences between characteristics in EMBRACA and aBC patients in the UK, UK experts concluded that the trial characteristics are comparable to UK clinical practice. Sensitivity analyses (probabilistic and deterministic) have been conducted to assess the impact of variability in these parameters.
The model applies a 3-week cycle length, which is assumed to be sufficiently granular to accurately reflect costs and benefits when modelling aBC.	Previous aBC evaluations assessed by NICE (TA423) had applied 3-week cycle lengths, which was considered appropriate by the ERG.[102] This cycle length is short enough to reflect the treatment cycles for patients, and reflects the frequency of follow-up for patients and is a realistic minimum time during which symptoms or response can change.
To reflect the nature of aBC and available evidence, the model assumes that health states are consecutive, and patients cannot revert to pre-progression from more advanced phases of the disease.	This assumption has been validated by clinicians and is in line with other HTAs and economic analyses assessing the aBC population.
Identification of most appropriate survival curves describing PFS and OS inform extrapolation.	Best-fit parametric distributions were fitted to talazoparib and PCT KM data for PFS. Fitting different distriutions to the talazoparib and PCT data was considered appropriate owing to the different mechanism of action of PARPi and conventional chemotherapies included in the PCT arm. Extensive analyses have been undertaken to identify appropriate and clinically plausible OS curves describing talazoparib efficacy, with reference to the guidance from the NICE (DSU)[83] and Bagust and Beale (2014)[111]). Due to immaturity of OS data, best parametric fit was applied to talazoparib KM data. The approach and identified survival extrapolations have been validated by clinical and health economic experts. The HR from the RPSFTM analysis adjusting for subsequent PARPi was applied to estimate long-term survival in the PCT arm to adjust for crossover in EMBRACA.
It was assumed the individual treatments (capecitabine, eribulin, and vinorelbine) have comparable efficacy, thus a pooled efficacy of PCT combined was derived from EMBRACA and was applied in the model.	Clinical advice received by UK clinical experts confirmed that capecitabine, eribulin, and vinorelbine are expected to have comparable efficacy in clinical practice.
The same utility was assumed for PFS regardless of response status (CR/PR or SD).	Treatment-specific utilities derived from EMBRACA have already considered the impact of treatment-specific response rates.

Assumption	Rationale
The AE decrements were applied over an assumed duration of two weeks and as a one-off decrement, and the same for all patients, regardless of the treatment arm.	Although utility derived from EMBRACA has already reflected the impact of AEs associated with talazoparib and PCTs on QoL, sourcing AE-related utility decrements from published studies explicitly incorporated for all treatment comparators. This approach may cause a double counting for talazoparib and PCTs; however, we would consider it to be conservative towards talazoparib given its total AE disutility (0.007) is higher than that for PCTs (0.003).
AE utility decrement values were assumed for certain AEs.	Values were assumed for those AEs where published data was not available. However, deterministic sensitivity analysis has been presented to show the impact of AE utility decrements.
It was assumed that both treatment arms receive PCT combined as subsequent treatment and incurs the same cost for subsequent treatment.	There is no sufficient published clinical data to fully reflect the treatment pathway for aBC following talazoparib treatment. Therefore, it is assumed that both intervention and comparator receive the same subsequent treatments.
Values for resource use frequencies were assumed.	Clinical advice received by UK clinical experts confirmed the assumptions made for the resource use frequencies in this submission.

AE: adverse events; CR: complete response; CI: confidence interval; OS: overall survival; PCT: physicians treatment choice; PFS: progression-free survival; PR: partial response; QoL: quality of life; SD: standard deviation; SE: standard error

B.3.10. Base-case results

B.3.10.1. Base-case incremental cost-effectiveness analysis results

The results of the base-case analysis are summarised in Table 47.

For patients treated with PCT combined, the model predicted [redacted] discounted LYs with an accrual of [redacted] discounted QALYs. Talazoparib was estimated to result in an additional [redacted] discounted QALYs (total [redacted] QALYs) and an additional [redacted] discounted LYs (total [redacted] LYs).

Total discounted costs associated with talazoparib were predicted to be [redacted]. Incremental costs were predicted to be [redacted] compared to PCT combined, under base-case assumptions. The resulting ICER estimate for talazoparib vs PCT combined was £34,644 per QALY gained. Therefore, the base-case ICER is under the £36,000 per QALY willingness-to-pay threshold.

Table 47. Base-case results (with PAS; discounted, £2021)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER inc. (£/QALY)
Talazoparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£34,664
PCT combined	[redacted]	[redacted]	[redacted]				
Inc., incremental; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

B.3.11. Exploring uncertainty

In order to assess the impact of parameters on the model outcomes, deterministic sensitivity analyses have been used to vary the data inputs by a set amount. Uncertainty around the input data has been assessed using probabilistic analyses, while alternative assumptions have been examined in scenario analyses.

B.3.11.1. Probabilistic sensitivity analysis

In the probabilistic sensitivity analysis (PSA), a non-parametric bootstrapping approach is taken, sampling values from distributions around the means of input parameters in the model. Sampling utilises information of the mean and SE of parameters to derive an estimated value using an appropriate distribution (costs: gamma, age and survival parameters: normal, utilities, probabilities and proportions: beta). These analyses are used to estimate the overall uncertainty that exists in the model results due to uncertainty in the chosen input parameters.

The majority of parameters included in the PSA are sampled independently, with the exception of semi-parametric survival estimates, where parameters associated with individual survival function are sampled using a common random number.

Several inputs are derived from sources where it has not been possible to ascertain SEs. To assess uncertainty surrounding these inputs, the SE has been assumed to be 20% of the mean value unless specified for the purposes of the PSA.

In order to enable the model results to converge to a sufficient degree of accuracy, 1,000 simulations of the model were required.

Results from 1,000 iterations of the model using probabilistic values can be seen in Table 48 and show that results are in line with the deterministic analysis. The scatterplot shows that there is limited spread in the values from each iteration and these are predominantly contained in the north-east quadrant under the willingness-to-pay threshold, demonstrating cost-effectiveness (Figure 20).

Table 48. Probabilistic sensitivity analysis results (combined CR/PR)

Technologies	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER inc. (£/QALY)
Talazoparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£32,110
PCT combined	[redacted]	[redacted]	[redacted]				

Inc., incremental; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years

Figure 20. Scatterplot of probabilistic results

[redacted]

Figure 21. Cost-effectiveness acceptability curve

[redacted]

B.3.11.2. Deterministic sensitivity analysis

A range of one-way (deterministic) sensitivity analyses have been conducted, regarding the following assumption and parameters as shown in Table 49:

Table 49. Assumptions and parameters of one way (deterministic) sensitivity analyses

Parameter	Assumption
Time horizon	5 and 15 years
Discounting	Costs 0% and 6%
	Benefits 0% and 6%
Baseline characteristics	Age ± 20%, impacting on all-cause mortality
	Weight ± 20%
	BSA ± 20%
Clinical Inputs	Response proportion, talazoparib ± 20%
	Response proportion, PCT combined ± 20%
Treatment costs	Relative dose intensity, capecitabine ± 20%
	Relative dose intensity, eribulin ± 20%
	Relative dose intensity, vinorelbine ± 20%
	Acquisition cost per pack, talazoparib ± 20%
	Acquisition cost per pack, subsequent treatment ± 20%
	Administration unit costs ± 20%
	Subsequent treatment, cost per cycle (Micro) ± 20%
AE cost	Talazoparib ± 20%
	PCT ± 20%
Utility for CR/PR	Talazoparib ± 20%
	PCT ± 20%
Utility for SD	Talazoparib ± 20%
	PCT ± 20%
Utility for PP	± 20%
AE related disutility	± 20%
AE related disutility duration	± 20%
Health state cost	PFS CR/PR ± 20%
	PFS SD ± 20%
	PFS PP ± 20%
Terminal care cost	± 20%
Health state cost	PP ± 20%

AE: adverse events; CR: complete response BSA: body surface area; PCT: physician's choice treatment; PP: post-progression; PR: partial response; SD: stable disease

Results of the deterministic sensitivity analysis are presented in Figure 22, which demonstrates the impact of specific parameters on the ICER estimate. Parameters

with the greatest impact on the ICER are subsequent treatment costs, utility for CR/PR and the acquisition cost of talazoparib.

Figure 22. Deterministic sensitivity analysis

B.3.11.3. Scenario analysis

Scenario analyses were performed exploring various inputs and combinations as described in Table 50.

Table 50. List of scenarios considered

Scenario	Scenario	Base case	Values assumed for the scenario analysis
PFS for talazoparib and PCT (HER2-)	1a	Log-normal for talazoparib and log-logistic for PCT	KM data
	1b		Generalized gamma for talazoparib and log-logistic for PCT
	1c		Log-logistic for talazoparib and log-logistic for PCT
OS for talazoparib and PCT (HER2-)	2a	Log-normal for talazoparib and RPSFTM adjusted HR applied to PCT	KM data
	2b		Log-normal for talazoparib and Weibull for PCT
Consider impact of response	3	Considered	No response
Consider relative dose intensity	4	Considered	No relative dose intensity
Treatment duration	5	Median treatment duration reported from trial	Treatment duration equals to PFS
Societal perspective	6	Excluded	Included

1L: first line; BRAC: breast cancer gene; HER2-: human epidermal growth factor receptor-negative; HR+: hormone receptor-positive; KM: Kaplan Meier; OS: overall survival; PCT: physician's choice therapy; PFS: progression-free survival; RPSFTM: rank preserving structural failure time model; TNBC: triple-negative breast cancer

B.3.11.3.1. PFS for talazoparib and PCT (HER2-)

In the PFS scenario analysis, three scenarios were performed to investigate the effect of changing the projection approach on economic outcomes, as described in Table 50. In addition to using PFS KM data, another two scenarios were chosen

based on AIC, BIC and best visual fit to explore the other plausible extrapolations of the PFS curves. The results are displayed in Table 50.

The use of KM data for both talazoparib and PCT yielded an ICER of £39,151 per QALY, which was slightly higher than the ICER in the base case (£34,644 per QALY). The KM data at the end of the trial period does not accurately reflect PFS due low patient numbers increasing uncertainty of outcomes.

The use of generalized-gamma for talazoparib and log-logistic for PCT resulted in an ICER of £32,314 per QALY, which was comparable to the base case ICER (£34,644 per QALY).

Table 51. Scenario analysis: Impact of distributions for PFS

Technologies	Incremental LYs	Incremental QALYs	Incremental Costs (£)	ICER (£/QALY)
Base case analysis	[redacted]	[redacted]	[redacted]	£34,644
Scenario: KM data	[redacted]	[redacted]	[redacted]	£39,151
Scenario: Generalized gamma for talazoparib and log-logistic for PCT	[redacted]	[redacted]	[redacted]	£32,314
Scenario: Log-logistic for talazoparib and log-logistic for PCT	[redacted]	[redacted]	[redacted]	£30,545
ICER, incremental cost-effectiveness ratio; LYs: life years; QALYs, quality-adjusted life years				

B.3.11.3.2. OS for talazoparib and PCT (HER2-)

Two scenarios were performed for the OS analysis to investigate the effect of changing the projection approach on economic outcomes, as described in Table 50. In addition to using OS KM data, another scenario was chosen based on AIC, BIC and best visual fit to explore plausible extrapolations of the PCT OS curves. The results are displayed in Table 52.

The use of KM data for both talazoparib and PCT yielded an ICER of £33,262 per QALY, which was lower than the ICER in the base case (£34,644 per QALY). This is due to the immaturity of the OS data and hence the lower costs.

The use of log-normal for talazoparib and Weibull for PCT yielded an ICER of £35,158 per QALY, which was slightly higher than the ICER in the base case (£34,644 per QALY).

Table 52. Scenario analysis: Impact of distributions for OS

Technologies	Incremental LYs	Incremental QALYs	Incremental Costs (£)	ICER (£/QALY)
Base case analysis	[redacted]	[redacted]	[redacted]	£34,644
Scenario: KM data	[redacted]	[redacted]	[redacted]	£33,262
Scenario: Log-normal for talazoparib and Weibull for PCT	[redacted]	[redacted]	[redacted]	£35,158
ICER, incremental cost-effectiveness ratio; LYs: life years; QALYs, quality-adjusted life years				

B.3.11.3.3. Considering impact of response

In the base-case analysis, the effect of treatment response is considered. To explore the effect of treatment response on the economic outputs of the model, a scenario in which treatment response is not considered was performed. This economic evaluation comparing talazoparib to PCT combined yielded an ICER of £39,975 per QALY, which was higher than the ICER in the base case (£34,644 per QALY). This is because talazoparib has an overall higher response rate. Therefore, excluding the impact of response underestimates the benefit of talazoparib, resulting in a higher ICER.

Table 53. Scenario analysis: Impact of response

Technologies	Incremental LYs	Incremental QALYs	Incremental Costs (£)	ICER (£/QALY)
Base case analysis	[redacted]	[redacted]	[redacted]	£34,644
Scenario: No response	[redacted]	[redacted]	[redacted]	£39,975
ICER, incremental cost-effectiveness ratio; LYs: life years; QALYs, quality-adjusted life years				

B.3.11.3.4. Considering relative dose intensity

In the base-case analysis, the effect of relative dose intensity is considered. To determine whether it has an effect on the outputs of the economic model, a scenario in which relative dose intensity is not considered was performed. This economic evaluation comparing talazoparib to PCT combined yielded an ICER of £40,248 per QALY, which was higher than the ICER in the base case (£34,644 per QALY). Excluding the impact of relative dose intensity neglects alternative dosing options, which overestimates the treatment costs for talazoparib, resulting in a higher ICER.

Table 54. Scenario analysis: Impact of RDI

Technologies	Incremental LYs	Incremental QALYs	Incremental Costs (£)	ICER (£/QALY)
Base case analysis	[redacted]	[redacted]	[redacted]	£34,644
Scenario: No RDI	[redacted]	[redacted]	[redacted]	£40,248
ICER, incremental cost-effectiveness ratio; LYs: life years; QALYs, quality-adjusted life years				

B.3.11.3.5. Treatment duration

Median treatment duration for each treatment is presented in Table 55.

Table 55. Scenario analysis: Median treatment duration

Treatment comparator	Median treatment duration (Months)	Source/assumption
Talazoparib	6.9	EMBRACA IPD
PCT Combined	3.9	
IPD: individual patient data; PCT: physician's choice therapy		

Scenario analysis was performed to investigate the effect of assuming treatment duration is equal to PFS rather than using the median treatment duration reported from the EMBRACA trial on economic outputs from the model. The economic evaluation with treatment duration equal to PFS yielded an ICER of £43,068 per QALY, which was higher than the ICER in the base case (£34,644 per QALY). This is because median treatment duration is shorter than mean PFS. Therefore, total costs for both arms increase, though the increase is more significant in the talazoparib arm.

Table 56. Scenario analysis: Impact of treatment duration

Technologies	Incremental LYs	Incremental QALYs	Incremental Costs (£)	ICER (£/QALY)
Base case analysis	[redacted]	[redacted]	[redacted]	£34,644
Scenario: ToT equal PFS	[redacted]	[redacted]	[redacted]	£43,068
ICER, incremental cost-effectiveness ratio; LYs: life years; QALYs, quality-adjusted life years				

B.3.11.3.6. Societal perspective

Although the base case was conducted from a third-party payer perspective, the model has the option to include loss of productivity associated with mBC from the UK societal perspective. Based on the Office for National Statistics (ONS) in UK,[131,132] 75.5% of the population are employed. The model assumed the same percentage of employment for patients with mBC. The average annual income for full-time employees in the UK is £32,194 based on the ONS data.[131] The model assigns monthly indirect costs to patients in each health state by applying percentages of patients who had productivity loss differences by health state. While all patients who had progressive disease were assumed to have productivity loss, 10% and 30% of patients who had CR/PR and SD, respectively, were assumed to have productivity loss, based on Verril 2017.[133] Inputs used to calculate monthly indirect costs are presented in Table 57.

Table 57. Indirect cost inputs

	All Health State			**Source**
% Employed	75.5%			ONS[131]
Average annual income	£32,194			ONS[131]
Productivity loss by health state	**PFS - CR/PR**	**PFS - SD**	**PD**	
% of patient had productivity loss	10%	30%	100%	CR/PR and SD: Verril 2017[133] PD: Assumption
Cost per month (£, calculated*)	£203	£608	£2,026	

CR: complete response; ONS: Office for National Statistics; PD: progressive disease; PFS: progression free survival; PR: partial response; SD: stable disease

* Indirect cost per month = % Patients employed × (average annual income / 12) × % patients who has productivity loss

Different productivity loss due to chemotherapy or non-chemotherapy was considered. Scenario analysis modelling a societal perspective yielded an ICER of £31,535 per QALY, which was lower than the ICER in the base case (£34,644 per QALY).

Table 58. Scenario analysis: Societal perspective

Technologies	Incremental LYs	Incremental QALYs	Incremental Costs (£)	ICER (£/QALY)
Base case analysis	[redacted]	[redacted]	[redacted]	£34,644
Scenario: societal perspective	[redacted]	[redacted]	[redacted]	£31,535
ICER, incremental cost-effectiveness ratio; LYs: life years; QALYs, quality-adjusted life years				

B.3.11.3.7. Scenario analysis result summary

Summary results for each scenario analysis described in Table 50 are shown in Table 59. The high-level overview allows for a clean picture of the impact of each parameter varied in sensitivity analysis on the key results measures.

Table 59. Summary of sensitivity analysis results (PAS; discounted, £2021)

Scenario		Values assumed for scenario analysis	Difference (Talazoparib versus PCT combined)			
			LY	QALYs	Total cost	ICER/QALY
Base case			[redacted]	[redacted]	[redacted]	£34,644
1a	PFS for talazoparib and PCT (HER2-)	KM data	[redacted]	[redacted]	[redacted]	£39,151
1b		Generalized gamma for talazoparib and log-logistic for PCT	[redacted]	[redacted]	[redacted]	£32,314
1c		Log-logistic for talazoparib and log-logistic for PCT	[redacted]	[redacted]	[redacted]	£30,545
2a	OS for talazoparib and PCT (HER2-)	KM data	[redacted]	[redacted]	[redacted]	£33,262
2b		Log-normal for talazoparib and Weibull for PCT	[redacted]	[redacted]	[redacted]	£35,158
3	Consider impact of response	No response	[redacted]	[redacted]	[redacted]	£39,975
4	Consider relative dose intensity	No relative dose intensity	[redacted]	[redacted]	[redacted]	£40,248
5	Treatment duration	Equal to PFS	[redacted]	[redacted]	[redacted]	£43,068
6	Societal perspective	Included	[redacted]	[redacted]	[redacted]	£31,535

ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year

*Less costly, more effective

**Note that in this scenario, talazoparib is less costly and less effective (bottom left quadrant)

The findings from the multiple scenario analyses for the comparison of talazoparib and PCT combined showed that treatment duration equal to PFS, relative dose intensity and impact of response have the biggest impact on the ICER (£43,068, £40,248 and £39,975 respectively).

The ICERs were close to the base-case result (within 25% variations) in all scenarios tested.

B.3.12. Subgroup analysis

No subgroup analyses were conducted for this submission as EMBRACA does not have sufficient data to run any subgroup analysis.

B.3.13. Benefits not captured in the QALY calculation

Novel treatment mechanism

Talazoparib is the first targeted treatment indicated for g*BRCA*m HER2- aBC in England. Some targeted treatment options are licensed for aBC; however, these only cover specific subpopulations (TNBC and PD-L1 TNBC patients). The majority of g*BRCA*m HER2−negative aBC patients therefore receive non-targeted treatments in the form of chemotherapy as standard of care (Section B.1.3.2). Talazoparib on the other hand is a PARPi with a dual cytotoxic mechanism, resulting in targeted cell death in *BRCA*1/2-deficient tumours.[68,69,72-74] As well as being efficacious, talazoparib provides a novel treatment mechanism and increases treatment choice, fulfilling a significant unmet need in this patient population.

Convenience of an oral therapy

Talazoparib is an oral once daily targeted treatment for g*BRCA*m HER2- aBC patients. Current chemotherapy treatments such as eribulin and vinorelbine require IV infusion in 21-day cycles, which is inconvenient to patients and oral capecitabine is a twice daily dose.[78] Oral administration offers a more convenient treatment option which improves adherence and consequently treatment exposure, as well as reducing treatment administration burden for both patients, carers, and healthcare professionals. For example, there is no need for patients, and their caregivers, to travel to hospital for outpatient appointments. In addition, patients are not required to stay in outpatients for hours, thus saving hospital resources.

Improving outcomes for patient with a history of CNS metastasis

Additionally, talazoparib is the first targeted therapy for g*BRCA*m HER2- aBC patients with a history of CNS metastasis, a patient group with a considerable unmet need for effective treatment.[134] Current recommendations for the treatment of this patient population are limited, and are most commonly a combination of surgical

resection, radiotherapy, and systemic chemotherapy.[134,135] While systemic chemotherapy is an attractive treatment option in many cases, most agents are incapable of crossing the blood-brain barrier, resulting in poor outcomes for patients with a history of CNS metastasis.[134,135]

In the EMBRACA trial, talazoparib treatment significantly improved PFS for patients with a history of CNS metastasis compared with PCT (5.7 vs. 1.6 months, respectively; HR 0.32, 95% CI: 0.15, 0.68, P = 0.0016).[64]

Improvement in BC specific PROs

In addition to the EORTC QLQ-C30 data from the EMBRACA trial, which was used to inform the utility values in the cost-effectiveness model, PROs were also recorded using the EORTC QLQ-BR23 breast cancer module (Section B.2.6.6.2). Talazoparib treatment showed a greater statistically significant overall change for body image. While future perspective was improved in both treatment arms, a greater improvement was seen with talazoparib treatment (15.3: 95% CI: 12.3, 18.3) compared with PCT (9.1: 95% CI: 3.7, 14.5).[67]

From a symptomatic perspective, talazoparib demonstrated a statistically significant greater improvement for breast symptoms, arm symptoms and systemic therapy side-effects, compared with PCT.[67]

B.3.14. Validation

B.3.14.1. Validation of cost-effectiveness analysis

In general, where no evidence was identified to validate the results of the cost-effectiveness analysis, simple assumptions have been made based on independent sources, such as published literature, aBC guidelines or previous aBC NICE appraisals. These assumptions were assessed for clinical plausibility, uncertainty was characterised through the use of sensitivity analyses.

A technical review of the cost-effectiveness model was conducted by an independent economist. Further, the relevance of the modelling assumptions were validated through consultation with UK clinicians. This allowed the model approach to be validated and permitted areas of disagreement to be resolved prior to generation of

model results. In addition, quality control was undertaken, whereby a cell-by-cell verification process was conducted to allow checking of all input calculation, formulae and visual basic code.

B.3.14.2. Validation of survival extrapolation

Despite the lack of real-world data, it was possible to validate the survival extrapolation for talazoparib and PCT combined against longer-term survival data from other literatures. Thirteen studies were identified, with three meta-analyses identified from the Decision Support Unit report and ten prospective observational studies or RCTs (Table 60). These studies reported median OS for a mixture of treated or untreated HR+/HER2- or TNBC aBC patients ranging from 12.9 to 38.4 months across different treatments. Median OS for talazoparib and PCT combined is within this range and is comparable with these studies. Detailed information on patient population, method of analysis, and survival findings of each study are presented in Table 60.

Table 60. Median OS in the literature

Author and Year	N*	Study Type	Primary Endpoint	Patient Population	Treatment	Median OS, Months (95% CI)
Dieras 2017[136]	116	Observational study	—	Untreated HER2- aBC patients	Bevacizumab, paclitaxel	38.4
				Untreated TNBC patients	Bevacizumab, paclitaxel	18.8
Robson 2017[57]/ Robson 2018[137]**	302	RCT	PFS	Patients with a g*BRCA*m and HER2- aBC who had received no more than two previous chemotherapy regimens for metastatic disease	Olaparib	19.3 / 19.3
					Standard therapy	19.6 / 17.1
Cannita 2016[138]	35	Observational study	Safety, ORR, clinical benefit rate, PFS, OS	First-line HER2- aBC patients	Bevacizumab, paclitaxel	36.0
Delalogue 2016[139]	3,426	Observational study	OS	First-line HER2- aBC patients	Paclitaxel-based chemo, bevacizumab	27.7 (25.7, 29)
					Paclitaxel-based chemo	19.8 (18.3, 21)
Schneeweiss 2016[140]	865	Observational study	Response rate, PFS, OS	HER2- aBC patients	Bevacizumab, paclitaxel	21.6 (19.4, 23.5)
Vrdolijak 2016[141]	494	RCT	PFS	HER2- locally recurrent/advanced breast cancer	Standard second-line chemo, bevacizumab	19.7 (17.6, 21.0)
					Standard second-line chemo	18.7 (15.4, 21.2)
Clemens 2015[142]	101	RCT	PFS	HER2- aBC patients	YM155, docetaxel	19.8
					Docetaxel	20.7

Author and Year	N*	Study Type	Primary Endpoint	Patient Population	Treatment	Median OS, Months (95% CI)
Piccart 2014[143]	724	RCT	PFS	HER2- aBC patients	Everolimus, exemestane	31.0 (28.0, 34.6)
					Placebo, exemestane	26.6 (22.6, 33.1)
Mansour 2013[144]	31	Observational study	ORR	First-line HER2- aBC patients	Vinorelbine	16.0 (11.3, 20.7)
Byrski 2012[145]	20	RCT	ORR	HER2-, *BRCA*1-positive aBC patients	Cisplatin	30.0
Bowater 2011[146]	95	Meta-analysis	—	aBC patients	Mix	20.6
Burzykowski 2008[147]	11	Meta-analysis	—	aBC patients	Arm A (anthracycline-based regimens or single-agent anthracycline)	13.9 – 28.0
					Arm T (anthracycline-taxane combination regimens or single-agent taxane regimens)	12.9 – 34.0
Sherrill 2008[148]	55	Meta-analysis	—	aBC patients	Mix	20.0

aBC: advanced breast cancer; g*BRCA*m: germline BRCA mutation; CI: confidence interval; HER2-: human epidermal growth factor receptor 2-negative; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; RCT: randomised controlled trial; TNBC: triple-negative breast cancer

*Number of patients included for prospective studies or number of RCTs reviewed for meta-analysis; ** Robson 2018 reported final OS based on a longer median duration of follow up (olaparib: 18.9 vs. 14.5 months; standard therapy: 15.5 vs. 14.1 months)

B.3.14.3. Comparison of outputs with TA819

A comparison of median OS of PCT combined for the current submission versus TA819 is provided in Table 61; TA819 is the only identified appraisal in breast cancer with PCT as comparator. Median OS is more comparable with the Evidence Review Group (ERG) proposed value from TA819.[53] Differences in median OS may be due to slight differences in patient population group, where median OS of advanced or metastatic TNBC was utilised in TA819.

Table 61. Comparison of outcomes for physician choice treatment

	Current appraisal	TA819[53]	
		Company	ERG
Median OS, Months	19.5	6.9	14.8
ERG: evidence review group; OS: overall survival			

B.3.14.4. Comparison of economic model output with EMBRACA data

A comparison between the economic model output and the EMBRACA data was carried out as an additional validation exercise, shown in Table 62. As can be seen, there is only a small variation between the EMBRACA data and the model output, confirming the model results provide a good representation of the available data.

Table 62. Comparison of economic model output with EMBRACA data

		Talazoparib		PCT combined	
		PLD	Model output (best parametric fit)	PLD	Model output (best parametric fit)
OS	1 year	72.11%	72.54%	74.15%	72.58%
	2 years	42.41%	43.64%	39.05%	42.05%
	3 years	27.77%	26.59%	20.84%	20.32%
	5 years	13.83%	11.97%	0%	3.76%
	10 years	0%	2.61%	0%	0.01%
OS: Overall survival; PCT: physician's choice treatment; PLD: Patient-level data					

B.3.15. Interpretation and conclusions of economic evidence

The cost-effectiveness analyses demonstrates that talazoparib is a cost-effective treatment option versus PCT at a £36,000/QALY WTP threshold.

B.3.15.1. Relevance and generalisability

The economic evaluation is based on the patient population of EMBRACA, which evaluated the efficacy and safety of talazoparib in patients with g*BRCA*1/2m who received no more than 3 prior cytotoxic chemotherapy regimens for LABC or mBC. Therefore, the evaluation is relevant to the full population described in the decision problem. The characteristics of the population of EMBRACA are considered generalisable to England, based on best available evidence (Section B.2.2), while the modelled treatment pathway and inputs have been designed and selected to be fully reflective of clinical practice in England.

B.3.15.2. Strengths of the economic evaluation

The key strengths of the economic analysis are:

- No cost-effectiveness studies of interventions in g*BRCA*1/2m HER2- aBC were identified to inform the economic analysis presented in this submission (Appendix G). Therefore, a de novo economic model was developed to address the decision problem which reflects original and novel research.
- Efficacy was based on EMBRACA, a large, high-quality RCT with 5.1 years of data available, that evaluated the intervention and relevant comparator in a population directly relevant to the decision problem.
- The efficacy for both arms was drawn from the same trial, limiting heterogeneity in the data, while the outcomes evaluated, a partitioned survival model was used to assess the OS and PFS of patients from studied population which is a common case for oncological indications.
- Patients were followed up until death where the long-term OS was calculated by applying best-fitted statistical distributions to observed KM data, while PFS was assessed directly from the trial as all patients had either progressed, died prior to progression or were censored within the clinical trial period.

B.3.15.3. Limitations of the economic evaluation

As with all economic analyses, there are some limitations. The main limitations are that:

- The efficacy of each of the chemotherapies comprising PCT (capecitabine, eribulin or vinorelbine) is assumed to be equal, as the efficacy results are combined in the analysis of OS and PFS data from EMBRACA.
- Due to lack of data, adverse event disutility for thrombocytopenia and vomiting are assumed to be equivalent to the disutility of neutropenia and nausea, respectively.
- In the base case, treatment duration was assumed to be equal to PFS where patients are treated for the entire time they are in PFS (12.8 months and 8.2 months for talazoparib and PCT combined, respectively).
- As EQ-5D data was not directly reported in the clinical trial, utilities were obtained through a mapping algorithm, described in Section B.3.4.2, which may be considered less robust.
- Subsequent treatments were assumed due to lack of published data beyond the treatment line where talazoparib is indicated.

B.3.15.4. Conclusions from the economic evidence

A de novo economic model was developed in Microsoft Excel® in order to assess the cost-effectiveness of talazoparib versus PCT, for the treatment of g*BRCA*1/2m HER2- aBC. The model uses data from the relevant EMBRACA trial studying talazoparib and PCT, as well as published sources and clinical expert elicitation. Uncertainty in the model was explored through extensive deterministic, probabilistic and scenario analyses.

Appendices

Appendix letter	Appendix title	Location
C	SmPC and UK public assessment report	Provided as a separate document
D	Identification, selection and synthesis of clinical evidence	Provided as a separate document
E	Subgroup analysis	Provided in the main body of the report
F	Adverse reactions	Provided in the main body of the report
G	Published cost-effectiveness studies	Provided as a separate document
H	Health-related quality-of-life studies	Provided as a separate document
I	Cost and healthcare resource identification, measurement and valuation	Provided as a separate document
J	Clinical outcomes and disaggregated results from the model	Provided in the main body of the report
K	Price details of treatments included in the submission	Provided in the main body of the report
L	Checklist of confidential information	Provided as a separate document
M	ABRAZO and supplemental EMBRACA clinical evidence	Provided as a separate document
N	Summary list of published cost-effectiveness studies	Provided as a separate document
O	Survival analysis report	Provided as a separate document

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Talazoparib for Treatment of BRCA-mutated, HER2-Negative, Locally Advanced or Metastatic Breast Cancer

Summary of Information for Patients (SIP)

9th January 2023

File name	Version	Contains confidential information	Date
ID1342_Talazoparib_Summary_ Information_Patients_09Jan23	FINAL	No	9th January 2023

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

Note to those filling out the template: Please complete the template using plain language, taking time to explain all scientific terminology. Do not delete the grey text included in each section of this template as you move through drafting because it might be a useful reference for patient reviewers. Additional prompts for the company have been in red text to further advise on the type of information which may be most relevant and the level of detail needed. You may delete the red text.

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

Response: Talazoparib, Talzenna®

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

Response: To be treated with talazoparib, people need to have a specific type of breast cancer and to have previously had certain treatments.[1] Talazoparib is for people with locally advanced or metastatic breast cancer. • Locally advanced breast cancer is when the tumour is larger than 5 centimetres in size or the cancer has spread to tissues around the breast such as the skin, chest wall or lymph nodes.[2] • Metastatic breast cancer is when cancer that has started in the breast has spread to other parts of the body to form new tumours. [3,4] To be treated with talazoparib, people need to have a genetic test, using blood or saliva, to test for changes in the genes *BRCA1* or *BRCA2*. Changes in a gene are also called mutations. Mutations are small changes in the DNA that makes up a gene. Genes contain information for proteins, which have different roles in cells. Mutations can change how these proteins work in the cell. • BRCA proteins help to repair damaged DNA inside the cell but if there is a mutation in *BRCA1* or *BRCA2*, the DNA repair process does not work well.

- This increases the development of mutations in the cell's DNA, which will increase a person's risk of developing cancer.
- Talazoparib is for people with *BRCA1* or *BRCA2* mutations.[1]

Before treatment, a sample of the tumour is taken, to understand more about which proteins the cancer cells are making. This can help to pinpoint a person's treatment options.

- To be treated with talazoparib, the persons cancer cells **should have a low amount of** a protein called human epidermal growth factor 2, also known as HER2 on their surface.[1] If a breast cancer cell has a low amount of HER2 on the surface, this is known as **HER2−negative**, or **HER2−**.[5]
  - HER2 is a receptor, found on both healthy and cancerous cells. Receptors are specialised proteins that bind to specific substances, to cause an effect in the cell. HER2 controls how fast cells grow.[5]
- The cancer cells **can have** oestrogen or progesterone receptors. The presence of either oestrogen or progesterone receptors on the breast cancer cells means they are known as **hormone receptor positive**, or **HR+**.[5] Talazoparib can be given if a tumour **is HR+ or not**.[1]
  - Progesterone and oestrogen are reproductive hormones which effect how the breasts work and cell growth in the breasts. [5]

When cancer cells are not HR+ and are also HER2−, they are called **triple negative**.[6-8] When cancer cells are HR+, but HER2−, it is known as **HR+/HER2−**. Talazoparib is for people with *BRCA1* or *BRCA2* caused metastatic or advanced breast cancer, whose tumours are either triple negative or HR+/HER2−.[1]

However, if the person's cancer cells **are** HR+, they should have been previously treated with hormonal therapies before taking talazoparib, unless these treatments were not suitable for them.[1] Hormonal therapies lower the amount of hormones in the body, or reduce their effect on cell growth.

People taking talazoparib also need to have been previously treated with chemotherapy, including types of chemotherapy drugs called anthracyclines and/or taxanes, unless these treatments were not suitable for them.[1]

In summary, to be prescribed talazoparib people would:[1]

- have locally advanced or metastatic breast cancer
- have mutations in their *BRCA1* or *BRCA2* gene
- have either HR+/HER2− or triple negative breast cancer
- have tried hormonal therapies for their cancer before, but only if their tumour is HR+/HER2−
- have had chemotherapy for their cancer before

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.

Response:
On 16 October 2018 talazoparib was approved by the Food and Drug Administration (FDA) in the USA.[10] Since then, talazoparib has been approved in the European Union, gaining approval from the European Medicines Agency (EMA's) Committee for Medicinal Products for Human Use

(CHMP) on 26 April 2019.[11] Talazoparib was authorized by the UK Medicines and Healthcare products Regulatory Agency (MHRA) on the 20 June 2019.[1]

Currently, talazoparib is being evaluated by the National Institute for Health Care and Excellence (NICE). This is required for a drug or treatment to be prescribed by the National Health Service (NHS) in the UK.

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:

Response:
Not applicable.

SECTION 2: Current landscape

Note to authors: This SIP is intended to be drafted at a global level and typically contain global data. However, the submitting local organisation should include country-level information where needed to provide local country-level context.

Please focus this submission on the **main indication (condition and the population who would use the treatment)** being assessed by NICE rather than sub-groups, as this could distract from the focus of the SIP and the NICE review overall. However, if relevant to the submission please outline why certain sub-groups have been chosen.

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.

Response:
Breast cancer is the most common cancer both in the UK and worldwide, with 2.26 million cases reported globally in 2020 alone.[12,13] Each year in the UK, breast cancer is diagnosed in around 56,000 people and 11,500 people die from the condition.[14] Approximately 3-5% of breast cancer cases may be caused by mutations in a person's *BRCA1* or *BRCA2* gene.[15]

It is estimated that for females born in the UK after 1960, the risk of developing breast cancer during their life is around 1 in 7, and it is the leading cause of female cancer death.[13,16] For females with *BRCA1* or *BRCA2* 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.[17]

People with *BRCA1* or *BRCA2* metastatic breast cancer are also likely to be younger at diagnosis, than people with breast cancer without the mutation.[17,18] Most breast cancers occur in females over the age of 50,[19] however the median age of diagnosis of breast cancer is 40–43 years old for people with the *BRCA1* or *BRCA2* mutation.[20]

Breast cancer can progress to locally advanced or metastatic breast cancer, in which the cancer tumour has spread throughout the breast, [2] or the cancer has travelled to other parts of the body to form new tumours.[3,4] The most common places for breast cancer tumours to spread for people with metastatic breast cancer are the central nervous system (CNS), lungs, bones, liver, distant lymph nodes.[4]

The symptoms people experience with metastatic breast cancer vary, depending on where their cancer has spread to, but pain, fatigue and emotional distress are very common for people living with metastatic breast cancer. [21] People with *BRCA1* breast cancer are at a higher risk of their tumours spreading to the CNS than people with breast cancer who do not have this mutation.[22] The presence of tumours in the CNS can reduce how long people live for before their cancer gets worse. [22-24]

For people living with breast cancer, their symptoms and how the condition changes their future, reduce their quality of life and wellbeing. [25] This may also affect their caregivers, families and people closest to them.

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?

Response:
Patients may notice the development of a new lump, an alteration in the size or shape of the breast, a lump or swelling in the armpit, a change in appearance or texture of the skin or nipple, bleeding or discharge from the nipple, and/or a rash or redness around the nipple area which leads to an assement by a doctor and subsequent investigations. This may include blood tests, imaging and biopsies. Depending on the results of the investigations, a breast cancer diagnosis and the type can be made.

People can sometimes be offered a genetic test, using samples of saliva or blood, to test whether they have a *BRCA1* or *BRCA2* mutation.[26,27] 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 important for talazoparib, because it works by targeting the *BRCA1* or *BRCA2* mutation in the cancer cell.

Genetic tests for *BRCA1* or *BRCA2* are given in the UK when it is suspected that a person could have the *BRCA1* or *BRCA2* mutation. This can include when:

- a person has breast cancer when they are under 40 years old [27]
- a person has breast cancer in both breasts when they are under 50 years old [26]
- a person has triple negative breast cancer when they are under 60 years old [27]
- a male has breast cancer [27]
- a person has breast cancer and Ashkenazi Jewish ancestry, [27] because *BRCA1/2 mutations are more common in this population*[28]
- There is a strong family history of breast cancer in relatives under 45 years old [27]
- a person's close relative has a *BRCA1* or *BRCA2* mutation [27]

In the UK, the current NICE guidelines recommend offering a genetic test when there is a greater than 10% chance that a person has the *BRCA1* or *BRCA2* mutation. [27] As a result, the genetic tests for *BRCA1* or *BRCA2* are not given to all people with breast cancer.

After breast cancer diagnosis, a sample of the tumour is taken through a biopsy 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, talazoparib can be given to people with HR+/HER2−, or triple negative breast cancer.[5]

Abbreviations: NICE, national institute for health care and excellence; HER2−, human epidermal growth factor 2 negative; HR+, hormone receptor positive.

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.

Response:

Currently, the treatment for *BRCA1* or *BRCA2* breast cancer, that is HR+/HER2− or triple negative includes **non-targeted** treatments. There is no specific treatment for breast cancer caused by *BRCA1* or *BRCA2* mutations.

Non-targeted treatments include **chemotherapy**, which is recommended in standard practice to be the first treatment given until the disease progresses. [26,31] Progression is when a cancer spreads further, or the tumours grow and get worse. Chemotherapy can be given if the cancer **is HR+/HER2−, or triple negative**. [26,31]

In metastatic breast cancer chemotherapy can help to control the growth of the cancer cells, or improve some cancer symptoms. However, chemotherapy itself can have a lot of side effects.

Often chemotherapy is given as a drip through a needle into a vein, known as an intravenous infusion. People who would be prescribed talazoparib need to have already had chemotherapy with types of drugs called anthracyclines and/or taxanes, [26] unless these were not suitable for them. If there are no clinical trial drugs that could be tried, chemotherapies that include platinum are also recommended for people with *BRCA1* or *BRCA2* metastatic breast cancer, [29] if they have not been tried before.

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. [26] The type of chemotherapy given depends on the type of breast cancer. [26] There is little information about whether combination treatment or single agent chemotherapy works best for people with *BRCA1* or *BRCA2* metastatic breast cancer. [32]

If the breast cancer **is HR+/HER2−**, then **hormonal therapies** can be given.[29,31] They cannot be given for triple negative breast cancer. Hormonal therapies lower the amount of oestrogen or progesterone in the body or reduce their effect on cell growth.[29,31] These therapies would not work for triple negative breast cancer, because triple negative breast cancer tumours do not use

oestrogen or progesterone to grow. Examples of hormonal therapies for breast cancer include tamoxifen, fulvestrant and aromatase inhibitors,.[31]

Current therapies are not specific for tumours that have spread to the CNS, which are common in *BRCA1* metastatic breast cancer.[22] Current options to treat *BRCA1* or *BRCA2* metastatic breast cancer in the CNS are surgery, radiotherapy and chemotherapy.[22-24] However, some chemotherapy drugs are not able to pass into the brain to slow tumour growth.[22-24] Therefore, there is a need for new drugs to effectively treat *BRCA1* or *BRCA2* metastatic breast cancer in the CNS.

Figure 2 shows where talazoparib would fit in the current treatment pathway, for people with HR+/HER2− or triple negative *BRCA1* or *BRCA2* metastatic or locally advanced breast cancer.

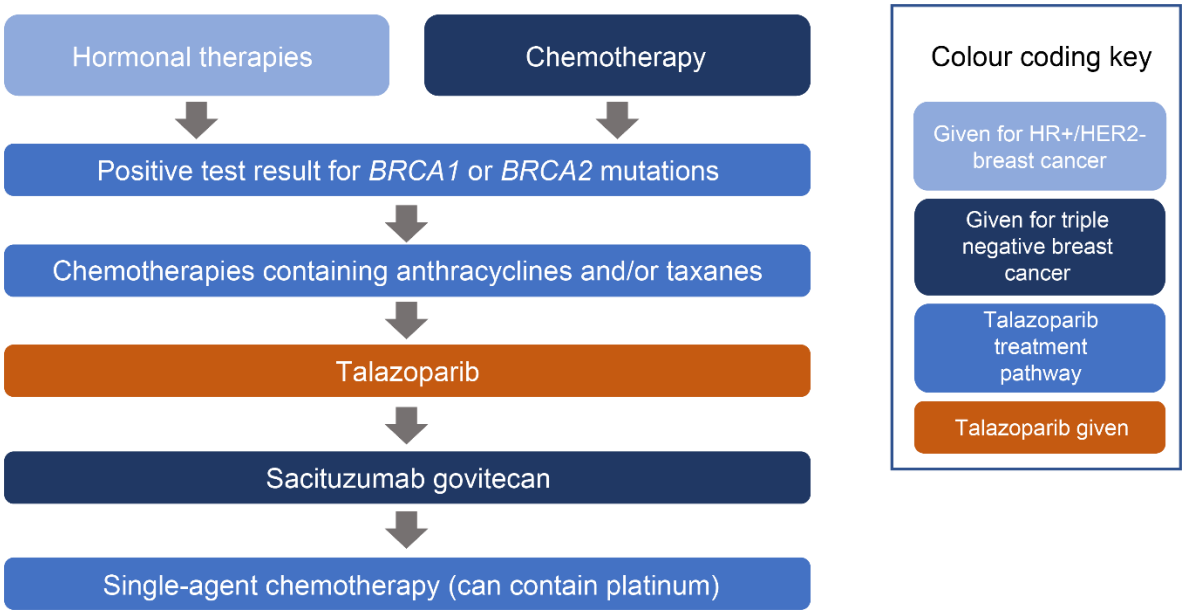

Figure 2. Where talazoparib would fit in the current treatment pathway

HER2−, human epidermal growth factor 2-negative; HR+, hormone receptor positive.

Abbreviations: CNS, central nervous system; HER2−, human epidermal growth factor 2 negative; HR+, hormone receptor positive.

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.

Response:
People living with breast cancer have shared their experiences of living with the condition. This includes the effect that it has upon their life, wellbeing, and symptoms and side effects of any medication they may be taking. These insights help pharmaceutical companies developing drugs to understand what needs these people have and what is most important to them. This means pharmaceutical companies can better plan clinical trials to measure factors that are most important for people with breast cancer. This is called **patient-based evidence**.

People with advanced breast cancer and *BRCA1* or *BRCA2* mutation reported worse physical health and emotional wellbeing than people with advanced breast cancer who did not have *BRCA1* or *BRCA2* mutations. [33] In particular, people with *BRCA1* or *BRCA2* mutations had more problems owing to pain, anxiety and depression.[33]Studies have also investigated the effect of breast cancer on quality of life based on age. The impact of breast cancer on people's health who were aged between 18 to 44 years old was four times larger, compared with those aged 45 years or over.[18] This is particularly important to consider for people with *BRCA1 or BRCA2* breast cancer, because they are likely to be younger than people with breast cancer without the mutation.

Progression of breast cancer in people with or without *BRCA1* or *BRCA2* mutation significantly worsens physical health. [21,25,34] Patient based evidence suggests there are increases in difficulty breathing, fatigue, diarrhoea and vomiting with breast cancer progression. [21,25,34] This leads to a reduction in people's quality of life overall, with their ability to do daily tasks specifically affected. [21,25,34] People with metastatic breast cancer who have stable disease, in which their cancer is not worsening, have improved scores in their quality of life than people who have progression, or people who have cancer that is not responding to treatment. [21,25,34]

Treatment-related side effects are also important when considering the physical health and quality of life of people with metastatic breast cancer. Studies have suggested that people with breast cancer receiving chemotherapy have more severe symptoms than people who had received targeted hormonal therapies, leading to reductions in how they rate their quality of life. [35,36] Furthermore, studies have suggested that people with *BRCA1* and *BRCA2* breast cancer have more side effects from chemotherapy, compared with people who have breast cancer without the *BRCA1* and *BRCA2* mutation. [33] Therefore, it is important that the frequency and severity of treatment-related side effects are considered in treatment decisions. The frequency is how often a person experiences a side effect and the severity is how impactful it is on their health.

SECTION 3: The treatment

Note to authors: Please complete each section with a concise overview of the key details and data, including plain language explanations of any scientific methods or terminology. Please provide all references at the end of the template. Graphs or images may be used to accompany text if they will help to convey information more clearly.

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.

Response:

Talazoparib works by causing certain cancer cells to die or by slowing their growth.[37-39]

BRCA1 and *BRCA2* genes contain the information for proteins that repair DNA damage.[39] When someone has a mutation in their *BRCA1* or *BRCA2* genes that affects their whole body, their BRCA1 or BRCA2 proteins do not properly repair damaged DNA. [39] If damaged DNA is not repaired, it can lead to a mutation in the cell. If a cell develops a lot of mutations, it can become cancerous and grow rapidly. BRCA1 and BRCA2 proteins are found in all cells, but they are particularly important in the breast and ovary cells for repairing damaged DNA. This is why people with *BRCA1* and *BRCA2* mutations have a high risk for breast and ovarian cancers.

There are other DNA repair machinery in all cells, one of which is called PARP. [39] If the BRCA1 or BRCA2 proteins aren't working properly, then the PARP is relied on heavily to repair any damaged DNA.[39] The repair of damaged DNA by PARP can enable cancer cells to survive and replicate, which causes tumours to grow. Talazoparib stops PARP from working, [40-43] this is summarized in Figure 3.[44]

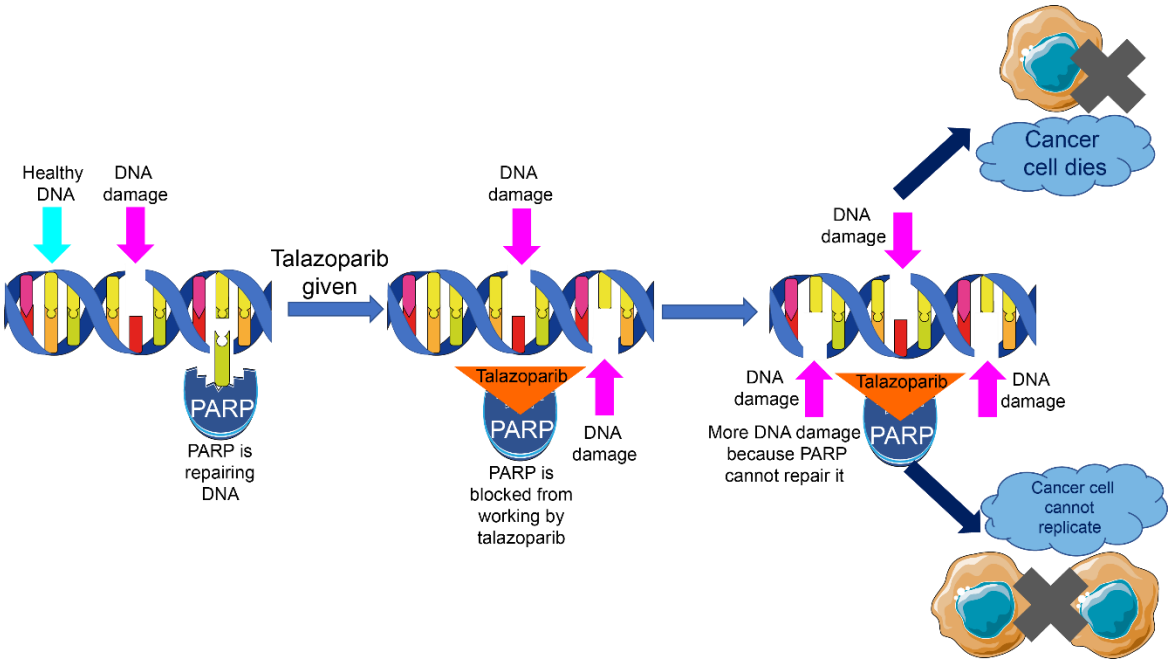

Figure 3. How talazoparib works to slow cancer cell growth

When talazoparib blocks the activity of PARP, this means that:

- DNA damage in cancer cells cannot be repaired
- the cancer cell cannot replicate because they have too much DNA damage
- the cancer cells develop so much DNA damage that they die

Blocking the activity of PARP does not affect the non-cancerous cells in the body in the same way, because healthy cells do not have as many mutations as cancer cells. [38]

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.

Response:
Not applicable, because talazoparib is not intended to be used together with other treatments for breast cancer.

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?

Response:
Talazoparib is taken as a hard capsule by mouth, also known as orally, once a day, and it can be taken with or without food.[1] The recommended dose is 1 milligram (mg) per day. This dose can be reduced if needed as advised by the treating doctor by using a different capsule that contains 0.25mg of talazoparib, if a person has too many side effects.[1] People should be treated with talazoparib until either their disease progresses, or they have too many harmful side effects from treatment.[1]

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.

Response:

Talazoparib has been investigated in two clinical trials, called ABRAZO (NCT02034916) and EMBRACA (NCT01945775).[45,46] The results from EMBRACA are most relevant for this appraisal of talazoparib, so their findings will be covered in this summary. This is because EMBRACA was a phase 3 trial including more people and the results from it were used for the drug to be approved by regulators, including the MHRA.[45] The data from EMBRACA were also used in understanding how cost-effective talazoparib could be, if it was used in the NHS.[45] Both trials were important in learning about talazoparib, and the results from ABRAZO helped to develop of EMBRACA and further our understanding of talazoparib.[11,45,46]

EMBRACA was a global clinical trial, including 431 people in 16 countries.[45] Of the 431 people on the trial, 287 took talazoparib, while 144 received the standard treatment for metastatic breast cancer, which is chemotherapy.[45] It started in October 2013 and ended in December 2019.

Before joining a clinical trial, people need to give consent and trial doctors need to do medical checks, to confirm if the people are able to join the trial or not. For EMBRACA, several things needed to be considered.[45]

To join the trial, people:

- had chemotherapy in the past
- were not able to have any other treatment
- had tumours large enough to be measured through scans
- were able to do some daily activities
- had functioning kidneys and liver
- their levels of haemoglobin, white blood cells and platelets in the blood were suitable

People could not join the trial if they:

- were badly affected by their cancer in their ability to do daily activities
- had previously had a PARP blocking drug
- had untreated CNS tumours
- were not able to have any of the trial chemotherapies
- had progression when they had been given chemotherapy containing platinum

In EMBRACA, there were several key measures to assess how well talazoparib works for treating the condition, also known as efficacy. The primary endpoint is the key marker of whether a drug or treatment is effective in a clinical trial.

In EMBRACA, the primary endpoint was progression free survival (PFS).[45] PFS is how long a person lives until their cancer gets worse.

All clinical trials monitor the safety of the drug, by recording any unexpected medical problems people had. The doctors assess whether these could be side effects linked to treatment.

Clinical trials also have secondary endpoints. These are measures for other factors researchers need to understand when developing a drug. EMBRACA had several secondary endpoints,[45] including:

- whether the people's tumours changed in size
- the overall survival (OS), which is how long people lived for
- how talazoparib was processed by the body
- what other medications people were taking

Throughout EMBRACA researchers also collected patient based evidence, to understand the effect treatment was having upon people quality of life, symptoms and wellbeing.

Abbreviations: CNS, central nervous system; MHRA, medicines and healthcare products regulatory agency; NHS, national health service.

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.

Response:

A significantly improved PFS was the main measure of the EMBRACA trial to study the efficacy of talazoparib. During EMBRACA, people taking talazoparib showed a **significantly improved PFS** than people who were taking chemotherapy.[45 47]

- The average PFS for people taking talazoparib was 8.6 months, compared with chemotherapy, which was 5.6 months.

- After 1 year of taking trial treatment, 37% of people taking talazoparib had not had disease progression, compared with 20% of people taking chemotherapy.
    - Extending PFS is an important factor for people with metastatic breast cancer, because it gives them a longer period of time without their illness worsening.

EMBRACA also included people whose breast cancer had spread to their CNS. Currently, the treatment options for CNS tumours in metastatic breast cancer are limited.[45,47]

- In people receiving talazoparib who had CNS tumours, their average PFS was 5.7 months, compared with 1.6 months for people receiving chemotherapy.
    - This suggests that talazoparib could be beneficial in improving PFS for people with CNS tumours, which is not specifically helped by current therapies.

As well as looking at PFS, EMBRACA investigated the OS of people in the talazoparib group, compared with the standard chemotherapies group.[45,47]

- The average OS for people taking talazoparib was 19.3 months, compared with chemotherapy, which was 19.5 months.
- After doing some statistical tests on the OS data, the researchers found that the differences between these results were considered too small to be meaningful. This means that there was no significant effect on OS by talazoparib.

The efficacy of a drug can be even better understood after a drug is approved, by studying data from thousands of people in routine clinical care in real-world evidence studies.

Abbreviations: CNS, central nervous system; OS, overall survival; PFS, progression free survival.

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.

Response:

In the EMBRACA trial, people were asked to complete questionnaires of their experiences of their cancer symptoms, the impact of these symptoms on their lives and how treatment affected these.[45] These are called patient reported outcomes (PROs). Multiple PROs were used to capture the impact of trial treatment on quality of life during EMBRACA. [48] PROs are important tools to capture patient based evidence.

Overall, PROs showed that the **quality of life was significantly improved** for people taking talazoparib, compared with chemotherapy.[45 48]

One PRO used throughout was called the EORTC QLQ-C30, which is a specific PRO for quality of life in people living with cancer. Compared with chemotherapy, there were significant improvements for people taking talazoparib in their:[45 48]

- physical health
- ability to undertake their roles in their daily life
- emotional health
- cognitive function

- social wellbeing.

The clinical trial also used a PRO called EORTC QLQ-BR23, which is specific for breast cancer. Compared with chemotherapy, there were significant improvements for people taking talazoparib in their:[45 48]

- treatment side effects
- breast and arm symptoms
- fatigue
- pain
- insomnia
- appetite loss
- body image
- ability to do daily tasks.

PRO results were collected on the time it took for people to report a worsening in quality of life. This is when the person taking treatment reports their quality of life has got worse, because of their condition. For people taking talazoparib, the average time for a worsening in quality of life was 24.3 months, compared with 6.3 months for people receiving chemotherapy.[45 48]

Together, these PRO data suggest that treatment with talazoparib significantly improves or maintains quality of life for people with *BRCA1* or *BRCA2* metastatic breast cancer, for a longer period of time, compared with currently available chemotherapies.[45 48]

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.

Response:

During all clinical trials, the safety of the trial treatments are monitored by recording any unexpected medical problems the people have. These are known as adverse events (AEs), which may or may not be related to the study treatment the participant is receiving. AEs can vary in their severity, so they are recorded as mild, moderate, or severe. Severity is how much an AE affects someone's health. Some AEs can be life threatening; these are also known as serious AEs.

The AEs that are shown in a clinical trial may be side effects caused by the treatment, but this can be uncertain. A lot of research is needed to know if an AE is definitely a side effect of a drug. However, researchers can learn about the possible side effects of a drug by learning about the AEs during a clinical trial. After a drug is approved it can be better understood by studying data from thousands of people taking the treatment in routine clinical care, which is known as a real-world evidence study. This also helps researchers and doctors better understand side effects.

Almost all people receiving talazoparib, or chemotherapy reported some AEs in the EMBRACA trial. [49-51] The most common AEs in the talazoparib group were anaemia and fatigue, affecting about half of people treated with talazoparib. [49-51] In the chemotherapy group the most common

AEs were nausea and a low level of white blood cells, affecting about 40% of people treated with chemotherapy. [49-51]

For people taking talazoparib, the AEs were often milder in severity than the chemotherapy group.[49-51] For example, people taking talazoparib had less severe hair loss, blisters on their hands and feet, and diarrhoea than the people receiving chemotherapy.[49-51] The people taking talazoparib also had less severe symptoms that required hospital treatment, including fluid around the lungs and low levels of white blood cells, compared with people receiving chemotherapy. [49-51]

In EMBRACA, from 412 people in total, there was 1 participant in the talazoparib group and 1 in the chemotherapy group who died because of an AE. [49-51]

During the trial less than 10% of people stopped taking talazoparib because of AEs, which was slightly lower than the chemotherapy group. [49-51] This suggests that potential side effects of talazoparib could be tolerable enough to continue treatment. If a person is having too many AEs, their dose of talazoparib could be lowered.

Overall, the results from EMBRACA suggest that the potential side effects of talazoparib are manageable.

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
-

Response:

Talazoparib is a targeted therapy for locally advanced or metastatic breast cancer, that is HR+/HER2− or triple negative, for people with *BRCA1* or *BRCA2* mutations, who have previously had chemotherapy and/or hormonal therapy, if these were suitable.[1]

In the EMBRACA trial, treatment with talazoparib extended PFS and improved quality of life compared with chemotherapy, including for people with CNS tumours. [45 48-51] Current therapies for this condition are chemotherapies, but sometimes these cannot pass into the brain to target CNS tumours, which are more common in people with *BRCA1* metastatic breast cancer.[22-24] There was no significant difference in OS for people taking talazoparib compared with chemotherapies. [45 48]

PRO results from people in the EMBRACA trial suggest that quality of life is improved for a longer period of time for people taking talazoparib, than in those receiving chemotherapy. [45 48] This may be in part due to the less severe side effects seen in the talazoparib group compared with the chemotherapy group. [49-51] The reduced effect of treatment upon people's lives and wellbeing may enable them to spend more time on activities that are important to them and feel in better health, than if they were having chemotherapies.

Talazoparib is also administered as a capsule by mouth, which can be taken at home. [1]This could be convenient for people taking it and reduces the time of hospital visits for themselves and their supporting caregivers.

Abbreviations: CNS, central nervous system; HER2–, human epidermal growth factor 2-negative; HR+, hormone receptor positive; OS, overall survival; PFS, progression-free survival.

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

Response:

To be treated with talazoparib, people must have received a genetic test for the *BRCA1* or *BRCA2* mutation. There are criteria people must meet to have access to these tests and they are not available to all people with breast cancer. Accessing talazoparib may be limited by the availability of *BRCA1* or *BRCA2* tests. [26,27]

In the EMBRACA trial, more people experienced fatigue and anaemia compared with chemotherapy, so the effect of these potential side effects may need to be managed. [49-51]

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.

Response:

To assess the value of the drug talazoparib to the NHS, a health economic model has been developed. It considers several factors that are important in assessing how a drug affects people's lives, its financial effects and the cost to the NHS in patient care.

For cancer drugs, data are added into the health economic model about the condition of the people that would be taking the drug. These are defined as follows:

- **Progression-free** - the person is responding well to treatment. Data from EMBRACA is inputted from:
    - people taking talazoparib
    - people receiving standard chemotherapies.
- **Progressed disease** – the person is not responding well to treatment and their disease is getting worse. Data from EMBRACA is inputted on:
    - any treatment the person is having after their disease has progressed.
- **Death** – the person has died because their disease got worse.

The model considered the quality of life of people receiving talazoparib compared with chemotherapy, then contrasted this with how long they lived for after starting the treatment. This measure is known as a quality-adjusted life year (QALY). This also used data from EMBRACA. [45]

- The quality of life data were collected using PROs.
- How long the person lived after starting treatment was calculated using OS data.

Overall, there were improvements in QALY for people taking talazoparib compared with people receiving chemotherapy.

- Treatment with talazoparib significantly improves PFS compared with chemotherapy.[45] This means that people taking talazoparib are spending more time in better health, compared with people taking chemotherapy.
    - If PFS is extended, treatment with talazoparib may extend the time that people do not need additional medical intervention and clinical care associated with disease progression.
- Quality of life is higher overall for those taking talazoparib than those receiving chemotherapy and the time until quality of life deterioration is longer than for those receiving chemotherapy.[45]
    - PRO results showed that with talazoparib treatment, people have an improved ability to undertake their daily activities and improvements in symptoms such as pain, compared with chemotherapy.
    - Owing to this, people taking talazoparib may be better able to undertake their daily activities and require less supportive care for a longer time than people receiving chemotherapy.
    - If people feel they can, they may be better able to continue in employment, than if they were having chemotherapy.

The economic model also considers the number of hospital visits required for talazoparib and chemotherapy to be given. Chemotherapy needs to be administered in a clinical setting, with specialised equipment and healthcare staff. In contrast, talazoparib is a capsule that can be taken at home without medical supervision. This reduces the economic cost for the healthcare provider in giving the drug, but talazoparib is a more expensive drug than chemotherapy.

Additionally, in the EMBRACA trial, fewer people taking talazoparib were hospitalised because of serious AEs, than people receiving chemotherapy. If serious AEs requiring hospitalisation are reduced in talazoparib treatment compared with chemotherapy, there may be lower economic costs of managing treatment-related side effects. [49-51] However, anaemia was a common side effect of talazoparib seen in EMBRACA. This can be managed in severe cases by having a red blood cell transfusion, which can be expensive, so this needs to be considered in healthcare costs for talazoparib treatment.

Economic models suggest that for all people with progressive disease, they will lose some of their employment productivity and some of their earnings as a result.[52] This affects 10% of people

whose cancer is responding to treatment and 30% of people whose cancer is stable, owing to their treatment. [52] An extended PFS in talazoparib treatment suggests that people could be more able to work and could be in a better financial situation, than if their condition had progressed in a short period of time.

NICE also considers how severe a disease is when considering a drug for use by the NHS. Metastatic breast cancer is considered to be a severe disease, because it has a substantial impact on how long a person with it could live. Pfizer has proposed a discount on talazoparib, known as a patient access scheme. When the patient access scheme is applied, talazoparib meets the threshold that is considered to be cost-effective by NICE.

The economic model of talazoparib has some uncertainty in the results because it uses data from EMBRACA. This does not give a full picture of the cost of treatment of talazoparib. The long-term OS was monitored for people taking part in EMBRACA, even after the trial ended. This could be compared with data from other studies, which share the OS for other treatments, including chemotherapies. However, more real-world evidence studies are needed to support the data from EMBRACA.

Furthermore, the model does not capture all of the patient experiences and benefits talazoparib could have. For example, it does not take into account the convenience of taking talazoparib at home, compared with having chemotherapy in a hospital. It also does not capture that PFS is also extended in people with CNS tumours, who do not benefit as much from current treatments as people without CNS tumours. It also did not take into account the results of PROs that are specific for breast cancer or capture the ongoing cost of care for a person living with cancer, for themselves and their caregivers.

Abbreviations: AE, adverse event; CNS, central nervous system; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; OS, overall survival; PFS, progression-free survival; PRO, patient-reported outcome; QALY, quality-adjusted life-year.

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)

Response:
Talazoparib would be the first targeted treatment for people with *BRCA1* or *BRCA2* breast cancer that would be available on the NHS.

Abbreviation: NHS, National Health Service.

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

Response:
There are not expected to be any equality issues in talazoparib treatment.

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.

Response:
Here are some further resources, where you can find out more background information, which may be relevant to breast cancer or talazoparib.

- Cancer Research UK information about:
  - 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/inherited-cancer-genes-and-increased-cancer-risk
  - breast cancer: https://www.cancerresearchuk.org/about-cancer/breast-cancer
- Breast cancer now information about:
  - metastatic breast cancer: https://breastcancernow.org/information-support/support-you/secondary-metastatic-breast-cancer
  - genetic testing for *BRCA1* or *BRCA2* mutations: https://breastcancernow.org/information-support/have-i-got-breast-cancer/family-history/genetic-testing-altered-breast-cancer-genes
  - PARP inhibitors for breast cancer: https://breastcancernow.org/information-support/facing-breast-cancer/going-through-breast-cancer-treatment/parp-inhibitors-in-breast-cancer-treatment
- NHS information about:
  - breast cancer in women: https://www.nhs.uk/conditions/breast-cancer/
  - breast cancer in men: https://www.nhs.uk/conditions/breast-cancer-in-men/
  - predictive genetic tests for cancer: https://www.nhs.uk/conditions/predictive-genetic-tests-cancer/
- Clinical trial information about talazoparib:
  - EMBRACA
    - ClincicalTrials.gov: https://clinicaltrials.gov/ct2/show/NCT01945775
    - Clinical trial results: https://www.nejm.org/doi/full/10.1056/nejmoa1802905
  - ABRAZO:
    - ClinicalTrials.gov: https://clinicaltrials.gov/ct2/show/NCT02034916
    - Clinical trial results: https://aacrjournals.org/clincancerres/article/25/9/2717/82587/A-Phase-II-Study-of-Talazoparib-after-Platinum-or

Further information on NICE and the role of patients**:**

- Public Involvement at 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

Response:

Life years	The number of additional years that people spend alive after treatment.
OS	Overall survival. The length of time that a patient lives with a disease until their death
PFS	Progression free survival. The length of time that a patient lives with a disease without it getting worse.
QALY	Quality-adjusted life year. The number of additional years patients spend alive, however this measure also takes into account the quality of these additional years.
Real-world evidence studies	Studies after a drug is approved of its use and effect in normal clinical practice.
Patient based evidence	Information given by a person with a condition about how it affects their daily life, their symptoms and how treatment affects them. These can help to investigate overall quality of life.
PRO	Patient reported outcome. Used to measure information given by a patient about how their condition or treatment affects their quality of life. These are used as part of patient based evidence.
Adverse event (AE)	An unexpected medical problem that happens during treatment with a drug or therapy. It may or may not be caused by the drug or therapy.
Side effect	A medical problem that happens during treatment that may be related to the drug or therapy
CNS	Central nervous system. This includes the brain and spinal cord.
Mutation	A change in a gene. This can sometimes make a protein work differently

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:

Response:

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Talazoparib for treating HER2-negative locally advanced or metastatic breast cancer with germline BRCA1/2 -mutations

[ID1342]

Clarification questions

February 2023

File name	Version	Contains confidential information	Date
Clarification questions_ Talazoparib_ID1342	FINAL	Yes	15/02/2022

Section A: Clarification on effectiveness data

A1. Priority question: Clinical advice to the external assessment group (EAG) is that clinical outcomes vary depending on line of treatment. Therefore, please provide EMBRACA trial patient baseline characteristics (Company Submission Document B [CS], Table 14), progression-free survival (PFS) (Table 9, Figure 7), final unadjusted and adjusted overall survival (OS) (Table 10, Figure 8 and Figure 10) and objective response rate (ORR) (Table 11) for the following patient groups:

i. **patients with triple-negative breast cancer (TNBC) who received talazoparib as first-line treatment for advanced breast cancer (aBC)**

ii. **patients with TNBC who received talazoparib as second-line or later treatment for aBC**

iii. **patients with hormone receptor positive (HR+) status advanced breast cancer (aBC) who received talazoparib as first-line treatment for aBC**

iv. **patients with HR+ status aBC who received talazoparib as second-line or later treatment for aBC.**

It should be noted that the EMBRACA trial was designed with adequate power to detect certain effect sizes in the intention-to-treat (ITT) population for PFS and OS endpoints (90% and 80%, respectively). Therefore, any analyses across these subgroups (i to iv) with small patient numbers would not be powered to detect significant differences. The number of patients in in the TNBC and HR+ populations with 0, 1 and ≥2 prior lines of CT are shown in Table 1 below.

Table 1. Population size in the TNBC and HR+ Populations in Those With 0, 1, ≥ 2 Prior Lines of CT in the Advanced Setting

	Talazoparib (N=287)	Overall PCT (N=144)
TNBC (CT by line in advanced setting)		
0L CT	52	26
1L CT	50	21
≥2L CT	28	13
TNBC (0L CT in advanced setting; based on prior platinum in earlier settings)		

Prior platinum received	12	7
No prior platinum received	40	19
HR+ (CT by line in advanced setting)		
0L CT	59	28
1L CT	57	33
≥2L CT	41	23
TNBC (0L CT in advanced setting; based on prior platinum in earlier settings)		
Prior platinum received	3	2
No prior platinum received	56	26

For patient baseline characteristics for TNBC and HR+ subgroups see Table 2 and Table 3 for outcomes. See Figure 1 and Figure 2 for PFS Kaplan-Meier curves for each subgroup.

Table 2. EMBRACA: Patient baseline characteristics – overall TNBC and HR+ subgroups

Patient characteristic		ITT		TNBC		HR+	
		TALA	PCT	TALA	PCT	TALA	PCT
Cohort size		287	144	130	60	157	84
Age	Median (range), years	45 (27-84)	50 (24-88)	43 (27-81)	44.5 (26-73)	47 (30-84)	52 (24-88)
	Mean (STD), years	47.5 (11.61)	49.4 (12.12)	NR	NR	NR	NR
Age category (years), n (%)	<50	182 (63.4)	67 (46.5)	92 (70.8)	37 (61.7)	90 (57.3)	30 (35.7)
	50 to <65	78 (27.2)	67 (46.5)	32 (24.6)	21 (35.0)	46 (29.3)	46 (54.8)
	≥65	27 (9.4)	10 (6.9)	6 (4.6)	2 (3.3)	21 (13.4)	8 (9.5)
Gender	Female	283 (98.6)	141 (97.9)	130 (100.0)	60 (100.0)	153 (97.5)	81 (96.4)
	Male	4 (1.4)	3 (2.1)	0 (0.0)	0 (0.0)	4 (2.5)	3 (3.6)
Height (cm)	Mean (STD)	163.2 (7.03)	162.4 (6.82)	NR	NR	NR	NR
	Median (range)	162.5 (142.0-188.0)	161.0 (147.0-180.0)	NR	NR	NR	NR
Weight (kg)	Mean (STD)	69.8 (17.24)	68.9 (16.36)	NR	NR	NR	NR
	Median (range)	65.6 (42.3-141.2)	66.0 (41.7-157.8)	NR	NR	NR	NR
BMI (kg/m^2)	Mean (STD)	26.1 (6.03)	26.1 (5.95)	NR	NR	NR	NR
	Median (range)	24.5 (17.2-49.6)	25.3 (17.3-56.2)	NR	NR	NR	NR
Race, n (%)	Asian	31 (10.8)	16 (11.1)	15 (11.5)	5 (8.3)	16 (10.2)	11 (13.1)
	Black or African American	12 (4.2)	1 (0.7)	8 (6.2)	1 (1.7)	4 (2.5)	0 (0.0)
	White	192 (66.9)	108 (75.0)	85 (65.4)	43 (71.7)	107 (68.2)	65 (77.4)
	Other	5 (1.7)	1 (0.7)	4 (3.1)	1 (1.7)	1 (0.6)	0 (0.0)
	Not reported	47 (16.4)	18 (12.5)	18 (13.8)	10 (16.7)	29 (18.5)	8 (9.5)
Ethnicity, n (%)	Not Hispanic or Latino	210 (73.2)	111 (77.1)	95 (73.1)	40 (66.7)	115 (73.2)	71 (84.5)
	Hispanic or Latino	31 (10.8)	15 (10.4)	17 (13.1)	10 (16.7)	14 (8.9)	5 (6.0)

Patient characteristic		ITT		TNBC		HR+	
		TALA	PCT	TALA	PCT	TALA	PCT
	Not reported	46 (16.0)	18 (12.5)	18 (13.8)	10 (16.7)	28 (17.8)	8 (9.5)
ECOG performance status, n (%)	0	153 (53.3)	84 (58.3)	(53.8)	(61.7)	(52.9)	(56.0)
	1	127 (44.3)	57 (39.6)	(43.8)	(38.3)	(44.6)	(40.0)
	2	6 (2.1)	2 (1.4)	(1.5)	(0.0)	(2.5)	(2.4)
	Missing	1 (0.3)	1 (0.7)	NR	NR	NR	NR
BRCA status, n (%)	*BRCA*1-positive	133 (46.3)	63 (43.8)	100 (76.9)	43 (71.7)	33 (21.0)	20 (23.8)
	*BRCA*2-positive	154 (53.7)	81 (56.2)	30 (23.1)	17 (28.3)	124 (79.0	64 (76.2)
BC stage, n (%)	Locally advanced	15 (5.2)	9 (6.2)	NR	NR	NR	NR
	Metastatic	271 (94.4)	135 (93.8)	NR	NR	NR	NR
History of CNS metastasis, n (%)	Yes	43 (15.0)	20 (13.9)	NR	NR	NR	NR
Visceral disease, n (%)	Yes	200 (69.7)	103 (71.5)	NR	NR	NR	NR
Previous cytotoxic regimens for aBC, n (%)	0	111 (38.7)	54 (37.5)	52 (40.0)	26 (43.3)	59 (37.6)	28 (33.3)
	1	107 (37.3)	54 (37.5)	50 (38.5)	21 (35.0)	57 (36.3)	33 (39.3)
	2	57 (19.9)	28 (19.4)	21 (16.2)	9 (15.0)	36 (22.9)	19 (22.6)
	3	12 (4.2)	8 (5.6)	6 (4.6)	4 (6.7)	5 (3.2)	4 (4.8)
	≥ 4	NR	NR	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)
Patients with ≥ 1 prior antineoplastic therapy for aBC		205 (71.4)	102 (70.8)	NR	NR	NR	NR

aBC, advanced breast cancer; BC, breast cancer; CNS, central nervous system, ECOG, Eastern Cooperative Oncology Group; ITT, intention-to-treat; NR, not reported; PCT, physician's choice treatment; STD, standard deviation, TALA, talazoparib, TNBC, triple-negative breast cancer.

Source: Eiermann 2018[1], Rugo 2019[2], EMBRACA subgroups data[3]

Table 3. EMBRACA: Outcomes – overall TNBC and HR+ subgroups

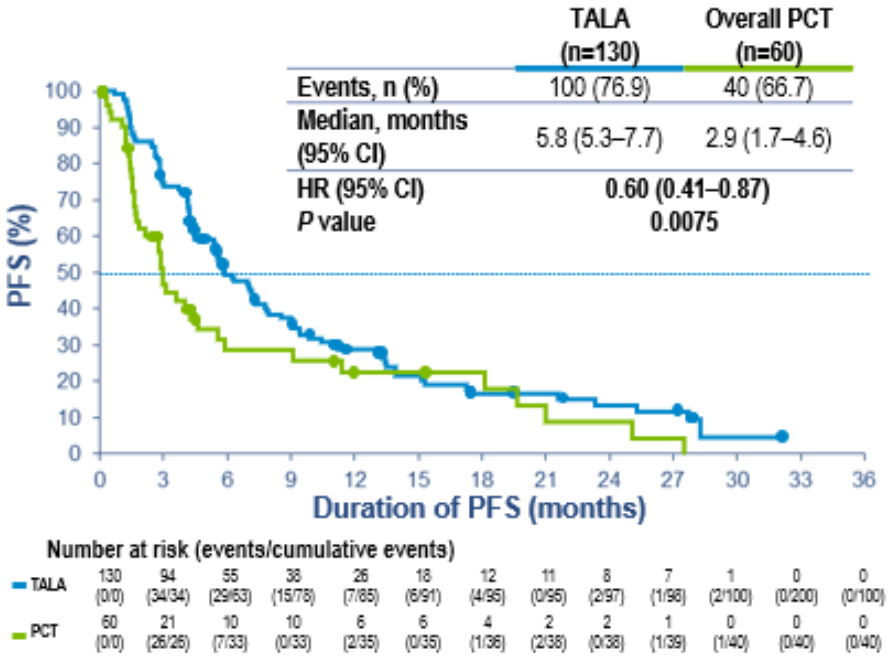
Outcome	ITT		TNBC		HR+	
	TALA	PCT	TALA	PCT	TALA	PCT
PFS						
Number of events, n (%)	186 (65)	83 (58)	100 (76.9)	40 (66.7)	86 (54.8)	43 (51.2)
Evaluable patients, n	287	144	130	60	157	84
Median, months (95% CI)	8.6 (7.2-9.3)	5.6 (4.2- 6.7)	5.8 (5.3-7.7)	2.9 (1.7-4.6)	9.4 (8.8-13.0)	6.7 (5.6-8.7)
HR (95% CI)	0.542 (0.41-0.71)		0.60 (0.41-0.87)		0.47 (0.32-0.71)	
OS						
Number of events, n (%)	216 (75.3)	108 (75.0)	102 (78.5)	47 (78.3)	114 (72.6)	61 (72.6)
Evaluable patients, n	287	144	130	60	157	84
Median, months (95% CI)	19.3 (16.6-22.5)	19.5 (17.4-22.4)	13.4 (10.9-16.3)	18.6 (11.3-20.7)	23.1 (19.3-27.3)	22.4 (17.4-27.5)
HR (95% CI)	0.848 (0.670-1.073)		0.899 (0.634- 1.276)*		0.827 (0.597-1.143)*	
Survival probability at month 12 (95% CI)	0.71 (0.66-0.76)	0.74 (0.66-0.81)	NR	NR	NR	NR
Survival probability at month 24 (95% CI)	0.42 (0.36-0.47)	0.38 (0.30-0.47)	NR	NR	NR	NR
ORR						
Evaluable patients, n	219	114	102	48	117	66
ORR, % (95% CI)	62.6 (55.8-69.0)	27.2 (19.3-36.3)	61.8 (51.61-71.21)	12.5 (4.73-25.25)	63.2 (53.84-71.97)	37.9 (26.22 to 50.66)
CR, n (%)	12 (5.5)	0 (0.0)	NR	NR	NR	NR
PR, n (%)	125 (57.1)	31 (27.2)	NR	NR	NR	NR
SD, n (%)	46 (21.0)	36 (31.6)	NR	NR	NR	NR
Could not be evaluated, n (%)	4 (1.8)	19 (16.7)	NR	NR	NR	NR

* HR is based on stratified Cox regression model with treatment as the only covariate (stratification factors: number of prior cytotoxic chemotherapy regimens, triple negative status, history of central nervous system) and is relative to overall PCT with <1 favouring Talazoparib.

aBC, advanced breast cancer; BC, breast cancer; CNS, central nervous system, ECOG, Eastern Cooperative Oncology Group; HR+, hormone receptor positive, ITT, intention-to-treat; NR, not reported; PCT, physician's choice treatment; STD, standard deviation, TALA, talazoparib.

Source: Eiermann 2018[1], Rugo 2019[2], EMBRACA subgroups data[3]

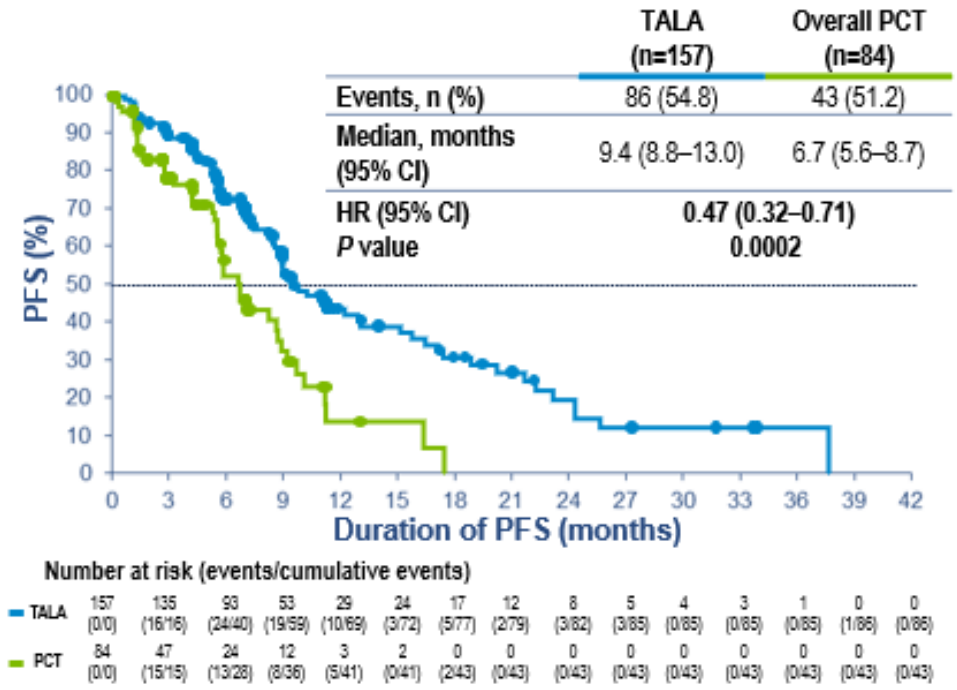
Figure 1. EMBRACA: PFS - overall TNBC subgroup



Source: Rugo 2020[4]; Eiermann 2018[5]

CI, confidence interval; HR, hazard ratio; PCT, physicians choice therapy; PFS, progression free survival; TALA, talazoparib.

Figure 2. EMBRACA: PFS - overall HR+ subgroup



Source: Rugo 2020[4]; Eiermann 2018[5]

CI, confidence interval; HR, hazard ratio; PCT, physicians choice therapy; PFS, progression free survival; TALA, talazoparib.

EMBRACA trial

A2. Priority question: The rank preserving structural failure time model (RPSFTM) was developed to adjust for patients in the control arm of a trial switching to receive treatment that was given to patients in the experimental arm of the trial (and/or vice versa). The RPSFTM incorporates data on how long each individual spent "on treatment" (i.e., received the experimental treatment) and "off treatment" (i.e., received the control treatment). However, the company has attempted to use the RPSFTM method to adjust for patients in the control arm switching to non-study therapy.

Please provide justification for using the RPSFTM method to estimate the treatment effect on OS adjusting for:

i. **subsequent treatment with a poly (ADP-ribose) polymerase (PARP) inhibitor, and**

Treatment switching to talazoparib or another PARP inhibitor (PARPi) in general was not part of the EMBRACA study design and was only examined during the follow-up period, thus representing real-world subsequent treatment use. Hence, RPSFTM sensitivity analysis was undertaken per statistical analysis plan[6] to assess the impact of post-baseline treatment on OS.

It is common for patients in the control group of an oncology trial to switch to the experimental drug which is usually the first of its kind on the market. However, in human epidermal growth factor receptor 2 (HER2)-negative aBC olaparib, another PARPi, was already approved (although not recommended in the UK) and was chosen as subsequent treatment for a portion of patients in EMBRACA after discontinuation of their initial treatment.

At the time of EMBRACA study talazoparib (a PARP inhibitor), was not available for patients with germline BRCA mutation locally advanced and/or metastatic breast cancer and therefore the general class of PARP inhibitors was assumed after study treatment as surrogate of "experimental treatment". Utilising a non-study PARPi in the RPSFTM analysis was deemed reasonable and permitted an unbiased estimation of treatment effect on OS as if patients in the physician's choice treatment

(PCT) arm had not taken a PARPi after discontinuation of PCT. The crossover adjusted hazard ratio (HR) for OS was 0.820 (95% confidence interval [CI]: 0.617-1.047),[2] which was applied to the unadjusted PCT OS data and included in the base-case to account for treatment switching to a PARPi.

ii. subsequent PARP inhibitor and/or platinum chemotherapy use.

Analysis based on PARPi and/or platinum chemotherapy was not included in the model, however results of the RPSFTM analyses for the subsequent use PARPi and/or platinum chemotherapy (HR: 0.756 [95% CI: 0.503-1.029])[2] were included in Document B for completeness.[7]

A3. Priority question: Please provide the results of proportional hazards assessments for the following outcomes for the overall population and the four subgroups identified in A1:

i. PFS

ii. unadjusted final OS

iii. final OS adjusted for subsequent PARP inhibitor only

iv. final OS adjusted for subsequent PARP inhibitor and/or platinum chemotherapy use

Curves were fit separately to the talazoparib and PCT treatment arms in the model, as it is generally considered unnecessary to rely on a proportional hazards assumption when patient-level data are available, as reported in NICE Technical Support Document 14. In addition, the maturity of the EMBRACA data means that we are not relying on the proportional hazards assumption for the extrapolation of trial data.

Section B: Clarification on cost-effectiveness data

B1. Priority question: Please provide a cost effectiveness model that generates results for the comparison of talazoparib versus physician's choice treatment (PCT) for the following EMBRACA trial patient subgroups:

- **patients with TNBC: first-line treatment for aBC**

- **patients with TNBC: second-line or later treatment for aBC**
- **patients with HR+ status: second-line or later treatment for aBC.**

The analyses should be carried out using:

- **EMBRACA trial OS, PFS and time on treatment data (extrapolated, where appropriate)**
- **treatment costs based on EMBRACA trial relative dose intensity (RDI) at the start of each cycle**
- **PFS health state utility values estimated independently for patients receiving first-line treatment and those receiving subsequent treatment.**

Please ensure that the model includes both aggregate monthly cost and micro-costing approaches to estimating subsequent treatment costs.

Once the EAG has had the opportunity to review these analyses, additional clarification questions may be submitted to the company relating to the cost effectiveness of talazoparib versus PCT.

As described in the response to question A1, the EMBRACA trial was designed with adequate power to detect certain effect sizes in the intention-to-treat (ITT) population for PFS and OS endpoints (90% and 80%, respectively). It would be inappropriate to assess cost-effectiveness in these patient subgroups as talazoparib is efficacious in the ITT population and has consistent benefit as shown in the response to A1. Cost-effectiveness analyses are not presented here due to the additional uncertainty that would be introduced in interpreting these results.

B2. Priority question: Please provide overall EMBRACA trial RDI for the intervention and comparator arms by model cycle.

Data are not available by model cycle, however median RDI at the interim analysis and final OS analysis are presented in Table 4 below, showing consistency in the RDI value for talazoparib over time.

Table 4. RDI values

	Talazoparib (N=286)	Capecitabine (N=55)	Eribulin (N=50)	Gemcitabine (N=12)	Vinorelbine (N=9)

Interim analysis	87.2% (26.2%-3000.0%)	87.9% (33.3% – 106.9%)	96.4% (49.0%-101.6%)	87.2% (65.6% - 100.0%)	64.3% (37%-100.0%
Final OS analysis	85.4% (26.2 – 3000.0%)	86.2% (33.3%-106.9%)	95.6% (49.0%-101.6%)	87.2% (65.6% - 100.0%)	64.3% (37.0% - 100.0%)

B3. Priority question: Please provide details of the methods and data used to implement the aggregate monthly cost and micro-costing approaches to estimating subsequent treatment costs.

Details of the methods and data used to implement the aggregate monthly cost approach to estimating subsequent treatment costs are included in the CS (Section B.3.5.1.1.).

The treatment compositions and usage for each treatment in the micro-costing approach were based on the latest EMBRACA supplemental OS clinical study report (CSR; February 18, 2020).[8] The monthly subsequent treatment cost was calculated based on an average cost of individual drugs, weighted by percentage of use in the subsequent treatment basket. Patients could receive multiple treatments subsequently and, thus, the proportions of all treatments do not necessarily sum to 100%. The compositions of subsequent treatment basket as used in the micro-costing approach are presented in Table 5 to Table 7 and present the dosing regimen and unit costs for treatments included in the subsequent treatment basket. Olaparib was removed from the subsequent treatment basket from the CSR because olaparib is not recommended by NICE.[9] Therefore, the subsequent treatment basket was reweighted without olaparib.

Table 5. Subsequent treatment basket

Treatment	% of Basket		Source
	Talazoparib	PCT	
Capecitabine	34.25%	17.70%	EMBRACA OS supplemental CSR[8]
Eribulin	26.45%	20.93%	
Gemcitabine	27.56%	29.72%	
Vinorelbine	14.09%	10.41%	
Talazoparib	0.00%	0.00%	
Carboplatin	39.22%	39.32%	
Cisplatin	10.23%	7.98%	
Cyclophosphamide	8.82%	11.22%	
Fulvestrant	12.36%	13.65%	
Letrozole	10.23%	7.29%	
Paclitaxel	15.50%	14.46%	

CSR, clinical study report; PCT, physician's choice therapy

Table 6. Drug dosing for subsequent treatments

Treatment	Dosing	Source
Capecitabine	1250 mg/m2 twice daily orally for 2 weeks followed by a 7-day rest period in 3-week cycles	Capecitabine SmPC[10]
Eribulin	1.23 mg/m^2 IV over 2 to 5 minutes on Days 1 and 8 of a 21-day cycle	Halaven SmPC[11]
Gemcitabine	1250 mg/m^2 over 30 minutes on Days 1 and 8 of each 21-day cycle	Gemcitabine SmPC[12]
Vinorelbine	25 mg/m^2 IV day 1, weekly	Navelbine SmPC[13]
Carboplatin	AUC6 IV every 3 weeks	Carboplatin SmPC[14]
Cisplatin	75 mg/m^2 IV every 3 weeks	Byrski 2012[15]
Cyclophosphamide	200 mg given in divided doses over 2 to 5 days	Cyclophosphamide SmPC[16]
Fulvestrant	500 mg at intervals of one month	Faslodex SmPC[17]
Letrozole	2.5 mg once daily	Letrozole SmPC[18]
Paclitaxel	260 mg/m^2 IV over 3 hours every 3 weeks	Paclitaxel SmPC[19]

AUC, area under curve; IV, Intravenous; SmPC, Summary of Product Characteristics

Table 7. Drug acquisition cost for subsequent treatments

Treatment	Strength/Unit	Unit/Pack	Cost per Pack	Source
Capecitabine	150 mg	60	£30	BNF[20]
Eribulin	0.88 mg	1	£361.00	BNF[21]
Gemcitabine	200 mg	1	£33.69	BNF[22]
Vinorelbine	50 mg	10	£159.46	eMIT[23]
Carboplatin	150 mg	1	£6.08	eMIT[23]
Cisplatin	50 mg	1	£6.03	eMIT[23]
Cyclophosphamide	50 mg	100	£52.46	eMIT[23]
Fulvestrant	250 mg	2	£522.41	BNF[24]
Letrozole	2.5 mg	14	£1.63	eMIT[23]
Paclitaxel	100 mg	1	£8.06	eMIT[23]
BNF, British National Formulary; eMIT, electronic market information tool				

B4. Priority question: For patients randomised to receive talazoparib, please provide values from the EMBRACA trial for rows entitled 'RBC [red blood cell] transfusions' (PFS [complete response/partial response]; and 8.3%; PFS [stable disease]: 8.3%) in Table 40 of CS and explain why Mahtani 2022 values were used in place of EMBRACA data.

EMBRACA trial values for 'RBC transfusions' in Table 40 of the CS were 38% for both PFS (complete response/partial response) and PFS (stable disease).

As detailed in the CS (Section B.3.5.2.), high transfusion rates in EMBRACA are attributed to the protocol which required haemoglobin (Hb) values to recover to grade 1 or better (10 g/dL) before resuming talazoparib after a dosing interruption. A protocol amendment was made so that talazoparib could be resumed at Hb of 9 g/dL or greater, leading to lower transfusion rates.[25] The rate of RBC transfusions declined by approximately 11% after the amendment. Nevertheless, the number of patients transfused in EMBRACA does not align with clinical practice in the UK.

NICE guidelines[26] recommend when using a restrictive RBC transfusion threshold, a threshold of 70 g/litre and a haemoglobin concentration target of 70–90 g/litre after transfusion should be considered. This is very similar to US guidelines where the restrictive RBC transfusion threshold is 7 g/dL,[27] rather than the more stringent 10 g/dL Hb threshold used in EMBRACA.

There is an absence of UK real-world data, however a real-world study of patients treated with talazoparib in the US published in Mahtani 2022[28] are expected to be more reflective of clinical practice in the UK than the EMBRACA results.

Section C: Textual clarification and additional points

Background (treatment pathway)

C1. In CS, Figure 1, please clarify what should be denoted by the missing footnote for 'everolimus‡'

Missing footnote for everolimus should read:
‡ In combination with exemestane, in postmenopausal women without symptomatic visceral disease after recurrence or progression following a non-steroidal aromatase inhibitor

C2. Priority question: In CS, Figure 2 and Figure 3, where single agent chemotherapy is a suggested treatment option, it is stated that platinum chemotherapy is preferred. Do you consider that platinum chemotherapy is a more appropriate comparator than capecitabine, vinorelbine or eribulin for patients with TNBC?

Publication of the TNT study suggests platinum chemotherapy is a relevant comparator, however as referenced in the scoping document for talazoparib (ID1342), clinical advice is that platinum chemotherapy is not a relevant comparator for patients with TNBC in the UK at the time of scoping. It was confirmed in a meeting between the EAG and company in November 2022 that platinum chemotherapy was not a relevant comparator, on the basis of clinical advice received. Furthermore, as outlined in the response to question A1, analyses across the TNBC and HR+ subgroups with small patient numbers are not powered to detect significant differences, and the scope of the submission covers the ITT population in EMBRACA.

EMBRACA trial

C3. Priority question: Please provide median OS data for all EMBRACA subgroups presented in the CS, Appendix D, Table 11.

Please see Table 8 below for detail.

Table 8. EMBRACA subgroups – median OS

Subgroups	Talazoparib		PCT	
	Population / subpopulation (n)	Median OS, months (95% CI)	Population / subpopulation (n)	Median OS, months (95% CI)
g*BRCA1*m	123	15.7 (12.9-20.7)	60	17.6 (11.1-19.3)
g*BRCA2*m	147	24.3 (18.8-27.9)	78	22.4 (17.8-28.7)
TNBC	130	13.4 (10.9-16.3)	60	18.6 (11.3-20.7)
HR+	157	23.1 (19.3-27.3)	84	22.4 (17.4-27.5)
history of CNS metastasis	43	12.9 (9.4-15.6)	20	13.4 (8.8-17.6)
no history of CNS metastasis	244	21.5 (17.9-24.2)	124	22.2 (19.0-26.7)
ITT				
0 previous CTs	111	27.8 (22.7-31.4)	54	29.1 (20.7-37.4)
1 previous CTs	107	16.6 (14.2-21.7)	54	17.4 (12.8-19.2)
≥2 previous CTs	69	13.6 (11.4-16.3)	36	17.4 (13.1-24.0)

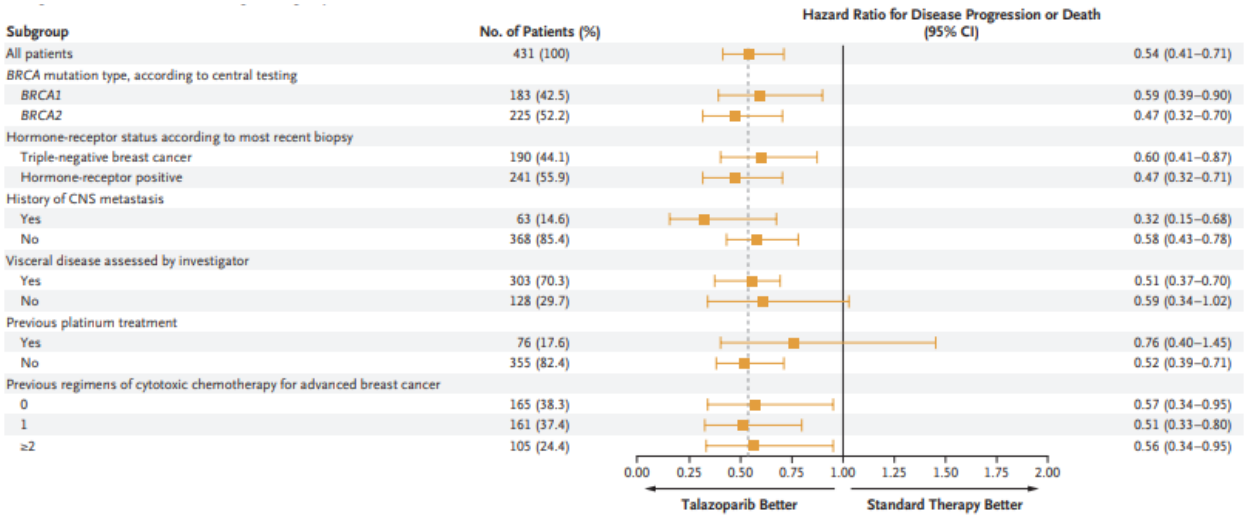
CI, confidence interval; CNS, central-nervous system; CTs, cytotoxic therapy; g*BRCA1/2*m, germline breast cancer susceptibility gene 1 or 2 mutation; HR+, hormone-receptor positive; ITT, intention-to-treat; TNBC, triple-negative breast cancer.

Source: Litton 2020[2]

C4. Priority question: In the CS, p77, it is stated that "a subset of patients experienced a substantially longer duration of treatment effect". Please provide baseline characteristics for this subset of patients.

The treatment effect was largely consistent throughout the relevant subgroups, as shown in Figure 3 below.

Figure 3. PFS according to subgroup



Systematic literature review (SLR) inclusion and exclusion

C5. It is stated in the CS (p38) that: "Full details of the process and methods to identify and select the relevant clinical evidence are summarised in Appendix D." It is stated in CS, Appendix D, Table 7 that trials which include a comparison with physician's choice were excluded because "there is direct evidence from the EMBRACA trial." It is also stated that phase I and combined phase I/II trials were excluded.

i. **Please further justify why studies with 'physicians' choice' were excluded**

The EMBRACA trial was the key trial for this SLR which compared talazoparib against existing interventions (included in the physicians' choice arm). To obtain clinical effectiveness data for each of the other interventions individually (i.e. vinorelbine, capecitabine, gemcitabine, eribulin, platinum based chemotherapy) comparator trials were restricted to direct monotherapy comparisons in order to provide transparency in effectiveness outcomes. The searches did not identify any trials which compared against physicians' choice where the intervention of interest matched the protocol requirement. Furthermore, trials where the only arm which matched the protocol interventions was the physicians' choice arm were excluded as the EMBRACA trial already provided the direct talazoparib and physicians' choice comparison. Additional physicians' choice data would not have added value in context of a potential network meta analysis.

ii. **Please further justify why phase I and combined phase I/II trials were excluded**

The decision to exclude phase I and phase I/II trials was based on the phase I trials presenting very early stage data, which have a small patient sample and are mainly designed to assess drug safety/tolerability, and determine drug dosage. Whereas, trials of phase II and above are powered to evaluate efficacy as well safety of treatments.

iii. **Please clarify how decisions about eligibility were made where no phase was specified in the abstract or published paper of a given study.**

The approach to dealing with uncertainty in the trial phase was to seek further information on the trials from other sources e.g. clinicaltrials.gov. Furthermore, if trials combined phase I/II, the results were checked for any separately reported phase II data, which would be included, prior to exclusion.

C6. It is stated in the CS (p38) that: "In total, the SLR identified 19 publications reporting on 5 studies which met the eligibility criteria for inclusion." The EMBRACA trial and ABRAZO, TBCRC009, TNT and ViTAL studies are listed as included studies in the CS (Appendix D, Table 9). However, only the EMBRACA trial, ABRAZO study and ViTAL study are referred to in the main body of the CS.

i. **Please clarify why TBCRC009 was included when this is described in the CS (Appendix D, Table 9) as being a trial of physician's choice**

TBCRC009 was included as the SLR scope was wider than the final decision problem.

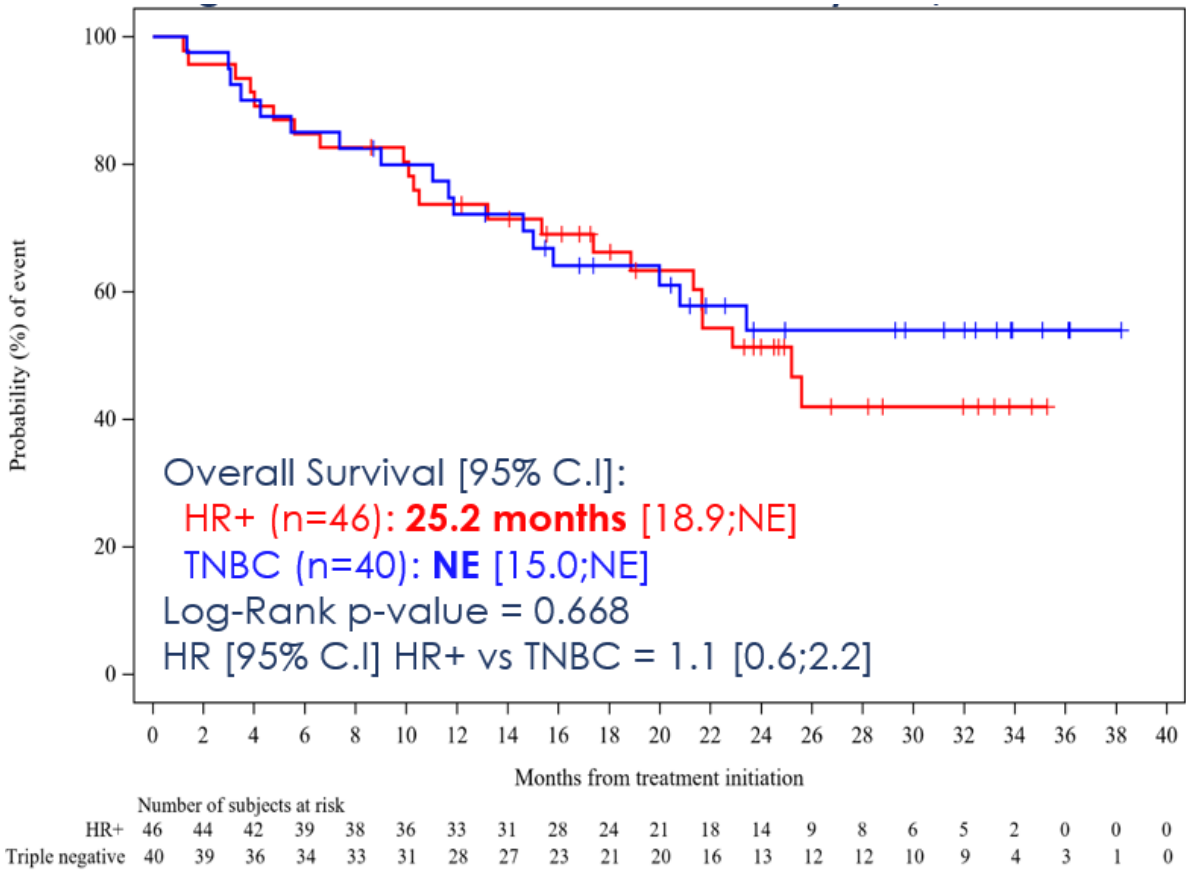
ii. **Please provide justification for including the TBCRC009 and TNT trials in the SLR but not in the main body of the CS.**

The clinical SLR was conducted prior to NICE's decision on whether to incorporate platinum-based chemotherapy into the final scope. Since the final NICE scope[7] does not include this intervention, it has been excluded from the main body of the CS.

C6. In addition to the ViTAL trial, real-world evidence is presented from a US retrospective chart review study and a Turkish retrospective real-world study (CS, Section B.2.4.7). Please clarify how these real-world evidence studies were identified.

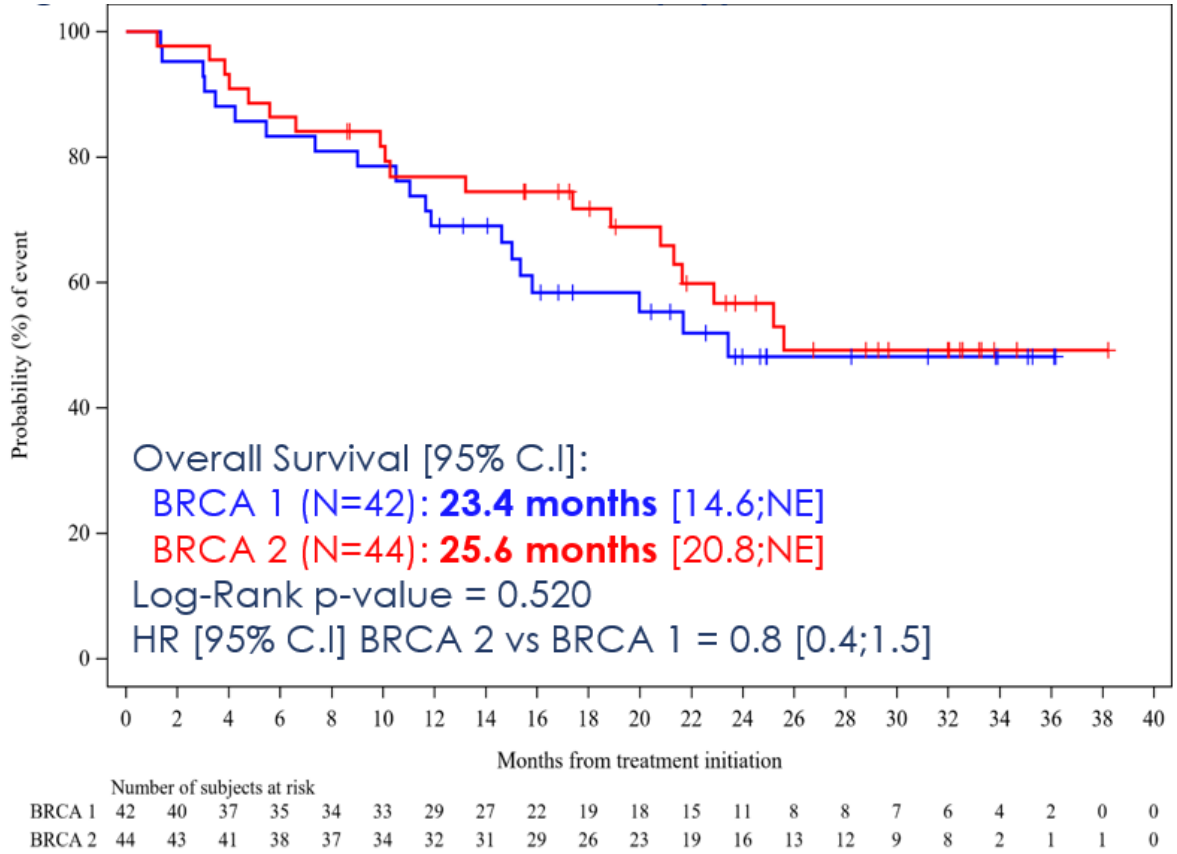
At the time of preparation of the company submission, the included real world evidence studies (namely the US, ViTAL, Russian and Turkish studies) were all the talazoparib specific real-world evidence studies that Pfizer were aware of. Since then, there has been an update from the ViTAL study with the main update being the mOS from cohort 1 (patients treated through the French Early Access program). The mOS for all population was 25.6 months (95% CI 20.8-NE) and the mOS by HR+/TNBC and by type of BRCA1/2 are detailed in Figure 4 and Figure 5 below:

Figure 4. Overall Survival of TALA by HR+/TNBC



CI, confidence interval; HR+, hormone receptor positive; NE, not estimable; TNBC, triple-negative breast cancer.
Source: Loirat 2022

Figure 5. Overall Survival of TALA by type of BRCA1/2 mutation



BRCA 1/2, breast cancer susceptibility gene 1 or 2; CI, confidence interval; NE, not estimable.
Source: Loirat 2022

ABRAZO study

C7. The number of sites and countries that patients were recruited from into the ABRAZO study are reported unredacted in the CS (Appendix M, Table 2, p7). However, similar data are marked as academic in confidence in the CS (Appendix M, p9). Please clarify whether these data are academic in confidence.

We confirm that these data are no longer academic in confidence.

C8. Please clarify what should be denoted by the missing footnote for 'Pre-planned subgroups†' in the CS (Appendix M, Table 2, p7).

The footnote for 'Pre-planned subgroups†' is no longer required in Appendix M, Table 2 and can be removed.

Cost effectiveness

C9. Please provide the reference for the US guidelines mentioned in the CS (Section B.3.5.2, p108).

Please find the reference for the US guidelines mentioned in the CS (Section B.3.5.2, p108) below:

Carson JL, Guyatt G, Heddle NM, et al. Clinical Practice Guidelines From the AABB: Red Blood Cell Transfusion Thresholds and Storage. JAMA. 2016;316(19):2025-2035. doi:10.1001/jama.2016.9185.[27]

C10. It is reported in the CS (Table 32), that the ten most frequently occurring treatment-related grade 3/4 adverse events (AEs) were included in the model. Please explain how the AEs listed in this table were chosen as they do not appear to match the top 10 listed in Table 10 of the Supplemental Safety clinical study report provided by the company.

Common and very common adverse events (based on a pooled dataset from five studies, N = 494) were included in the model (https://www.ema.europa.eu/en/documents/product-information/talzenna-epar-product-information_en.pdf).

C11. Medical resource use unit costs are provided in the CS (Table 39). Please provide resource use setting (e.g., elective inpatient, day case, etc) and the health care resource group codes that were used to identify costs for CT scan, RBC transfusion, platelet transfusion and immunostimulants.

The table was updated and contains all the sources in more detail (Table 9).

Table 9. Medical resource use costs

Resource	Unit Cost	Source
General practitioner visits	£39	PSSRU 2021[29] (Code 10.3b)
Oncology consultant visits	£225	National Cost Collection data 2020/21[30] (service code 370, consultation led)
Community nurse	£44	PSSRU 2021[29] (Code 10.2)
Clinical nurse specialist	£90	National Cost Collection data 2020/21[30] (Code N10AF)
CT Scan	£202	National Cost Collection data 2020/21[30] (Code RD22Z, outpatient)
Red blood cell (RBC) transfusion	£746	It is assumed that unit cost per transfusion = unit RBC cost *1 + unit transfusion visit cost. **Unit RBC cost** is £249.05; Source: NHS Blood and Transplant Price List 2022/23 (Code BC004)[31] **Unit transfusion cost** is £497.06; Source: National Schedule of Reference Costs 2020/21[30] (Code SA44A)
Platelet transfusion	£738	It is assumed that unit cost per transfusion = unit platelet cost *1 + unit transfusion visit cost. **Unit platelet cost** is £240.90; Source: NHS Blood and Transplant Price List 2022/23 (Code BC044)[31] **Unit transfusion cost** is £497.06; Source: National Schedule of Reference Costs 2020/21[30] (Code SA44A)
Immunostimulants	£92	BNF 2022[32] (Filgrastim is the growth factor used in EMBRACA and therefore only considered for this calculation; drug cost per mg)

CT: computerised tomography; NHS: National Health Service; PSSRU: Personal Social Services Research Unit

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Talazoparib for treating HER2-negative locally advanced or metastatic breast cancer with germline BRCA1/2-mutations [ID1342]

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 does receive 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. In the last 12 months (January 2022-January 2022), we have received funding from the following company listed in the appraisal stakeholder list: - In November 2021, we received £107,747 from Pfizer towards our Service Pledge programme. In 2021/2022, our Service Pledge has been jointly sponsored by Pfizer Limited and Eli Lilly and Company Limited. These companies have not had any control or involvement in this programme. Breast Cancer Now funded researchers contributed to the discovery and testing of 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

4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None
5. How did you gather information about the experiences of patients and carers to include in your submission?	At Breast Cancer Now we utilise our various networks of people affected by breast cancer to gather information about patient experience, including our online Breast Cancer Now Forum, as well as our online and face to face services. It has been difficult to find patients with direct experience of this treatment but we have spoken to one patient who has direct experience of this treatment through the drug company's compassionate access scheme.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Secondary (also known as advanced, metastatic or stage 4) breast cancer is when cancer originating in the breast has spread to other parts of the body; most commonly the lungs, brain, bones or liver. There is no cure for secondary breast cancer, so treatment aims to control and slow down the spread of the cancer, relieve symptoms and give patients the best quality of life for as long as possible. A patient can be diagnosed with secondary cancer from the start (de novo metastatic), or they can develop the condition months or years after treatment for their primary breast cancer has ended. The symptoms of secondary breast cancer can vary depending on where the cancer has spread to. For example, if it has spread to the bones the main symptoms can include pain in the bones or bone fractures. If breast cancer has spread to the lungs, someone may experience symptoms such as breathlessness or pain when breathing. In addition, all breast cancer treatments can cause some side effects and although everyone reacts differently to drugs, for those people who experience more side effects than others, it can cause a significant impact on their day to day lives and health and wellbeing. Around 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 can be diagnosed at a younger age and have young children and face the frightening prospect of the uncertainty of knowing whether they will see key milestones. Patients with BRCA tell us the additional burdens they can feel, of knowing children and family members may have the altered gene. A group of the patients that would be eligible for this treatment if made available would be those whose breast cancer is triple negative. 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 prognoses. Being diagnosed with secondary breast cancer is extremely difficult to come to terms with both for patients and their family and friends and it can affect patients in different ways. Many people may feel upset and shocked or anxious, as well as angry and alone. These common feelings can have a huge impact on people’s mental health. As well as the huge emotional toll of living with secondary breast cancer, patients often have to cope with numerous practical concerns, such as managing their day-to-day activities, which may include

	working, household and parental responsibilities as well as travelling to and from regular hospital appointments. A patient diagnosed with this type of breast cancer told us: “I was diagnosed with secondary breast cancer de novo, with spread to the liver and bones. I was 37 at the time. The diagnosis was completely out of the blue and originally I was being treated for back pain. The impact has been devastating for my husband and two girls who are aged 7 and 9 as it poses a constant worry. I have lots of close family who provide me with support and positive attitudes”. Patients are keen to find treatments that will halt progression and extend life for as long as possible. As patients’ time is limited, people tell us that quality of life is just as important to take into account as length of life, as this enables them to spend quality time with their loved ones. Therefore, the type and severity of treatment side effects are also important for patients.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Currently, no PARP inhibitors are available on the NHS to treat patients whose tumours have a germline BRCA mutation. 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 ateolizumab/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. For the hormone-receptor 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?	Yes. PARP inhibitors (olaparib and talazoparib) have been licensed in this group of patients for a number of years and we are now pleased that one of these is now going through the appraisal process. The use of PARP inhibitor monotherapy is included in international guidelines including the ESMO 'Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer' where it states that olaparib or talazoparib should be considered for patients with germline BRCA1/2 mutations as a treatment. ASCO guidelines also recommend that for BRCA1/2 mutation carriers with metastatic HER2 –negative breast cancer, olaparib or talazoparib should be offered as an alternative to chemotherapy in the first-to third-line settings. We have heard from a number of patients since both olaparib and talazoparib were licensed a number of years ago who have been keen to access these novel treatments as they feel they are specifically targeted towards their type of breast cancer which can bring significant comfort and hope that they are receiving the optimum treatment.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	In the clinical trial (EMBRACA), talazoparib prolonged progression-free survival (PFS) compared to chemotherapy, with a median PFS of 8.6 months versus 5.6 months. This is an important improvement and patients have told us that they value this, as delaying disease progression can mean more quality time to spend with relatives and friends. Maintaining a good quality of life for as long as possible is currently the best outcome for this patient group. Delaying progression can have a positive impact on patients' emotional wellbeing and mental health, as it may mean that patients may be able to continue to work and do the activities they enjoy. Increasing the time until a patient's disease progresses is also likely to bring some comfort to their relatives and friends. Whilst there was no statistically significant difference in overall survival between talazoparib and the comparators (and we understand that subsequent treatment use may have impacted this), it is important to reiterate the importance of improved progression free survival for this group of patients and the benefits of increasing the time before patients disease gets worse. A key benefit of this treatment is its administration method. An oral tablet can be easy for patients to take for many patients 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. The trial has also shown that there was a significant improvement in the time to deterioration of health related quality of life among patients treated with talazoparib compared to chemotherapy which is an important advantage of this treatment option – with 26.3 months in the talazoparib arm compared to 6.7 months for the chemotherapy arms. Improving quality of life for as long as possible for patients with incurable secondary breast cancer is highly valued by patients and their loved ones. A patient who is currently receiving talazoparib for the indication being assessed explains: "I started Talzenna on the 9th January 2023. For me the main advantage is that this treatment is in tablet form. For me with two young children in school it is difficult to navigate attending the hospital twice a week for the IV chemo. Usually for IV chemo in the past I have had bloods on the Wednesday and then the chemo on the Thursday. I personally found this quite challenging especially with the bloods and the cannulas. For me a tablet at home

	provides convenience and I can still look after my children without horrendous side effects from IV chemo. Up to now I have not experienced any side effects and I feel like I am tolerating the drug very well." "This drug has been developed to target the BRCA gene and in my opinion all women with this genetic deficiency should have access to this drug. It has already been approved in America. I would like to add that I am accessing this drug via a Compassionate Scheme at Pfizer and I would like to point out I found this out from my own research, my oncologist did not know about the schemes! There are probably thousands of women who are waiting for this drug and they should be made aware of these compassionate programs whilst NICE and the NHS discuss this treatment for NHS use."

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Every treatment for breast cancer has some side effects and each patient's situation will be different, with side effects affecting some patients more than others. Patients' willingness to have treatment will understandably vary. The most common side effects were anaemia, fatigue, nausea, neutropenia and headaches. Discontinuation levels were lower in patients who received talazoparib compared to chemotherapy (5.9% of patients versus 8.7% patients). We understand that this treatment can be generally well-tolerated and that when required, it can be manageable with dose reductions.

Patient population

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

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	

Other issues

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

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• A diagnosis of secondary breast cancer can cause considerable anxiety and fear for people and their loved ones, impacting on all aspects of their lives. The uncertainty can be the hardest part for many people. There is no cure for secondary breast cancer, so the aim of treatment is to extend the length of life, whilst providing a good quality of life. • This treatment offers a significant improvement in progression free survival which would be welcomed by patients, enabling them more time to do things that matter most to them before their disease gets worse. • Patients are looking for kinder treatments. Every treatment for breast cancer has some side effects and each patient's situation will be different, with side effects affecting some patients more than others. Broadly speaking, we understand that this treatment is generally well tolerated and can be managed with dose modifications and supportive medications when required. • The administration method – one tablet daily – will be welcomed by patients. Patients tell us being able to take medication at home and reduce hospital time brings them huge relief. Whilst monitoring appointments will still be required, this will also help with staff capacity.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Talazoparib for treating HER2-negative locally advanced or metastatic breast cancer with germline BRCA1/2-mutations [ID1342]

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

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- Your response should not be longer than 10 pages.

NICE National Institute for Health and Care Excellence

About you

1.Your name	[redacted]
2. Name of organisation	METUPUK
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	METUPUK is a volunteer led patient advocacy organisation working for the unmet needs of patients with metastatic breast cancer. Our three main objectives are raising MBC awareness and education, campaigning for equitable treatment including access to drugs and improvements in patient care. Our services aim to inform patients with primary breast cancer, their family and friends and clinicians of the red flag signs and symptoms of secondary breast cancer. For patients with metastatic breast cancer we campaign for improved access to drugs and treatments. This may include addressing disparities in accessing treatment and clinical trials in the four nations of the UK, or between different commissioning groups within a given nation. We also campaign for access to new therapeutics and radiotherapy treatments so NHS and private patients have the same access to treatment. We call on Trusts to collect accurate and timely data on their patients with MBC. Through our social media channels offer we offer signposting for peer support. We became a registered charity in 2021, but the organisation began as a small group of patients frustrated by the poor prognosis for MBC in 2016 and has grown since then. We are not a membership organisation, but do reach out to the metastatic patient community with over 4000 followers on social media platforms. Our funding is entirely from public donations, and all our trustees and volunteers are unpaid.

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.**	No
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	We used our social media channels of Facebook, Instagram and Twitter to reach out to patients with germline BRCA1/2 mutations. We also reached out to a smaller WhatsApp group of active volunteers including those who have taken part in previous breast cancer awareness campaigns.

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?	Living with MBC is living with uncertainty. We live scan to scan, and even if our treatment appears to be working well, we never know if our cancer is progressing. It is incredibly difficult to plan anything beyond three or six months in the future. Even with the best available drug therapy, for most patients decades of life will be lost. Many of us mourn the loss of jobs and the future loss of families including children or even children that were planned but now will never be born. Patient advocate Ann describes living with MBC in these words: Living with MBC brings a level of sadness which is always there and cannot be shifted. You are constantly aware that your life is time limited and planning of any kind is exceptionally difficult. You feel helpless and despair that you have no control over your illness, and are wholly dependent on the availability of drugs to keep you alive. The psychological benefits of knowing that medical advancements continue to be pursued and will be made available cannot be emphasised enough- it reduces the mental stress of MBC and brings real hope. Living with a germline BRCA1/2 mutation brings its own particular challenges. Many patients have aggressive subtypes of breast cancer including triple negative with limited treatment options. Patients worry about other family members who may be affected. If patients have children, there is the additional concern about passing it on to children, and the guilt associated with living with a genetic disease. Helen describes the impact her diagnosis has on her: My sister and I have both got faulty BRACA2 genes, we aren't surprised at the news as we have a very strong family history. We now have the worry and dread though that we have passed this on to our children, and that is the part that breaks our hearts. MBC is also incredibly difficult for carers. Partners find their role in a family changes quite suddenly from lover to carer for the patient, often balancing this with the financial need to work and sometimes manage childcare. Patients' parents face the awful prospect of their children dying before them, with very little support. Many patients have children under 18 living with them, and these children also face the considerable difficulties of being a young carer while balancing their studies. Alessandro's wife has an aggressive form of MBC. He writes: It's much easier to take care of someone who has stability on their drug regime; my wife has not had that yet and it's been a struggle. Also when

	drugs are denied by NICE it feels that the system doesn't care about patients like my wife.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	There is currently no parp inhibitor available on the NHS for HER2-negative locally advanced or metastatic breast cancer with germline BRCA1/2-mutations. In recent years there have been successive media announcements hailing genomics as a future treatment for cancer. But in reality, many patients find it frustrating that parp inhibitors are available in peer countries but not within the NHS for metastatic breast cancer. Many patients with germline BRCA1/2-mutations have triple negative breast cancer, and have particularly limited treatment options associated with poor prognosis and quality of life. Any additional treatment line to delay chemotherapy with its often gruelling side effects is welcome.
8. Is there an unmet need for patients with this condition?	Yes there is an unmet need. There are no parp inhibitors currently available on the NHS for HER2-negative locally advanced or metastatic breast cancer with germline BRCA1/2-mutations. Patients with BRCA1/2 mutatated metastatic breast cancer have limited treatment options.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	Talazoparib increases the length of time before cancer gets worse. For most patients this will translate into a better quality of life for a longer period of time. Many patients with germline BRCA1/2 cancers have limited treatment options other than chemotherapy. Delaying chemotherapy is highly valued by patients.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Talazoparib can be associated with side effects such as fatigue and lower blood cell and platelet counts. However, many alternative drug choices are also associated with side effects. Patients may need to alter their daily activities to manage the side effects. It is uncercertain if talazoparib increases the length of life. For most patients increasing overall survival time is highly valued. However, if this is not possible, then increasing quality of life so remaining time can be spent in a way that reflects individual's preferences is also valued.

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.	No comments, patient selection is a clinical decision.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	None noted.

Other issues

13. Are there any other issues that you would like the committee to consider?	Many patients with breast cancer struggle to access BRCA testing because there are restrictive eligibility criteria around age at diagnosis, breast cancer subtype and number of first or second degree relatives affected. Some patients with a BRCA1/2 mutation will be missed because of these rules. Not every patient has a good (or any) knowledge of the family medical history of both their parents. BRCA1/2 mutations can be passed down male lines for generations. We would like to see an expansion of genetic testing beyond current eligibility criteria. The number of people living in England with all types metastatic breast cancer is underestimated because of a lack of robust data collection. The number of breast cancer patients with BRCA1/2 germline mutations is unknown partly down to insufficient testing, and also because of a lack of robust data collection.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• Talazoparib increases the length of time before a patient's cancer gets worse. • Patients prefer targeted treatments over chemotherapy because quality of life is superior. • Improvements in quality of life allow patients to have more choice about how they spend their remaining time with their family and friends, reflecting their preferences. • There are barriers to accessing genetic testing within the NHS, so some patients with a BRCA1/2 germline mutations are not identified. • Talazoparib meets an unmet need because there is no parp inhibitor available on the NHS for HER2-negative locally advanced or metastatic breast cancer with germline BRCA1/2-mutations.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Talazoparib for treating HER2-negative locally advanced or metastatic breast cancer with germline BRCA1/2-mutations [ID1342]

Professional organisation submission

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

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 13 pages.

About you

1. Your name	[redacted]
2. Name of organisation	NCRI-ACP-RCP-RCR
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? A specialist in the clinical evidence base for this condition or technology? Other (please specify):
5a. Brief description of the organisation (including who funds it).	NCRI-ACP-RCP-RCR
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	No
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To improve survival and quality of life in patients with metastatic Her2 negative germline BRCA1/2 positive breast cancer
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Delaying time to progression using a therapy which maintains quality of life and function
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. Currently there are no BRCA specific treatments available for use in this cohort of patients with metastatic breast cancer

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	ER+ Her2 negative BRCA metastatic breast cancer: Options comprise standardly available chemotherapy/endocrine therapy approaches ER-, PR- Her2 negative BRCA metastatic breast cancer: Options comprise standardly available chemotherapy
9a. Are any clinical guidelines used in the	NICE CG81 provides UK advanced breast cancer management however this was last updated August 2017 so is somewhat outdated. For example, the guidance does not describe the place in ER+ve disease for CD4/6 inhibitors (where there is a mutation) PIK3CA inhibitor (alpelisib) and in TNBC the place of check point inhibitors

treatment of the condition, and if so, which?	for PDL1 positive disease and second line Sacituzumab govitecan. These agents are supported by NICE (TA816, TA819, TA836, TA801, TA725, TA639) and available in the UK via CDF funding. However, none have specific role in the 5% of BRCA associated breast cancer.
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Approaches to management of metastatic ER+ HER2 negative and Triple negative breast cancer are well defined and in my experience there is very little discordance in approach between professionals across the UK
9c. What impact would the technology have on the current pathway of care?	Germline mutations in breast cancer susceptibility genes 1 and 2 (*BRCA1* and *BRCA2*) are present in around 5 percent of patients with metastatic breast cancer. PARP inhibitors have demonstrated single agent activity in BRCA associated metastatic breast cancer. FDA approval for Talazoparib based on the the EMBRACA trial data was secured in 2018. However currently clinicians are not able to offer this option to UK patients on the NHS.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	In line with the results from the EMBRACA trial talazoparib would be used in preference to current options (capecitabine, eribulin, gemcitabine, or vinorelbine chemotherapies) for gBRCAm HER2-negative locally advanced or metastatic breast cancer treated with no more than 3 lines of therapy.
10a. How does healthcare resource use differ between the technology and current care?	Compared to current standard of care alternatives there will be no change in imaging monitoring procedures. Chemotherapy unit chair/nursing/pharmacy time will be reduced compared to chemotherapy comparators (capecitabine, eribulin, gemcitabine, or vinorelbine)
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care specialist oncology metastatic breast cancer clinics
10c. What investment is needed to introduce the	Funding for talazoparib will be required as this is not currently available on the NHS

technology? (For example, for facilities, equipment, or training.)	Would not expect significant training investment as oral agent with very manageable side effect profile. Compared to the current standard of care alternatives there will be no change in imaging response procedures Chemotherapy unit chair/nursing/pharmacy time will be reduced compared to chemotherapy comparators (capecitabine, eribulin, gemcitabine, or vinorelbine) which may have capacity benefits for treatment units.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes
11a. Do you expect the technology to increase length of life more than current care?	Yes. The phase 3 EMBRACA trial met its primary endpoint demonstrating a progression free survival advantage (median 8.6 versus 5.6 months; HR 0.54, 95% CI 0.41-0.71). The PFS benefit with talazoparib was seen across all predetermined patient subgroups (BRCA1, BRCA2, ER status, history of CNS metastasis, visceral disease, prior platinum treatment and number of prior lines of treatment) . At 1 year 37% of patients in the talazoparib group compared to 20% in the standard therapy group were free from disease progression or death. Overall Survival (OS), evaluated as a secondary endpoint in the EMBRACA trial, was not significantly improved with talazoparib compared with chemotherapy (HR 0.848; 95% CI 0.670-1.073; P = 0.17). Adjusting for post-study treatment reduced the hazard ratio and lowered the upper bound of the confidence interval. The difference in median OS still did not reach statistical significance compared with chemotherapy in patients who received subsequent PARP inhibitor and/or platinum therapy (19.3 vs 17.4 months, respectively; HR, 0.756; 95% bootstrap CI, 0.503-1.029). However, these data suggest subsequent treatments may have impacted the OS results, potentially underestimating the talazoparib benefit. The 2021 Cochrane systematic review evaluating PARP inhibitors (PARPi) for locally advances metastatic breast cancer confirm that PARPi offer improvements in PFS. Pooled analysis from the 4 studies reporting overall survival (singe agent PARPi vs chemo in EMBRACA and OLYMPIAD; chemo-PARPi vs chemo in BROCADE 1 and 2) support overall survival (HR 0.87 (95% CI 0.760-1.00; p=0.05; high certainty evidence with no significant heterogeneity.

11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes. The phase 3 EMBRACA trial demonstrated significant improvements in quality of life and compared to standard therapy resulted in significant delay in onset of clinically meaningful deterioration
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	This treatment is very specifically for the subset of metastatic breast cancer patients with germline mutations in breast cancer susceptibility genes 1 and 2 (*BRCA1* and *BRCA2*). It is not being considered for the more general metastatic breast cancer population where it would be expected to be less efficacious

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	This oral agent will be easier for patient and health professional than standard of care chemotherapy options which consume greater pharmacy and day unit chair time than talazolparib which is an oral fixed dose agent
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these	Currently most patients diagnosed with TNBC (and all those under 60 years) will be offered testing for germline mutations in breast cancer susceptibility genes 1 and 2 (*BRCA1* and *BRCA2*). There may be a subset of patients with ER+ Her2 negative breast cancer who don't currently qualify for testing and miss out of this agent if undetected underlying BRCA mutation. Considering the current technology appraisal

include any additional testing?	AND the adjuvant olaparib data they may be need to expand criteria for BRCA testing beyond the scope currently defined by NICE (CG164).
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	The emotional burden of BRCA mutation on patients and their families will likely be beneficially impacted by availability of treatment options more specific to their genetic susceptibility
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes.
16a. Is the technology a 'step-change' in the management of the condition?	Yes
16b. Does the use of the technology address any particular unmet need of the patient population?	This technology specifically addresses the needs of the metastatic breast cancer subset who carry germline BRCA mutation
17. How do any side effects or adverse effects of the technology affect the management of the	The AE profile and QOL date from EMBRACA is extremely reassuring in this regard, clearly demonstrating significant clinical benefit to talazoparib and no increase in toxicity compared to physicians' choice chemotherapy. Within this trial only 3.6% of patients discontinued treatment due to side effects supporting good tolerability with this agent.

condition and the patient's quality of life?	

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
18a. If not, how could the results be extrapolated to the UK setting?	N/A
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Given the lines of treatment options in the clinic for metastatic HER2 negative breast cancer choosing PFS rather than OS as the primary outcome measure was appropriate in the EMBRACA trial
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Surrogate outcome measures not used
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No. Experience from their use in other settings for example ovarian cancer populations reassures that single agent PARPi are consistently well tolerated and manageable
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No

20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]?	No
21. How do data on real-world experience compare with the trial data?	Mahtani et al have published real world data reporting for 543 patents treated for BRCAm metastatic breast cancer using physician's choice across the spectrum of platinum and non-platinum containing chemotherapy, chemo- immunotherapy, PARPI monotherapy, endocrine based therapy of the cohort n=79 received PARPi monotherapy using talazoparib or olaparib. The real-world study population were overall older and less likely to be PS0 than the phase 3 EMBRACA or OlympiAD study participants. Reassuringly the real world PARPI experience described less frequent AE rates than were seen in the EMBRACA study and high levels of physical satisfaction with PARPi treatment option and therefore complement the phase 3 data.

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
22b. Consider whether these issues are different from issues with current care and why.	-

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.	• For patients with BRCA associated metastatic breast cancer Talazoparib has demonstrated significant progression free survival benefit compared to standard therapy • For patients with BRCA associated metastatic breast cancer Talazoparib has demonstrated significant improvements in quality of life and compared to standard therapy resulted in significant delay in onset of clinically meaningful deterioration • Talazoparib benefits are seen in both triple negative and ER+ Her2 negative subsets • The Talazoparib AE profile and QOL data supports significant clinical benefit to talazoparib and no increase in toxicity compared to physicians choice chemotherapy

Thank you for your time.

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EAG STA REPORT V2

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Talazoparib for HER2-negative locally advanced or metastatic breast cancer with germline *BRCA1/2*-mutations [ID1342]

Confidential until published

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 127892

Completed 14 March 2023
Updated 31 March 2023

CONTAINS ACADEMIC IN CONFIDENCE AND COMMERCIAL IN CONFIDENCE DATA

UNIVERSITY OF LIVERPOOL
LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

Title: Talazoparib for HER2-negative locally advanced or metastatic breast cancer with germline *BRCA1/2*-mutations [ID1342]

Produced by: Liverpool Reviews & Implementation Group (LR*i*G)

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Table of contents

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

aBC	advanced stage breast cancer
AE	adverse event
BC	breast cancer
BRCA	BReast CAncer gene
BRCA1/2	BReast CAncer gene 1/2
CDK4/6i	cyclin-dependent kinase 4/6 inhibitor(s)
CHMP	Committee for Medicinal Products for Human Use
CR	complete response
CS	company submission
CSR	clinical study report
DNA	deoxyribonucleic acid
EAG	External Assessment Group
ECOG PS	Eastern Cooperative Oncology Group performance status
eBC	early stage breast cancer
EORTC QLQ-BR23	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-breast cancer module
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EPAR	European Medicines Agency Public Assessment Report
g*BRCA*m	germline BReast CAncer gene mutation(s)
GHS	global health status
HER2	human epidermal growth factor receptor 2
HER2-	human epidermal growth factor receptor 2-negative
HER2+	human epidermal growth factor receptor 2-positive
HR	hazard ratio
HR-	hormone receptor-negative
HR+	hormone receptor-positive
HRQoL	health-related quality of life
ITT	intention-to-treat
LA	locally advanced
mBC	metastatic breast cancer
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
OR	odds ratio
ORR	objective response rate
PARP	poly (ADP-ribose) polymerase
PARPi	poly (ADP-ribose) polymerase inhibitor(s)
PAS	Patient Access Scheme
PCT	physician's choice treatment

PD-L1	programmed death-1 ligand-negative
PFS	progression-free survival
PR	partial response
PSS	Personal Social Services
QoL	quality of life
RCT	randomised controlled trial
RWE	real-world evidence
SLR	systematic literature review
SmPC	Summary of Product Characteristics
TNBC	triple-negative breast cancer
TPC	treatment of physician's choice

1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the External Assessment Group (EAG) as being potentially important for decision making.

Section 1.1 provides an overview of the key issues identified by the EAG. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the incremental cost effectiveness ratio (ICER) per quality adjusted life year (QALY) gained. Sections 1.3 to 1.5 explain the key issues identified by the EAG in more detail. Section 1.6 outlines the key cost effectiveness issues identified by the EAG.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1 Overview of the EAG's key issues

Table A Summary of key issues

Issue	Summary of issue	Report sections
Issue 1	EMBRACA trial included a heterogeneous population	2.3.3
Issue 2	Platinum chemotherapy is not included as a comparator	2.3.4
Issue 3	Is it appropriate to assume that the effectiveness of the individual EMBRACA trial PCT arm drugs have similar efficacy?	2.3.4 and 3.2.3
Issue 4	Prior treatments received by EMBRACA trial patients may not reflect prior treatments received by NHS patients	3.2.3
Issue 5	Interpretation of EMBRACA trial OS results is problematic	3.3.2
Issue 6	Appropriateness of using EMBRACA trial ITT data in the company model	6.1
Issue 7	EMBRACA trial talazoparib RBC transfusion rates were not used in the model	6.3
Issue 8	The derivation of the relative dose intensity multipliers used in the model are not clearly described	6.5

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a QALY. An ICER is the ratio of the extra cost for every QALY gained.

Overall, the company model assumptions that have the biggest effects on costs and QALYs are:

- EMBRACA trial red blood cell transfusion rate not derived from the EMBRACA trial
- EMBRACA trial median time to treatment discontinuation data used to estimate treatment costs
- company relative dose intensity adjustments included in the model
- progression-free survival (PFS) health state resource use varies by response to treatment
- different PFS health state utility values for patients treated with talazoparib and physician choice treatment (PCT).

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

Issue 1 EMBRACA trial included a heterogeneous population

Report section	2.3.3
Description of issue and why the EAG has identified it as important	The EMBRACA trial recruited patients with HR+/HER2- BC and patients with TNBC. EMBRACA trial results and clinical advice to the EAG suggest that efficacy differs depending on hormone receptor status. The EMBRACA trial recruited patients who received talazoparib as a first-, second- or later-line of treatment. EMBRACA trial results and clinical advice to the EAG suggest that efficacy differs depending on line of treatment. The EAG recognises that subgroup analyses were not included in the final scope issued by NICE. However, the EAG considers that EMBRACA trial ITT results may not represent the efficacy of treatment for patients in the different hormone receptor status or line of treatment subgroups. **Talazoparib OS K-M results** The EAG highlights that the EMBRACA trial talazoparib OS K-M data extracted from the company model show that hormone receptor status and line of treatment are likely to affect OS.
What alternative approach has the EAG suggested?	In the clarification letter, the EAG asked the company to provide additional clinical and cost effectiveness subgroup results by **both** hormone receptor status and line of treatment. The company, however, did not provide all the requested information; the company explained that the EMBRACA trial was only powered to show a statistically significant treatment effect for the ITT population.
What is the expected effect on the cost-effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	Clinical advice to the EAG (supported by available EMBRACA trial subgroup results) is that it is important to consider treatment effects by hormone receptor status and line of treatment. If clinical subgroups are considered by the NICE AC to be relevant, then cost effectiveness subgroup results are required.

aBC=advanced breast cancer; AC=Appraisal Committee; EAG=External Assessment Group; HER2-=human epidermal growth factor 2 negative; HR+=hormone-receptor positive; ITT=intention-to-treat; NICE=National Institute for Health and Care Excellence; TNBC=triple-negative breast cancer

Issue 2 Platinum chemotherapy is not included as a comparator

Report section	2.3.4
Description of issue and why the EAG has identified it as important	Platinum chemotherapy was not listed as a comparator in the final scope issued by NICE. The company's treatment pathways for patients with g*BRCA*m aBC show that platinum chemotherapy is: 1. an option for patients with HR+/HER2- BC (CS, Figure 1) 2. an option for newly diagnosed patients with TNBC and is the preferred option for PD-L1- patients (CS, Figure 2) 3. the preferred option for previously treated patients with TNBC who have not previously received platinum chemotherapy (CS, Figure 3). In the three treatment pathways, platinum chemotherapy is an option at the same point in the pathway as the company's proposed positioning of talazoparib. The EAG clinical experts, the CHMP and the company consider that platinum chemotherapy is a relevant comparator to talazoparib for patients with TNBC. The EAG clinical experts and the CHMP consider that platinum chemotherapy is a relevant comparator to talazoparib for patients with HR+/HER2- BC .
What alternative approach has the EAG suggested?	None.
What is the expected effect on the cost-effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	If platinum chemotherapy is considered by the NICE AC to be a relevant comparator, then cost effectiveness results for the comparison of talazoparib versus platinum chemotherapy are required.

aBC=advanced stage breast cancer; AC=Appraisal Committee; CHMP=Committee for Medicinal Products for Human Use; CS=company submission; EAG=External Assessment Group; HER2-=human epidermal growth factor 2 negative; HR+=hormone-receptor positive; NICE=National Institute for Health and Care Excellence; PD-L1-=programmed death-1 ligand-negative; TNBC=triple-negative breast cancer

Issue 3 Is it appropriate to assume that the effectiveness of the individual EMBRACA trial PCT arm drugs have similar efficacy?

Report section	2.3.4 and 3.2.3
Description of issue and why the EAG has identified it as important	There is a lack of evidence for the relative efficacy of eribulin, capecitabine and vinorelbine (i.e., the clinically relevant EMBRACA trial PCT arm drugs). None of the available evidence relates to patients with g*BRCA*m aBC. Data reported in the EMBRACA trial CSR show that adverse events differ depending on whether patients receive eribulin, capecitabine or vinorelbine. Clinical advice to the EAG is that eribulin, capecitabine and vinorelbine are used to treat NHS patients with aBC.
What alternative approach has the EAG suggested?	None.
What is the expected effect on the cost-effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	If eribulin, capecitabine and vinorelbine are considered by the NICE AC to have similar efficacy (and differences in AE rates are not important), then combined PCT results are meaningful. Further discussion with clinicians would improve understanding of EMBRACA trial effectiveness results.

AC=Appraisal Committee; aBC=advanced breast cancer; AE=adverse event; EAG=External Assessment Group; CSR=clinical study report; gBRCAm=germline BReast CAncer gene mutation(s); NICE=National Institute for Health and Care Excellence; PCT=physician's choice treatment

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

Issue 4 Prior treatments received by EMBRACA trial patients may not reflect prior treatments received by NHS patients

Report section	3.2.3
Description of issue and why the EAG has identified it as important	The EAG recognises that treatment options for patients with eBC and aBC are constantly evolving and therefore it is not surprising that very few EMBRACA trial patients had received treatments that are currently available to NHS patients (for example, CDK4/6i <6%; immunotherapy <1%; platinum chemotherapy <21%). The effect of prior treatment on the efficacy of talazoparib and PCT is unknown.
What alternative approach has the EAG suggested?	None.
What is the expected effect on the cost-effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	None.

aBC=advanced breast cancer; eBC=early breast cancer; CDK4/6i=cyclin-dependent kinase 4/6 inhibitor; EAG=External Assessment Group; PCT=physician's choice treatment

Issue 5 Interpretation of EMBRACA trial OS results is problematic

Report section	3.3.2
Description of issue and why the EAG has identified it as important	The company has provided ITT and subgroup OS results. As the OS PH assumption is likely not to hold for the ITT population, the presented ITT OS HR is uncertain. It is not known whether the OS PH assumption holds for any of the subgroups. **Median OS and HR differences by hormone receptor status (talazoparib versus PCT)** ITT population: 19.3 versus 19.5 months (HR=0.85) HR+/HER2- BC subgroup: 23.1 versus 22.4 months (HR=0.83) TNBC subgroup: 13.8 versus 18.6 months (HR=0.90) The EAG highlights that, for the TNBC subgroup, median OS and OS HR results require explanation. **Differences by previous regimen of cytotoxic chemotherapy for aBC (a proxy for line of treatment) (talazoparib versus PCT)** ITT population: 19.3 versus 19.5 months (HR=0.85) 0: 27.8 versus 29.1 months (HR=0.89) 1: 16.6 versus 17.4 months (HR=0.70) ≥2: 13.6 versus 17.4 months (HR=1.10; favours PCT) Median OS results by **both** hormone receptor status and line of treatment are not available; however, HR results are available and all favour treatment with talazoparib. The EAG considers that EMBRACA trial ITT and subgroup OS results are difficult to interpret.
What alternative approach has the EAG suggested?	None.
What is the expected effect on the cost-effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	Further exploration of all EMBRACA OS results (ITT and subgroups) would improve the EAG's understanding of EMBRACA trial effectiveness results.

aBC=advanced breast cancer; EAG=External Assessment Group; CHMP=Committee for Medicinal Products for Human Use; HER2-=human epidermal growth factor 2 negative; HR=hazard ratio; HR+=hormone-receptor positive; ITT=intention-to-treat; OS=overall survival; PCT=physician's choice treatment; PH=proportional hazards; TNBC=triple-negative breast cancer

1.5 The cost effectiveness evidence: summary of the EAG's key issues

Issue 6 Appropriateness of using EMBRACA trial ITT data in the company model

Report section	6.1
Description of issue and why the EAG has identified it as important	The EAG has concerns about the appropriateness of using EMBRACA trial ITT data to populate the company model given the likely effect of hormone receptor status and line of treatment on patient outcomes (see Issue 1 and Issue 5).
What alternative approach has the EAG suggested?	Additional data were requested during the clarification process (see clarification letter for full details of requested information and Section 2.3 for a list of the information that was not provided).
What is the expected effect on the cost-effectiveness estimates?	Unknown.
What additional evidence or analyses might help to resolve this key issue?	If hormone receptor status and line of treatment subgroups are considered to be important clinical subgroups by the NICE AC, then cost effectiveness subgroup results are required.

AC=appraisal committee; EAG=External Assessment Group; ITT=intention-to-treat; NICE=National Institute for Health and Care Excellence

Issue 7 EMBRACA trial talazoparib RBC transfusion rates were not used in the model

Report section	6.3
Description of issue and why the EAG has identified it as important	The company modelled the PCT RBC transfusion rate using EMBRACA trial data. However, the EMBRACA trial talazoparib RBC transfusion rate was not used in the model. As EMBRACA trial efficacy and HRQoL data are affected by the trial RBC transfusion rates, the EAG considers that the EMBRACA trial talazoparib RBC transfusion rate should also have been used in the model.
What alternative approach has the EAG suggested?	The EAG used the EMBRACA trial talazoparib RBC transfusion rate in the model (38.1%).
What is the expected effect on the cost-effectiveness estimates?	The company used a talazoparib RBC transfusion rate of 8.3%. Any rate higher than the company rate will increase costs of treatment with talazoparib and will therefore increase the size of the ICER per QALY gained.
What additional evidence or analyses might help to resolve this key issue?	None.

EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; PCT=physician's choice treatment; HRQoL=health related quality; QALY=quality adjusted life year; RBC=red blood cell

Issue 8 The derivation of the relative dose intensity multipliers used in the model are not clearly described

Report section	6.5
Description of issue and why the EAG has identified it as important	It is not clear whether RDI has been applied appropriately for patients treated with talazoparib. The company's clarification response did not provide sufficient detail to resolve this issue.
What alternative approach has the EAG suggested?	Remove RDI from both arms of the model.
What is the expected effect on the cost-effectiveness estimates?	This increased the ICER per QALY gained to £38,412
What additional evidence or analyses might help to resolve this key issue?	Accurate EMBRACA trial talazoparib RDI data would resolve this issue.

ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year; RDI=relative dose intensity

1.6 Summary of EAG's preferred assumptions and resulting ICER

The EAG considers that the efficacy of talazoparib is likely to be affected by hormone receptor status and line of treatment. However, the company has only submitted cost effective results for adults with g*BRCA*m who have HER2- aBC. Even if the NICE Appraisal Committee considers that the modelled population is appropriate, the EAG has concerns about the EMBRACA trial OS estimates used to populate the company model.

Summary cost effectiveness results showing the effect of EAG revisions on the company base case are presented in Table A (deterministic) and Table B (probabilistic). Details of the modelling issues identified and corrected by the EAG are described in Section 6.1 to Section 6.9 and, for further details of the exploratory and sensitivity analyses carried out by the EAG, see Section 6.10.

Table A Deterministic cost effectiveness results (talazoparib PAS price)

Scenario	Incremental		ICER	
	Cost	QALYs	£/QALY	Change from base case
Company's base case	[redacted]	[redacted]	***£33,016***	-
R1) Weibull function used to model OS for patients receiving PCT	[redacted]	[redacted]	£33,646	£630
R2) EMBRACA trial RBC transfusion rate used for patients receiving talazoparib	[redacted]	[redacted]	£43,121	£10,105
R3) EMBRACA trial TTD K-M data used to estimate treatment costs	[redacted]	[redacted]	£50,938	£17,922
R4) RDI removed from model	[redacted]	[redacted]	£38,412	£5,396
R5) Resource use in the PFS health state set to not vary by response to treatment	[redacted]	[redacted]	£38,328	£5,312
R6) Subsequent treatments reweighted and micro-costing approach applied	[redacted]	[redacted]	£33,168	£152
R7) Lambert-Obry (2018) study later line PD utility value used to represent HRQoL in the PD health state	[redacted]	[redacted]	£33,164	£148
R8) PFS health state talazoparib utility value used in both treatment arms	[redacted]	[redacted]	£38,679	£5,663
R9) Cost of treating neutropenia removed from PFS state and add to neutropenia treatment cost	[redacted]	[redacted]	£37,774	£4,758
B. EAG preferred scenario (R1-R8)	[redacted]	[redacted]	**£85,911**	**£52,895**

EAG=External Assessment Group; HRQoL=health-related quality of life; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; PCT=physician's choice treatment; PD=progressed disease; QALYs=quality adjusted life years

Table B Probabilistic cost effectiveness results (talazoparib PAS price)

Scenario	Incremental		ICER	
	Cost	QALYs	£/QALY	Change from base case
Company's base case	[redacted]	[redacted]	***£32,193***	
EAG's preferred scenario	[redacted]	[redacted]	**£95,322**	**£63,129**

EAG=External Assessment Group; HRQoL=health-related quality of life; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; PCT=physician's choice of treatment; QALYs=quality adjusted life years

2 INTRODUCTION, BACKGROUND AND DECISION PROBLEM

2.1 Introduction

This appraisal focuses on talazoparib for treating human epidermal growth factor receptor 2-negative (HER2-) locally advanced (LA) or metastatic breast cancer (mBC) with germline BReast CAncer gene (*BRCA1/2*) mutations (g*BRCA*m). Patients should have been previously treated with an anthracycline and/or a taxane (any setting) unless they were not suitable for these treatments. Patients with hormone receptor hormone receptor-positive (HR+) HER2- breast cancer should have been treated with a prior endocrine-based therapy, or be considered unsuitable for endocrine-based therapy.

In this External Assessment Group (EAG) report, references to the company submission (CS) are to the company's Document B, which is the company's full evidence submission. The Summary of Product Characteristics (SmPC) and European Medicines Agency Public Assessment Report (EPAR), which are also referred to, were provided as part of the CS (Appendix C). Additional evidence was provided by the company at the clarification stage.

2.2 Background

2.2.1 Breast cancer

Breast cancer (BC) is a heterogeneous disease. Prognosis and treatment depend on many factors including disease stage, positive or negative hormone receptor status (HR+ or HR-), HER2 status (HER2+ or HER2-) and the presence of pathogenic variants such as g*BRCA*m.

It is estimated that approximately 70% of patients with BC have HR+/HER2- BC[1] and 15% have HR-/HER2- BC (typically referred to as triple-negative BC [TNBC]).[2] The remaining 15% have HER2+ BC; these patients are outside the scope of this current appraisal.[2] Approximately 3% to 5%[3] of all patients with BC and 9% to 18%[4] of patients with TNBC have a g*BRCA*m. It has been reported that patients with g*BRCA1*m are more likely to have TNBC than patients with g*BRCA2*m (68% and 16%, respectively).[5] Patients with a g*BRCA*m often develop BC at a younger age than patients without the mutation; median age of diagnosis is 40 years for patients with *BRCA1*m BC and 43 years for patients with g*BRCA2*m BC.[5]

Approximately 80% to 85% of all patients with BC are diagnosed with early breast cancer (eBC; stage 1 or stage 2)[6] and approximately 30% of these experience a recurrence and develop advanced breast cancer (aBC).[7] Approximately 15% of patients are diagnosed with de novo aBC (locally advanced breast cancer [LABC]: 9%; mBC: 5%).[6]

Prognosis is worse for patients with mBC than for patients with LABC and is also worse for patients with TNBC than for patients with HR+/HER2- BC.[8,9] Reported 5-year survival rates are 72% for all patients with LABC,[9] 65% for patients with LA TNBC,[8] 26% for all patients with mBC[9] and 12% for patients with metastatic TNBC.[8]

2.2.2 Talazoparib

Talazoparib (TALZENNA®) is a poly (ADP-ribose) polymerase (PARP) 1 and PARP 2 inhibitor and plays important roles in the single-strand deoxyribonucleic acid (DNA) repair pathway. PARP inhibitors (PARPi) exert cytotoxic effects via two mechanisms: i) inhibition of PARP catalytic activity[10] and ii) by PARP trapping at sites of damaged DNA.[11] In *BRCA1*- and *BRCA2*-deficient cells, treatment with a PARPi results in synthetic lethality, preventing cancer cells from repairing damaged DNA, resulting in DNA alterations and subsequent tumour cell death, whilst non-cancer cells remain largely intact.[12-15]

The Medicines and Healthcare products Regulatory Agency (MHRA) marketing authorisation for talazoparib was issued on 20 June 2019.[16] Talazoparib is indicated as a monotherapy for the treatment of adult patients with g*BRCA*m who have HER2- aBC. Patients should have been previously treated with an anthracycline and/or a taxane unless contraindicated. Patients with HR+/HER2- BC should have been treated with a prior endocrine-based therapy, unless contraindicated.

Talazoparib is available as 0.25mg and 1mg capsules (SmPC, CS, Appendix C). The recommended dose is 1mg once a day (with or without food) until disease progression. Dose modifications are recommended in response to toxicity (Table 1).

Table 1 Talazoparib dose modification and management

Dose modification required if:	Withhold talazoparib until levels resolve to:	Resume talazoparib
Haemoglobin <8g/dL	≥9g/dL	Resume talazoparib at next lower dose
Platelet count <50,000/uL	≥75,000/uL	
Neutrophil count <1,000/uL	≥1,500/uL	
Non-haematological adverse reaction Grade 3 or Grade 4	<Grade 1	Consider resuming talazoparib at next lower dose or discontinue

CS=company submission; SmPC=Summary of Product Characteristics
Source: SmPC (CS, Appendix C), Table 2

Talazoparib is not the only PARPi licensed as a treatment for patients with g*BRCA*m who have HER2- aBC. Olaparib, which is also administered orally (300mg twice daily), has a similar marketing authorisation to talazoparib.[17] However, the NICE appraisal of olaparib as a treatment for HER2- aBC with g*BRCA*m was terminated in February 2022 as the company (AstraZeneca) did not submit evidence to NICE.[18]

2.2.3 Overview of current service provision

The company has presented current NHS treatment pathways, and the anticipated NHS treatment pathways should talazoparib be recommended by NICE for treating:

- de novo and recurrent HR+/HER2- aBC with g*BRCA*m (CS, Figure 1)
- de novo advanced TNBC with g*BRCA*m (CS, Figure 2)
- previously treated/recurrent advanced TNBC with g*BRCA*m (CS, Figure 3).

The company's pathways were informed by the clinical advice received by the company and stated in NICE guidelines (CG81[19] and NG101[20]), NICE guidance (TA819[21]) and international consensus guidelines for aBC (ABC 5[22]); this advice is summarised in the CS (Table 4). The company has presented talazoparib as a treatment option for patients with aBC; the position of talazoparib in the pathways depends on hormone receptor status and line of treatment:

- HR+/HER2- BC: second- or third-line treatment, largely dependent on whether an anthracycline and/or taxane was received for eBC (second-line if yes, third-line if not)
- TNBC: first- or second-line treatment, largely dependent on whether immunotherapy and/or chemotherapy was received for eBC (first-line if yes, second-line if not).

Clinical advice to the EAG is that the treatment pathways for eBC and aBC are constantly evolving but that the pathways presented by the company largely reflect current and anticipated NHS clinical pathways for treating aBC. However, the EAG highlights:

- clinical advice to the EAG is that, in NHS clinical practice, g*BRCA*m testing would usually occur earlier in the treatment pathway than depicted in CS Figures 1 to 3, most commonly in the eBC setting (as acknowledged by the company in CS, Table 1)
- for patients with HR+/HER2- BC, the company suggests current second-line treatment for aBC (endocrine-based therapy [alone or in combination with everolimus or alpelisib] or single-agent chemotherapy) would become fourth-line treatment after talazoparib (CS, Figure 1); clinical advice to the EAG is that in some instances, some current second-line treatment options (particularly endocrine-based therapy) may be preferred before talazoparib
- for patients with TNBC, it is stated that, where platinum chemotherapy (carboplatin or cisplatin) is a potential treatment option, this is usually preferred to other single agent chemotherapy options (CS, Figures 2 and 3); clinical advisors to the EAG agreed. Further, clinical advisors to the EAG suggested that platinum chemotherapy may also be preferred for patients with HR+/HER2- BC and g*BRCA*m.

The EAG notes that although platinum chemotherapy is a treatment option for aBC in NHS clinical practice (CS, Figures 1 to 3), it is not considered in the NICE aBC clinical guidelines (CG81),[19] nor has it ever been appraised as an intervention by NICE; the NICE aBC clinical guidelines (CG81[19]) do not make any recommendations specifically for patients with gBRCAm aBC. The EAG further notes that the company treatment pathways suggest that, for some patients, single agent chemotherapy, including platinum chemotherapy, may become a later line of treatment if talazoparib is recommended for use in NHS clinical practice; this is because patients need to have received an anthracycline or a taxane before starting treatment with

talazoparib. It should also be noted that some patients with recurrent BC will have already received platinum chemotherapy (for eBC and/or aBC) and, for patients who responded, re-challenge with platinum chemotherapy is not uncommon.

2.3 Critique of company's definition of decision problem

A summary of the decision problem outlined in the final scope issued by NICE and addressed by the company is presented in Table 2. Each parameter is discussed in more detail in the text following Table 2 (Section 2.3.1 to Section 2.3.8).

Table 2 Summary of decision problem

Parameter	Final scope issued by NICE	Decision problem addressed in the CS	EAG comment
Intervention	Talazoparib	Talazoparib	As specified in the NICE scope.
Population	Adults with HER2- LA or mBC with g*BRCA*m that has previously been treated with an anthracycline and/or a taxane in the (neo)adjuvant, LA or metastatic setting or for whom these treatments would not be suitable.	Adult patients with g*BRCA*m, who have HER2- LA or mBC. Patients should have been previously treated with an anthracycline and/or a taxane in the (neo)adjuvant, LA or metastatic setting unless patients were not suitable for these treatments. In addition, patients with HR+/HER2-BC should have been treated with a prior endocrine-based therapy, or be considered unsuitable for endocrine-based therapy.	Largely as specified in the NICE scope. The pivotal EMBRACA trial includes patients with HR+/HER2- aBC and HR-/HER2- aBC (i.e., TNBC). Line of treatment also varies (first-, second- or third-line). As prognosis differs by hormone receptor status and line of treatment, the EAG considers that these subgroup results would be informative. The EAG requested baseline characteristics and analyses of PFS, OS and ORR for these subgroups at the clarification stage but they were not provided.
Comparator(s)	• Vinorelbine • Capecitabine • Eribulin (after ≥2 chemotherapy regimens)	PCT Talazoparib was compared with PCT (capecitabine, eribulin, gemcitabine, vinorelbine) in the clinical pivotal trial, EMBRACA. It was assumed that the four individual treatments (capecitabine, eribulin, gemcitabine, and vinorelbine) have comparable efficacy, thus a pooled efficacy of PCT combined was derived from EMBRACA and was applied in the model. The proportion of patients receiving each treatment was re-weighted [for cost estimation purposes] to remove gemcitabine, reflecting the final scope issued by NICE and UK clinical practice.	Largely as specified in the NICE scope. Effectiveness data for the comparators are only available in aggregated form (EMBRACA trial PCT combined arm) for capecitabine, eribulin, gemcitabine, and vinorelbine. If eribulin, capecitabine and vinorelbine are considered by the NICE AC to have similar efficacy (and differences in AE rates are not important), then combined PCT results are meaningful. In contrast to the NICE scope, clinical advice to the EAG is that, for many patients, platinum chemotherapy is a relevant comparator for patients with g*BRCA*m.
Outcomes	The outcome measures to be considered include: • OS • PFS • response rate • AEs • HRQoL	The outcome measures presented include: • OS • PFS • response rate • AEs • HRQoL	As specified in the NICE scope. These are appropriate outcome measures.

Parameter	Final scope issued by NICE	Decision problem addressed in the CS	EAG comment
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and 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 talazoparib is conditional on the presence of germline *BRCA*-mutations. The economic modelling should include the costs associated with diagnostic testing for germline *BRCA*-mutations in people with 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.[23]	The cost associated with *BRCA* diagnostic testing is excluded from the analysis. Individuals in UK clinical practice receive *BRCA* testing before BC is diagnosed, due to family history of *BRCA* positive breast or ovarian cancer.[24] Furthermore, NICE recommends that genetic testing is offered to women under 50 years with TNBC, including those with no family history of breast or ovarian cancer.[20] Eligible patients for talazoparib are expected to be identified by the current guidelines, therefore the cost of *BRCA* testing was not included in the analysis.	Largely as specified in the NICE scope. The EAG agrees with the company that the cost associated with *BRCA* diagnostic testing should not have been included in the analysis.
Subgroups	None specified.	The submission covers the full marketing authorisation of talazoparib.	Clinical subgroup analyses are presented in the CS and company response to clarification question A1 by hormone receptor status and/or number of prior cytotoxic chemotherapy regimens for aBC (EAG proxy for line of treatment). Not all clinical subgroup analyses requested by the EAG were provided by the company. See text and Table 4 for a list of the information that was not provided by the company.

aBC=advanced stage breast cancer; AEs=adverse events; BC=breast cancer; *BRCA*=BReast CAncer gene; CS=company submission; EAG=External Assessment Group; g*BRCA*m=germline BReast CAncer gene mutation(s); HER2-=human epidermal growth factor receptor 2 negative; HR(+/-)=hormone receptor (positive/negative); HRQoL=health-related quality of life; LA=locally advanced; mBC=metastatic breast cancer; OS=overall survival; PCT=physician's choice treatment; PFS= progression-free survival; PSS=Personal Social Services; TNBC=triple-negative breast cancer
Source: Final scope issued by NICE and CS, Table 1

2.3.1 Source of direct clinical effectiveness data

The primary source of the clinical effectiveness evidence presented in the CS and used to obtain regulatory approval is the EMBRACA trial. This is an open label, multicentre, phase III, randomised controlled trial (RCT) designed to compare the clinical effectiveness of talazoparib (N=287) versus physician's choice treatment (PCT; N=144). Patients were randomised in a 2:1 ratio to talazoparib or PCT between May 2014 and February 2016. Results from this trial have been previously published in peer-reviewed journals[25-27] (see Table 3 for key publications that have also informed the EAG's understanding and critique of this trial).

Table 3 Key publications used by to inform this EAG report

Source	Key information utilised in this EAG report
Litton (2018)[27]	Results for analyses of PFS and ORR
Ettl (2018)[25]	Patient reported outcomes: HRQoL
Litton (2020)[26]	Results for final analysis of OS and information about subsequent therapy

EAG=External Assessment Group; HRQoL=health-related quality of life; ORR=objective response rates; OS=overall survival; PFS=progression-free survival

2.3.2 Intervention

The company has presented evidence for talazoparib as per its licensed indication (see Section 2.2.2).

2.3.3 Population

The population addressed by the company largely matches the population specified in the final scope issued by NICE.

It is stipulated in the marketing authorisation (SmPC, CS, Appendix C) that patients with HR+/HER2- BC should have been treated with a prior endocrine-based therapy or be considered unsuitable for endocrine-based therapy. This criterion does not substantially modify the population described in the final scope issued by NICE as in NHS clinical practice, patients with HR+/HER2- BC (historically and currently) receive endocrine-based therapy as their first therapy in either the adjuvant or aBC settings (see Section 2.2.3). However, the EAG highlights that prior endocrine-based therapy was not an inclusion criterion for patients with HR+/HER2- BC in the EMBRACA trial.

Generalisability of EMBRACA trial results to NHS patients may be affected by the fact that 29/241 (12.0%) of patients with HR+/HER2- BC in the EMBRACA trial had not received prior endocrine-based therapy (EPAR p101/140, Appendix C). Clinical advice the EAG is that <5% of patients in NHS clinical practice would be expected to be contraindicated to endocrine-based therapy.

The EMBRACA trial population is heterogeneous; it comprises patients with HR+/HER2- BC and TNBC who received first-line, second-line or a later line of treatment for aBC. The EAG considers that clinical and cost effectiveness subgroup results by **both** hormone receptor status and line of treatment should be considered as prognosis is expected to differ by **both** hormone receptor status and by line of treatment.

Some clinical effectiveness subgroup results are provided in the CS by hormone receptor status and/or the number of prior lines of cytotoxic chemotherapy for aBC (Figures 15 to 16 and Appendix D, Tables 11 to 13). However, the EAG considered that further information was required and requested baseline characteristics and PFS, OS (adjusted and unadjusted for treatment crossover) and objective response rate (ORR) results for the following (post-hoc) subgroups (clarification questions A1 and B1):

- patients with HR+/HER2- BC who received talazoparib as first-line treatment for aBC (clinical effectiveness only as this subgroup is not expected to receive talazoparib)
- patients with HR+/HER2- BC who received talazoparib as second-line or later treatment for aBC
- patients with TNBC who received talazoparib as first-line treatment for aBC
- patients with TNBC who received talazoparib as second-line or later treatment for aBC.

While patients with HR+/HER2- BC who received talazoparib as a first-line treatment for aBC were not considered by the company as candidates for treatment with talazoparib, the EAG considers information for this subgroup would be useful as it would provide information on how results for this subgroup align with the EMBRACA trial ITT population results. The other three subgroups reflect the patients that the company considered would receive talazoparib. The EAG recognises that the subgroup analyses requested are post-hoc analyses, and therefore the results could only be considered exploratory.

The company did not provide all the subgroup analysis results requested by the EAG. The company's reason for not providing the information was that the EMBRACA trial was only powered to detect differences in the intention-to-treat (ITT) population. The company, however, provided baseline characteristics and clinical effectiveness results (PFS, OS unadjusted for crossover and ORR) for: i) all patients with HR+/HER2- BC and ii) all patients with TNBC.

2.3.4 Comparators

As shown in the CS (Figures 1 to 3) and described in Section 2.2.3, platinum chemotherapy is an option for patients with HER2- aBC and, if recommended, talazoparib could displace platinum chemotherapy for some patients. Therefore, clinical advice to the EAG is that

platinum chemotherapy should have been considered as a comparator to talazoparib alongside capecitabine, eribulin and vinorelbine.

The EAG further highlights:

- in the EPAR (p99/140, CS, Appendix C), it is stated that the Committee for Medicinal Products for Human Use (CHMP) advised the company to include platinum chemotherapy as one of the comparators in the EMBRACA trial
- in the EPAR (p104/140, CS, Appendix C), it is highlighted that the Scientific Advisory Group (SAG) "further noted that the control group of the pivotal clinical study excluded the use of a platinum-containing regimen, which is considered more efficacious than the physician's choice monotherapies used in the pivotal trial"
- the company states "clinical advice is that platinum chemotherapy is not a relevant comparator for patients with TNBC in the UK at the time of scoping" (company response to clarification question C2); however, in response to the draft scope[28] issued by NICE, the company commented that platinum chemotherapy, specifically carboplatin, may also be considered a relevant comparator for patients with *BRCA*m TNBC. However NICE responded that: "[C]arboplatin is not recommended for use in locally advanced or metastatic breast cancer"[29] and therefore was not included as a comparator in the final scope issued by NICE.

The EAG notes that although platinum chemotherapy is not considered in CG81,[19] the CHMP, the SAG, the company (for TNBC) and EAG clinical advisors all consider that platinum chemotherapy is a relevant comparator. The EAG recognises that, as stated in the clinical study report (CSR,[30] Section 9.2), "platinum [chemotherapy] was not chosen as one of the control arm drugs, as limited data were available at the time Study 673-301 [EMBRACA trial] was designed." Clinical advice to the EAG is that the number of patients with g*BRCA*m aBC treated with platinum chemotherapy increased following the results from the TNT trial,[31] which showed that platinum chemotherapy (carboplatin) was more efficacious than a taxane (docetaxel) for this population. The results from the TNT trial[31] were published in 2018, i.e., after the publication of the original EMBRACA trial protocol had been finalised (2013) and after randomisation into the EMBRACA trial had started (October 2013).

The comparators included in the final scope issued by NICE are capecitabine, eribulin and vinorelbine; clinical advice to the EAG is that these are also relevant comparators to talazoparib. However, the efficacy of the drugs that make up the PCT combined arm (capecitabine, eribulin, vinorelbine and gemcitabine) has not been evaluated separately in the EMBRACA trial.

The main advantage of using a PCT combined trial arm is that the range of different chemotherapy options available is likely to more closely reflect real-world practice, particularly as patients are treated with different lines of therapy in the EMBRACA trial. However, gemcitabine (one of the four drugs used in the PCT arm) is not listed as a comparator in the

final scope issued by NICE and clinical advice to the EAG is that gemcitabine is not commonly used in NHS clinical practice. In the EMBRACA trial, the number of patients treated with gemcitabine was small (PCT: n=12/126; 9.5%); most patients were treated with capecitabine (PCT: n=55/126; 43.7%) or eribulin (PCT: n=50/126; 39.7%). Clinical advice to the EAG is that, after platinum chemotherapy, capecitabine and eribulin are the two PCT arm drugs that are most commonly used in NHS clinical practice to treat aBC, usually in the second- and third-line settings, respectively. NICE TA423[32] and TA515[33] guidance stipulate that eribulin is only available as a third-line treatment option for patients with aBC, whereas capecitabine (and vinorelbine) can be used earlier in the treatment pathways.

The main disadvantage of using a PCT combined arm is that if there are differences in the effectiveness of the drugs, the PCT arm overall treatment effect is diluted by the less effective drug(s) and/or enhanced by efficacy of the most effective drug(s). Clinical advice to the EAG is that there may be differences in the effectiveness of the individual PCT arm drugs, although the evidence base is weak as head-to-head trial comparisons of these drugs are lacking. For example, only one trial, Study 301 trial,[34] compared eribulin to capecitabine; results from this phase III RCT[34] showed that after one previous line of treatment for aBC, treatment with eribulin improved OS but not PFS. However, it was noted in the NICE appraisal of eribulin for treating LA or mBC after one chemotherapy regimen (TA515),[33] that the OS benefit (shown in Study 301 trial[34]) may be attributable to post-progression treatments. The NICE recommendation for eribulin after two or more previous lines of therapy (TA423[32]) was made based on effectiveness evidence from the phase III EMBRACE trial;[35] this trial only compared eribulin versus a treatment of physician's choice (TPC) in a mixed HER2 population (HER2-: 72%). TPC was comprised of chemotherapy (vinorelbine [25%], gemcitabine [19%], capecitabine [18%], taxanes [15%], anthracyclines [10%], other [10%]) or endocrine-based therapy (4%). Neither capecitabine nor vinorelbine has been appraised by NICE. However, in CG81,[19] NICE recommends capecitabine and vinorelbine as treatment options for patients with aBC. The EAG is unaware of any RCTs comparing capecitabine versus vinorelbine. A European Organisation for Research and Treatment of Cancer phase II/III trial which compared treatment with capecitabine versus vinorelbine was terminated in December 2004 due to low patient accrual rates.[36] A recent network meta-analysis (NMA)[37] of eribulin versus other chemotherapies only included comparisons versus capecitabine (utilising data from Study 301[34]), the TPC arm from the EMBRACE trial[35] and other comparators not used in NHS clinical practice. Results from this NMA[37] also showed that treatment with eribulin resulted in statistically significantly longer OS but not PFS, than treatment with capecitabine. The EAG highlights that that none of available trial evidence comparing single agent chemotherapies explicitly included patients with g*BRCA*m aBC.

2.3.5 Outcomes

The outcomes specified in the final scope issued by NICE are standard outcomes used in oncology clinical trials and are the most important outcome measures for this appraisal.

EMBRACA trial ITT population absolute effects for survival outcomes (OS and PFS) were reported as medians and relative effects were reported as hazard ratios (HRs). EMBRACA trial ITT population Kaplan-Meier (K-M) data were also available.

For subgroup analyses, medians and HRs were reported for all PFS results (CS, Appendix D, Table 12). However, for most OS subgroups, only HRs were reported (CS, Appendix D, Table 11). The EAG requested median OS results for all subgroups where these data were missing (clarification question C3); the company did not provide this information for all subgroups.

As expanded upon in Section 3.2.5, the EAG considers that, for the ITT population, the proportional hazards (PH) assumption is likely to be violated for OS. This means that a HR may not be an appropriate measure of effect for this outcome.

For the four subgroups highlighted in Section 2.3.3, the EAG requested analyses of outcomes presented in the same format as for the ITT population (CS Tables 9 to 11 and Figures 7 to 8 and Figure 10) (clarification question A1), namely:

- PFS: median, HR and number of events
- OS: median, HR, number of events and survival probabilities at 12, 24, 36 and 48 months
- ORR, complete response (CR), partial response (PR) and stable disease
- K-M data for PFS and OS (adjusted and unadjusted)

The company did not provide any of these data.

2.3.6 Economic analysis

As specified in the final scope issued by NICE, the cost effectiveness of treatments was expressed in terms of the incremental cost per quality adjusted life year (QALY) gained. Outcomes were assessed over a 10-year time period (which the company considered to be equivalent to a lifetime horizon) and costs were considered from an NHS and Personal Social Services (PSS) perspective.

2.3.7 Subgroups

No subgroup analyses were specified in the final scope issued by NICE. The company reported findings from EMBRACA trial subgroups for the following outcomes: PFS, OS and ORR (CS Section 2.7 and Appendix M to the CS, Section 1.5). The EAG has presented and

critiqued EMBRACA trial ITT population evidence. The EAG has also presented and critiqued evidence for the following subgroups:

1. By hormone receptor status
    - patients with HR+/HER2- BC
    - patients with advanced TNBC

2. By number of prior regimens of cytotoxic chemotherapy for aBC (EAG proxy for line of treatment)
    - all patients who had received no prior regimens of cytotoxic chemotherapy for aBC
    - all patients who had received one prior regimen of cytotoxic chemotherapy for aBC
    - all patients who had received two or more prior regimens of cytotoxic chemotherapy for aBC

3. By **both** hormone receptor status and number of prior regimens of cytotoxic chemotherapy for aBC (EAG proxy for line of treatment)
    - patients with HR+/HER2- BC who had received no prior regimens of cytotoxic chemotherapy for aBC
    - patients with HR+/HER2- BC who had received one prior regimen of cytotoxic chemotherapy for aBC
    - patients with HR+/HER2- BC who had received two or more prior regimens of cytotoxic chemotherapy for aBC
    - patients with TNBC who had received no prior regimens of cytotoxic chemotherapy for aBC
    - patients with TNBC who had received one prior regimen of cytotoxic chemotherapy for aBC
    - patients with TNBC who had received two or more prior regimens of cytotoxic chemotherapy for aBC.

The EAG considers that the number of prior regimens of cytotoxic chemotherapy for aBC can be a proxy for line of treatment, i.e., no prior cytotoxic chemotherapy for aBc can be considered a proxy for first-line treatment, one prior regimen of cytotoxic chemotherapy for aBC can be considered a proxy for second-line treatment, and so on. Number of prior regimens of cytotoxic chemotherapy for aBC is only a proxy for line of treatment because there are non-cytotoxic treatment options for patients with HR+/HER2- aBC (endocrine-based therapy with or without CDK4/6i, everolimus or alpelisib, see CS, Figure 1).

A comparison of how similar the data available were to the data requested by the EAG is summarised in Table 4.

Table 4 Subgroup analyses from the EMBRACA trial provided by the company

Subgroup	Baseline characteristics	PFS			OS			ORR	
		Median	HR	K-M curve	Median	HR	K-M curve	ORR	OR
HR+/HER2- BC Any L [a]	Yes [b]	Yes [c]	Yes [c]	Yes [d]	Yes [e]	Yes [f]	Yes [g]	Yes [h]	Yes [h]
HR+/HER2- BC 1L	**-**	**Yes [i]**	**Yes [i]**	**Yes [g]**	**-**	**Yes [j]**	**Yes [g]**	**-**	**-**
HR+/HER2- BC ≥2L	**-**	**-**	**-**	**Yes [g]**	**-**	**-**	**Yes [g]**	**-**	**-**
HR+/HER2- BC 2L	-	Yes [i]	Yes [i]	-	-	Yes [j]	-	-	-
HR+/HER2- BC ≥3L	-	Yes [i]	Yes [i]	-	-	Yes [j]	-	-	-
TNBC Any L [a]	Yes [b]	Yes [c]	Yes [c]	Yes [k]	Yes [e]	Yes [f]	**Yes [g]**	Yes [h]	Yes [h]
TNBC 1L [h]	**-**	**Yes [i]**	**Yes [i]**	**Yes [g]**	**-**	**Yes [j]**	**Yes [g]**	**-**	**-**
TNBC ≥2L [h]	**-**	**-**	**-**	**Yes [g]**	**-**	**-**	**Yes [g]**	**-**	**-**
TNBC 2L	-	Yes [i]	Yes [i]	-	-	Yes [j]	-	-	-
TNBC ≥3L	-	Yes [i]	Yes [i]	-	-	Yes [j]	-	-	-

Subgroups **in bold** were those for which the EAG requested information at clarification; the EAG considers the number of prior lines of cytotoxic chemotherapy for aBC can be a proxy for line of treatment, i.e., 0 prior lines of cytotoxic chemotherapy can be considered to be 1L,1 prior line of cytotoxic chemotherapy for aBC can be considered to 2L, and so on

[a] Only subgroup analyses for PFS and OS by hormone receptor status were pre-specified
[b] Data were provided in the company response to clarification question A1, Table 2
[c] Data were provided in CS, Figure 15
[d] The K-M curve was provided in the company response to clarification question A1, Figure 2
[e] Data were provided in the company response to clarification question A1, Table 3
[f] Data were provided in the CS, Figure 16
[g] K-M data were provided in company model
[h] Data were provided in the company response to clarification question A1, Table 3 and were available in the EPAR, Table 48 (CS, Appendix C)
[i] Data were provided in CS, Appendix D, Table 12
[j] Data were provided in CS, Appendix D, Table 11
[k] The K-M curve was provided in the company response to clarification question A1, Figure 1 and K-M data were provided in company model

HER2-=human epidermal growth factor receptor 2 negative; HR=hazard ratio; HR+=hormone-receptor positive; K-M=Kaplan-Meier; L=line of treatment; OR=odds ratio; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; TNBC=triple-negative breast cancer

2.3.8 Other considerations

The company highlights (CS, Section B.1.4) that:

> "It is well known that g*BRCA* mutations are more common in certain ethnicities and population groups due to the founder effect. Therefore, it is important to raise awareness of this and strive so that all eligible patients from all ethnic backgrounds have equal access to genetic testing and subsequent treatment."

The EAG agrees with the company but notes that most of evidence presented in the CS has been derived from populations in which patients are predominantly described as being 'White'. The proportion of patients described as being 'White' was 300/431 (70%) in the EMBRACA trial and 61/84 (73%) in the phase II ABRAZO study[38] (which provided supporting evidence).

The company has submitted a confidential Patient Access Scheme (PAS) application for talazoparib. The company has used the anticipated talazoparib PAS price to generate the company base cost effectiveness results presented in the CS.

Eribulin has a confidential PAS price and filgrastim (an immunostimulant which may be used alongside talazoparib or chemotherapy for treating neutropenia) has a Commercial Medicines Unit (CMU) price. Company and EAG cost effectiveness results using all available discounted prices (and NICE price tracker eMIT prices) are presented in the confidential appendix.

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

Full details of the methods used by the company to identify and select clinically relevant evidence of the effectiveness of talazoparib versus PCT are presented in the CS (Appendix D). The company literature searches, which were comprehensive, were completed <6 months prior to the company submission to NICE. The EAG therefore considered that it was not necessary to carry out its own literature searches. An assessment of the extent to which the company's review was conducted in accordance with the LR*i*G in-house systematic review checklist is summarised in Table 5. The EAG considers that the company's systematic review methods were appropriate.

Table 5 EAG appraisal of the company's systematic review methods

Review process	EAG response	Note
Was the review question clearly defined in terms of population, interventions, comparators, outcomes and study designs?	Yes	CS, Appendix D, Table 7 In addition to studies of talazoparib and the comparators listed in the final scope issued by NICE (i.e., capecitabine, eribulin and vinorelbine), the company searched for studies of platinum chemotherapy and gemcitabine
Were appropriate sources searched?	Yes	CS, Appendix D, Section D.1.2
Was the timespan of the searches appropriate?	Yes	CS, Appendix D, Section D.1.2
Were appropriate search terms used?	Yes	CS, Appendix D, Tables 1 to 6
Were the eligibility criteria appropriate to the decision problem?	Partially	CS, Appendix D, Table 7 The eligibility criteria were broader than the decision problem as studies of platinum chemotherapy and gemcitabine, as well as studies of talazoparib and the comparators listed in the final scope issued by NICE (i.e., capecitabine, eribulin and vinorelbine), were eligible for inclusion
Was study selection applied by two or more reviewers independently?	Yes	CS, Appendix D, Section D.1.8
Was data extracted by two or more reviewers independently?	Yes	CS, Appendix D, Section D.1.9 One reviewer extracted data and the data were then checked by a second (independent) reviewer
Were appropriate criteria used to assess the risk of bias and/or quality of the primary studies?	Yes	CS, Section B.2.6 and CS, Appendix D, Section D.3
Was the quality assessment conducted by two or more reviewers independently?	Yes	CS, Appendix D, Section D.3
Were attempts to synthesise evidence appropriate?	Yes	No meta-analyses or indirect comparisons were performed; only narrative synthesis of trial and real-world evidence were reported in the CS

CS=company submission; EAG=External Assessment Group; NICE=National Institute for Health and Care Excellence
Source: EAG in-house checklist

3.2 Critique of studies of the technology of interest, the company's analysis and interpretation

3.2.1 Included and excluded studies

The company's systematic literature review (SLR) was broader than was required to address the final scope issued by NICE as the company searched for studies of platinum chemotherapy and gemcitabine in addition to studies of talazoparib, capecitabine, eribulin and vinorelbine. The company (CS, Appendix D, Table 9) identified five potentially relevant studies:

the EMBRACA trial, the ABRAZO study,[38] the ViTAL study,[39] the TNT trial[31] and the TNBCRC009 study[40] (Table 6).

Table 6 Characteristics of studies included in the CS from the company SLR

Trial	Study design	Patient population	Intervention	Comparator
EMBRACA trial	Phase III, open-label RCT	Patients with HER2-aBC	Talazoparib (N=287)	PCT (capecitabine, eribulin, gemcitabine or vinorelbine; N=144)
ABRAZO study[38]	Phase II, two-cohort, open-label, single-arm study	Patients with HER2-aBC with g*BRCA*m who had received prior platinum chemotherapy (cohort 1, N=49) or 3 prior cyctotoxic therapies and no prior platinum chemotherapy (cohort 2, N=35)	Talazoparib (N=84)	-
ViTAL study[39]	Phase IV, longitudinal cohort study	Patients with HER2-aBC with s*BRCA*m or g*BRCA*m	Talazoparib (N=86)	-
TNT trial[31]	Phase III, parallel design, open-label RCT	Patients with advanced TNBC and no known *BRCA*m (n=338/376, 89.9%) and patients with any HR and HER2 status with g*BRCA*m (n=43/376, 11.4%) [a]	Carboplatin (N=188) [b]	Docetaxel (N=188)
TBCRC009 study[40]	Phase II, open label, single-arm study	Patients with advanced TNBC (including 11 patients with known g*BRCA*m)	Cisplatin (n=43) or carboplatin (n=43)	-

[a] 29 patients had a known g*BRCA*m at trial entry; central testing identified an additional 14 patients with g*BRCA*m
[b] The company only extracted data for the carboplatin arm
aBC=advanced stage breast cancer; HER2-=human epidermal growth factor receptor 2 negative; g*BRCA*m=germline BReast CAncer gene mutations; PCT=physicians choice treatment; RCT=randomised controlled trial; s*BRCA*m=somatic BReast CAncer gene mutations; TNBC=advanced stage triple-negative breast cancer;
Source: CS, Appendix D, Table 9, Isakoff 2015,[40] Litton 2018,[27] Loirat 2022,[39] Turner 2019,[38] and Tutt 2018[31]

The company presented evidence for talazoparib from the EMBRACA trial (CS, Section B.2.3 to Section B.2.6, Section B.2.4.8 to Section B.2.8), the ABRAZO study[37] (CS, Appendix M) and the ViTAL study[38] (CS, Section B.2.4.7).

Two of the identified studies[31,40] provided evidence for platinum chemotherapy: the TNT trial[31] and the TBCRC009 study[40] (CS, Appendix D). However, the company did not synthesise or interpret the data and data were not presented in the main body of the CS as platinum chemotherapy was not listed as a comparator in the final scope issued by NICE.

The company also presented evidence for talazoparib from three additional real-world studies: a US retrospective chart review study,[41] a retrospective real-world study carried out in Turkey[42] and a multicentre compassionate use program carried out in Russia.[43] All three real-world evidence (RWE) studies[41-43] had been excluded studies from the company's SLR (CS, Appendix D, Table 21) due to having a retrospective study design[41,42] or because the

publication was not written in English.[43] The EAG sought clarification on how these studies were identified (clarification question C6); the company responded that they were "talazoparib-specific real-world evidence studies that Pfizer were aware of."

The EAG's summary of the clinical effectiveness evidence from the EMBRACA trial is presented in Sections 3.2 to 3.5. The EAG's consideration of the clinical effectiveness evidence from all the additional sources is presented in Section 3.6.

3.2.2 Characteristics of the EMBRACA trial

The company provided details of the EMBRACA trial in the CS (CS, Section B.2.2). The EMBRACA trial was a phase III, multicentre, international, open-label RCT that compared talazoparib versus PCT for patients with HER2- aBC with g*BRCA*m. Patients were randomised to receive talazoparib or PCT (2:1); patients in the PCT arm received either capecitabine, eribulin, gemcitabine or vinorelbine.

Clinical advice to the EAG is that it was appropriate to use PCT (capecitabine, eribulin, gemcitabine and vinorelbine) as a single comparator arm. Capecitabine (55/126, 43.7%) and eribulin (50/126, 39.7%) were the most commonly prescribed drugs in the EMBRACA trial PCT arm, and these proportions are likely to be representative of use in NHS clinical practice (See Section 2.3.4). Gemcitabine is not commonly used in NHS clinical practice. However, the number of patients in the EMBRACA trial PCT arm treated with gemcitabine was small (n=12/126; 9.5% of PCT arm). Clinical advice to the EAG is that there may be differences in the efficacy and tolerability of the individual EMBRACA trial PCT arm drugs which may impact on the overall treatment effect estimate for the PCT arm.

The key characteristics of the EMBRACA trial are presented in Table 7.

Table 7 Key characteristics of the EMBRACA trial

Trial parameter	EMBRACA trial
Design	• Phase III, multicentre, international, open-label RCT • 145 sites in 16 countries (US, Belgium, France, Germany, Ireland, Italy, Poland, Spain, UK [redacted], Israel, Russia, Ukraine, Brazil, South Korea, Australia, and Taiwan). • Treatment continued until disease progression, unacceptable toxicity, withdrawal of consent or physician's decision • Randomisation was central (2:1 ratio for talazoparib versus PCT) and was stratified by: ○ number of prior cytotoxic chemotherapy regimens for aBC (0 versus 1, 2, or 3) ○ TNBC status (yes versus no) ○ history of central nervous system (CNS) metastases (yes versus no).
Patient population	• Patients (≥18 years old) with histologically or cytologically confirmed HER2- LABC not amenable to curative radiation or surgical cure and/or mBC appropriate for systemic single cytotoxic chemotherapy • (suspected) deleterious g*BRCA*m • ≤3 prior cytotoxic regimens for LABC or mBC • Prior treatment with a taxane and/or anthracycline (adjuvant, neoadjuvant or advanced setting) unless contraindicated [a] • ECOG PS≤2 [b] • Patients who had received platinum chemotherapy in the adjuvant or neoadjuvant setting and who had stable disease for ≥6 months after their last dose of platinum chemotherapy and patients who had received platinum chemotherapy for aBC without having experienced disease progression while being treated with platinum chemotherapy were eligible for inclusion [c] • Patients with CNS metastases were eligible to participate in the trial if their CNS metastases had not progressed since previous scans and they did not require corticosteroids for the management of CNS symptoms.
Intervention	• 1mg/day talazoparib orally (N=287)
Comparator	PCT (N=144) • 1250mg/m^2 capecitabine orally twice daily on Days 1 to 14 of 21-day cycle (n=55) • 1.4mg/m^2 eribulin mesylate IV infusion on Days 1 and 8 of 21-day cycle (n=50) • 1250mg/m^2 gemcitabine IV infusion on Days 1 and 8 of 21-day cycle (n=12) • 30mg/m^2 vinorelbine IV infusion on Days 1, 8, and 15 of 21-day cycle (n=9)
Primary outcome	• Radiographic PFS by blinded independent clinical review
Secondary outcomes	• ORR • CBR • OS • Safety • Talazoparib PK (not reported in the CS)
Exploratory endpoints	• DoR for objective responders • Time to end of first post-study therapy • QoL (EORTC QLQ-C30 and EORTC QLQ-BR23)

[a] In the SmPC (CS, Appendix C), it is stated that patients with HR+/HER2- BC should have been treated with an endocrine-based therapy prior to treatment with talazoparib, unless contraindicated. The EAG highlights that prior endocrine-based therapy for patients with HR+/HER2- BC was not an inclusion criterion for the EMBRACA trial.
[b] In version 1 of the EMBRACA trial protocol (dated 17 July 2013), only patients with ECOG PS≤1 were eligible for enrolment. Based on advice from CHMP, the company amended the protocol (dated 14 December 2015) to include patients with ECOG PS≤2 (CS, Appendix C)
[c] In version 1 of the EMBRACA trial protocol (dated 17 July 2013), only patients who had received platinum chemotherapy in the adjuvant or neoadjuvant setting and who had stable disease for ≥12 months after their last dose of platinum chemotherapy were eligible for enrolment.[30]
aBC=advanced stage breast cancer; CBR=clinical benefit rate; CHMP=Committee for Medicinal Products for Human Use; DoR=duration of response; ECOG PS=Eastern Cooperative Oncology Group performance status; EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EORTC QLQ-BR23=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire breast cancer module; g*BRCA*m=germline breast cancer susceptibility gene 1 or 2 mutation; HER2-=human epidermal growth factor receptor 2 negative; IV=intravenous; LABC=locally advanced breast cancer; mBC=metastatic breast cancer; ORR=objective response rate; OS=overall survival; PCT=physician's choice treatment; PFS=progression-free survival; PK=pharmacokinetics; QoL=quality of life; RCT=randomised controlled trial
Source: clinical study report[30] and EPAR Tables 7 to 8 (CS, Appendix C)

3.2.3 Characteristics of EMBRACA trial patients

The company provided baseline characteristics for whole EMBRACA trial population (CS, Section 2.4.10.2 and Table 14) and the whole trial population stratified by hormone receptor status (company response to clarification A1, Table 2). The EAG highlights that:

- on average, patients in the talazoparib arm were younger than patients in the PCT arm (median age: 45 and 50 years, respectively)
- more patients in the talazoparib arm were in the <50 years age category (182/287, 63.4%) compared to the PCT arm (67/144, 46.5%)
- fewer patients in the talazoparib arm were in the 50 years to <65 years age category (78/287, 27.2%) compared to the PCT arm (67/144, 46.5% on average, patients in the talazoparib arm were younger than patients in the PCT arm (median age: 45 and 50 years, respectively)
- on average, patients with TNBC were younger (median age: 43 [talazoparib] and 44.5 years [PCT]) than patients with HR+/HER2- BC (median age: 47 [talazoparib] and 52 years [PCT]); clinical advice to the EAG is that this age difference is reflective of that observed between patients with TNBC and HR+/HER2- BC treated in NHS clinical practice.

Data presented in the talazoparib EPAR (Table 37, p99/140 and p101/140, CS, Appendix C,), show that:

- the proportion of patients who had a prior anthracycline was greater in the talazoparib arm (243/287, 84.7%) than in the PCT arm (115/144, 79.9%)
- similar proportions of patients in the talazoparib arm (262/287, 91.3%) and PCT arm (130/144, 90.3%) had a prior taxane
- the proportion of patients who had received prior platinum chemotherapy (any setting) was higher in the PCT arm (30/144, 20.8%) than in the talazoparib arm (46/287, 16.0%) but similar proportions of patients in the talazoparib arm (6%) and PCT arm (8%) had received prior platinum chemotherapy for aBC
- only a small proportion (22/431, 5.1%) of patients had received a CDK4/6i; CDK4/6i are now recommended by NICE for patients with HR+/HER2- BC (see Section 2.2.3):
- a small proportion (3/431, 0.7%) of patients had received immunotherapy; immunotherapy is now recommended by NICE for patients with TNBC (see Section 2.2.3)
- the proportion of patients who had not received “any form of anti-hormonal treatment” was higher in the PCT arm (16.7%) than in the talazoparib arm (9.6%); clinical advice to the EAG is that these proportions are greater than the proportion of patients with HR+ BC who would be expected to be contraindicated for endocrine-based therapy in NHS clinical practice (<5%); the EAG also highlights that prior endocrine-based therapy for patients with HR+/HER2- BC was not an inclusion criterion for the EMBRACA trial but that it is stated in the SmPC (CS, Appendix C), that patients with HR+/HER2- BC should be treated with an endocrine-based therapy prior to treatment with talazoparib, unless contraindicated.

Clinical advice to the EAG is that:

- most of the EMBRACA trial patients were fitter (most were ECOG PS 0 to 1) than patients with HER2- aBC who are typically treated in NHS clinical practice (most are ECOG PS 1 to 2)

- nearly all patients with HR+/HER2- BC receive prior endocrine-based therapy (any setting; 95%) and most (85%) receive a CDK4/6i for aBC in NHS clinical practice
- approximately 30% to 45% of patients with early TNBC receive immunotherapy in NHS clinical practice.

Differences between the EMBRACA trial ITT population and patients treated in NHS clinical practice may limit the generalisability of the EMBRACA trial results to NHS clinical practice.

Table 8 Baseline characteristics of EMBRACA trial patients

Baseline characteristic	All patients (N=431)		HR+/HER2- BC subgroup (N=241)		TNBC subgroup (N=190)	
	Talazoparib (N=287)	Overall PCT (N=144)	Talazoparib (N=157)	Overall PCT (N=84)	Talazoparib (N=130)	Overall PCT (N=60)
Age, years						
Mean (SD)	47.5 (11.61)	49.4 (12.12)	[redacted]	[redacted]	[redacted]	[redacted]
Median (range)	45 (27 to 84)	50 (24 to 88)	[redacted]	[redacted]	[redacted]	[redacted]
Age category (years), n (%)						
<50	182 (63.4)	67 (46.5)	90 (57.3)	30 (35.7)	92 (70.8)	37 (61.7)
50 to <65	78 (27.2)	67 (46.5)	46 (29.3)	46 (54.8)	32 (24.6)	21 (35.0)
≥65	27 (9.4)	10 (6.9)	21 (13.4)	8 (9.5)	6 (4.6)	2 (3.3)
Race, n (%)						
Asian	31 (10.8)	16 (11.1)	16 (10.2)	11 (13.1)	15. (11.5)	5 (8.3)
Black or African American	12 (4.2)	1 (0.7)	4 (2.5)	0 (0.0)	8 (6.2)	1 (1.7)
White	192 (66.9)	108 (75.0)	107 (68.2)	65 (77.4)	85 (65.4)	43 (71.7)
Other	5 (1.7)	1 (0.7)	1 (0.6)	0 (0.0)	4 (3.1)	1 (1.7)
Not reported	47 (16.4)	18 (12.5)	29 (18.5)	8 (9.5)	18 (13.8)	10 (16.7)
ECOG PS, n (%)						
0	153 (53.3)	84 (58.3)	83 (52.9)	47 (56.0)	70 (53.8)	37 (61.7)
1	127 (44.3)	57 (39.6)	70 (44.6)	34 (40.4)	57 (43.8)	23 (38.3)
2	6 (2.1)	2 (1.4)	4 (2.5)	2 (2.4)	2 (1.5)	0 (0.0)
Missing	1 (0.3)	1 (0.7)	NR	1 (1.2)	1 (0.8)	NR
***BRCA* status, n (%)**						
*BRCA*1-positive	133 (46.3)	63 (43.8)	33 (21.0)	20 (23.8)	100 (76.9)	43 (71.7)
*BRCA*2-positive	154 (53.7)	81 (56.2)	124 (79.0)	64 (76.2)	30 (23.1)	17 (28.3)
Breast cancer stage, n (%)						
Locally advanced	15 (5.2)	9 (6.2)	[redacted]	[redacted]	[redacted]	[redacted]
Metastatic	271 (94.4)	135 (93.8)	[redacted]	[redacted]	[redacted]	[redacted]
Time from initial BC diagnosis to diagnosis of aBC, n (%)						
<12 months	108 (37.6)	42 (29.2)	[redacted]	[redacted]	[redacted]	[redacted]
Previous antineoplastic therapy for aBC, n (%)						
≥1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Baseline characteristic	All patients (N=431)		HR+/HER2- BC subgroup (N=241)		TNBC subgroup (N=190)	
	Talazoparib (N=287)	Overall PCT (N=144)	Talazoparib (N=157)	Overall PCT (N=84)	Talazoparib (N=130)	Overall PCT (N=60)
Previous cytotoxic regimens for aBC, n (%)						
0	111 (38.7)	54 (37.5)	[redacted]	[redacted]	[redacted]	[redacted]
1	107 (37.3)	54 (37.5)	[redacted]	[redacted]	[redacted]	[redacted]
2	57 (19.9)	28 (19.4)	[redacted]	[redacted]	[redacted]	[redacted]
≥3	12 (4.2)	8 (5.6)	[redacted]	[redacted]	[redacted]	[redacted]
Prior treatment in any setting, n (%)						
Anthracycline only	18 (6.3)	9 (6.3)	[redacted]	[redacted]	[redacted]	[redacted]
Taxane only	37 (12.9)	24 (16.7)	[redacted]	[redacted]	[redacted]	[redacted]
Anthracycline and taxane	225 (78.4)	106 (73.6)	[redacted]	[redacted]	[redacted]	[redacted]
Immunotherapy	2 (0.7)	1 (0.7)	[redacted]	[redacted]	[redacted]	[redacted]
Platinum	46 (16.0)	30 (20.8)	[redacted]	[redacted]	[redacted]	[redacted]
Endocrine-based therapy	161 (56.1)	77 (53.5)	142 (90.4)	70 (83.3)	19 (14.6) [a]	7 (11.7) [a]
CDK4/6 inhibitor	16 (5.6)	6 (4.2)	[redacted]	[redacted]	[redacted]	[redacted]

[a] The EAG calculated the proportion of patients with TNBC who received treatment with endocrine-based therapy by subtracting the number of patients with HR+/HER2- BC (EPAR, p101/140, CS, Appendix C,) who received prior endocrine-based therapy from the total number of patients who received prior endocrine-based therapy in each treatment arm (EPAR, Table 37, CS, Appendix C) reported (EPAR, Table 37, CS, Appendix C) that 161/287 patients in the talazoparib arm and 77/144 patients in the PCT arm received

aBC=advanced stage breast cancer; *BRCA*=breast cancer susceptibility; ECOG PS=Eastern Cooperative Oncology Group performance status; HER2-=human epidermal growth factor receptor 2 negative; HR+=hormone receptor positive; NR=not reported; PCT=physician's choice treatment; SD=standard deviation; TNBC=triple-negative breast cancer

Source: CS, Table 1; company response to clarification A1, Table 2; EPAR, p101/140 and Table 37 (CS, Appendix C)

3.2.4 Quality assessment of the EMBRACA trial

The company assessed the quality of the EMBRACA trial using the quality assessment checklist for clinical trials[44] devised by the Centre for Reviews and Dissemination (CRD) at the University of York (CS, Table 16). The company's assessments and EAG comments are presented in Appendix 1 (Section 8.1, Table 33). The EAG considers that the EMBRACA trial was of good methodological quality; however, there was an imbalance in the proportions of patients who did not receive the study drug between treatment arms (0.3% of patients in the talazoparib arm and 12.5% of patients in the PCT arm). Clinical advice to the EAG is that this imbalance may have occurred due to patients not wishing to receive PCT (as the trial was open-label), and subsequently withdrawing from the study before receiving treatment. The imbalance between treatment arms may have introduced bias as efficacy outcomes may have been impacted by patients not receiving treatment with the assigned study drug. The impact of this bias is unknown as the company did not report the proportion of patients who withdrew from study drug treatment only (and were still included in the analyses) versus the proportion of patients who withdrew from study drug treatment plus radiographic imaging and long-term follow up (and data for these patients would be censored or treated as missing in analyses).

3.2.5 Statistical approach adopted for the analysis of the EMBRACA trial

Information relevant to the statistical approach taken by the company to analyse EMBRACA trial data has been extracted from the CS, the clinical study report (CSR) and supplemental CSRs,[30,45,46] the trial statistical analysis plan (TSAP) and the trial protocol. The TSAP and trial protocol are available from the supplementary materials published alongside the trial report (Litton et al 2018[27]). A summary of the EAG checks of the pre-planned statistical approach used by the company to analyse data from the included trial is provided in Appendix 2 (Section 8.2.1, Table 34). The EAG notes that the company analysed PFS and OS data using Cox PH models. This analysis approach is only reliable if the assumption of PH holds, i.e., the event hazards associated with the intervention and comparator data are proportional over time. The company did not provide PH assessment results for PFS and OS (see company response to clarification A2). The EAG therefore used K-M data provided in the company's economic model to generate log-log plots and perform Grambsch-Therneau tests of Schoenfeld residuals (Appendix 2, Section 8.2.2). The EAG considers that the PH assumption is likely to be violated for OS (log-log plots show the survival curves are not parallel), although the test of Schoenfeld residuals was not statistically significant (p=0.0835). Therefore, the EAG considers that a OS HR may not be an appropriate measure of effect for the ITT population.

3.3 EMBRACA trial efficacy results

At the time of the primary PFS analysis (data cut-off date: 15 September 2017), median follow-up was 11.2 months ([redacted]) and an interim OS analysis was also conducted (CS, p47 and Figure 8; data not reported in this EAG report).

At the time of the final OS analysis (data cut-off date: 30 September 2019), median follow-up was 44.9 months (95% CI: 37.9 to 47.0) and 36.8 months (95% CI: 34.3 to 43.0) for patients treated with talazoparib and PCT, respectively.

As outlined in Section 2.3.3, the EAG considers that prognosis differs by hormone receptor status and by line of treatment. The EAG has therefore presented PFS, OS and ORR results for:

- the whole trial population and the whole trial population stratified by hormone receptor status (HR+/HER2- BC and TNBC; Table 9)
- the whole trial population and the whole trial population stratified by number of prior regimens of cytotoxic chemotherapy for aBC (0, 1, ≥2; Table 10)
- the whole trial population stratified by **both** hormone receptor status (HR+/HER2- BC and TNBC) and number of prior regimens of cytotoxic chemotherapy for aBC (0, 1, ≥2; Table 11).

Table 9 EMBRACA primary and secondary efficacy endpoints in all patients, and in subgroups defined by hormone receptor status

Endpoint	All patients		HR+/HER2- BC subgroup		TNBC subgroup	
	Talazoparib	Overall PCT	Talazoparib	PCT	Talazoparib	PCT
Primary efficacy endpoint: PFS by IRF [a]						
ITT population, N	287	144	157	84	130	60
Number of events, n (%)	186 (64.8)	83 (57.6)	86 (54.8)	43 (51.2)	100 (76.9)	40 (66.7)
Median, months (95% CI)	8.6 (7.2 to 9.3)	5.6 (4.2 to 6.7)	9.4 (8.8 to 13.0)	6.7 (5.6 to 8.7)	5.8 (5.3 to 7.7)	2.9 (1.7 to 4.6)
HR (95% CI)	0.54 (0.41 to 0.71)		0.47 (0.32 to 0.71)		0.60 (0.41 to 0.87)	
Secondary efficacy endpoint: final OS [b]						
ITT population, N	287	144	157	84	130	60
Number of events (%)	216 (75.3)	108 (75.0)	114 (72.6)	61 (72.6)	102 (78.5)	47 (78.3)
Median, months (95% CI)*	19.3 (16.6 to 22.5)	19.5 (17.4 to 22.4)	23.1 (19.3 to 27.3)	22.4 (17.4 to 27.5)	13.4 (10.9 to 16.3)	18.6 (11.3 to 20.7)
HR (95% CI)	0.85 (0.67 to 1.07)		0.83 (0.60 to 1.14)		0.90 (0.63 to 1.28)	
Secondary efficacy endpoint: ORR by investigator assessment [a]						
ITT with measurable disease population, N	219	114	117	66	102	48
ORR, % (95% CI)	62.6 (55.8 to 69.0)	27.2 (19.3 to 36.3)	63.2 (53.8 to 72.0)	37.9 (26.2 to 50.7)	61.8 (51.6 to 71.2)	12.5 (4.7 to 25.3)
OR (95% CI)	4.99 (2.93 to 8.83)		2.89 (1.43 to 5.83)		11.89 (4.54 to 41.37)	
CR, n (%)	12 (5.5)	0	NR	NR	NR	NR
PR, n (%)	125 (57.1)	31 (27.2)	NR	NR	NR	NR
SD, n (%)	46 (21.0)	36 (31.6)	NR	NR	NR	NR
Could not be evaluated, n (%)	4 (1.8)	19 (16.7)	NR	NR	NR	NR

Highlighted cell shows that result favours PCT
[a] The data cut-off date for PFS and ORR was 15 September 2017
[b] The data cut-off date for final OS was 30 September 2019
CI=confidence interval; CR=complete response; EPAR=European Public Assessment Report; HER2-= human epidermal growth factor receptor 2 negative; HR=hazard ratio; HR+=hormone receptor positive; IRF=independent radiology facility; ITT=intention-to-treat; NR=not reported; OR=odds ratio; ORR=objective response rate; PCT=physician's choice treatment; PFS=progression-free survival; PR=partial response; SD=stable disease; TNBC=triple-negative breast cancer
Source: company response to the EAG clarification letter, Table 3; EPAR, Table 48 (CS, Appendix C)

Table 10 EMBRACA primary and secondary efficacy endpoints in all patients, and in subgroups defined by number of prior regimens of cytotoxic chemotherapy for aBC

Endpoint	All patients		Prior regimens of cytotoxic chemotherapy for aBC					
			0		1		≥2	
	Talazoparib	PCT	Talazoparib	PCT	Talazoparib	PCT	Talazoparib	PCT
Primary efficacy endpoint: PFS by IRF [a]								
ITT population, N	287	144	111	54	107	54	69	36
Number of events, n (%)	186 (65)	83 (58)	NR	NR	NR	NR	NR	NR
Median, months (95% CI)	8.6 (7.2 to 9.3)	5.6 (4.2 to 6.7)	9.8 (8.5 to 13.3)	8.7 (5.5 to 18.0)	8.1 (5.7 to 9.2)	4.6 (3.3 to 8.2)	5.8 (4.4 to 8.9)	4.2 (1.5 to 5.7)
HR (95% CI)	0.54 (0.41 to 0.71)		0.57 (0.34 to 0.95)		0.51 (0.33 to 0.80)		0.56 (0.34 to 0.95)	
Secondary efficacy endpoint: final OS [b]								
ITT population, N	287	144	111	54	107	54	69	36
Number of events (%)	216 (75.3)	108 (75.0)	74	33	85	47	57	28
Median, months (95% CI)*	19.3 (16.6 to 22.5)	19.5 (17.4 to 22.4)	27.8 (22.7 to 31.4)	29.1 (20.7 to 37.4)	16.6 (14.2 to 21.7)	17.4 (12.8 to 19.2)	13.6 (11.4 to 16.3)	17.4 (13.1 to 24.0)
HR (95% CI)	0.85 (0.67 to 1.07)		0.89 (0.58 to 1.36)		0.70 (0.48 to 1.01)		1.10 (0.68 to 1.76)	
Secondary efficacy endpoint: ORR by investigator assessment [a]								
ITT with measurable disease population, N	219	114	83	41	79	40	57	33
ORR, % (95% CI)	62.6 (55.8 to 69.0)	27.2 (19.3 to 36.3)	79.5 (69.2 to 87.6)	36.6 (22.1 to 53.1)	57.0 (45.3 to 68.1)	20.0 (9.1 to 35.7)	45.6 (32.4 to 59.3)	24.2 (11.1 to 42.3)
OR (95% CI)	4.99 (2.93 to 8.83)		6.86 (2.65 to 16.81)		5.06 (1.95 to 14.18)		2.66 (0.88 to 7.80)	

Highlighted cell shows that result favours PCT
[a] The data cut-off date for PFS and ORR was 15 September 2017
[b] The data cut-off date for final OS was 30 September 2019
Data for complete response, partial response and stable disease not reported for all subgroups
aBC=advanced stage breast cancer; CI=confidence interval; EPAR=European Public Assessment Report; HR=hazard ratio; IRF=independent radiology facility; ITT=intention-to-treat; NR=not reported; ORR=objective response rate; PCT=physician's choice treatment; PFS=progression-free survival; OR=odds ratio; ORR=objective response rate;
Source: CS, Tables 9 to 11, Figures 15 and 16; CS, Appendix D, Table 13; company response to the EAG clarification letter, Table 3; EPAR, Table 48 (CS, Appendix C)

Table 11 EMBRACA PFS and OS in subgroups defined by both hormone receptor status and number of prior regimens of cytotoxic chemotherapy for aBC

Endpoint	Prior regimens of cytotoxic chemotherapy for aBC					
	0		1		≥2	
	Talazoparib	PCT	Talazoparib	PCT	Talazoparib	PCT
PFS by IRF [a]						
HR+/HER2- BC patients						
N	59	28	57	33	41	23
Number of events, n (%)	NR	NR	NR	NR	NR	NR
Median, months (95% CI)	12.2 (NR)	8.9 (NR)	9.0 (NR)	5.9 (NR)	7.6 (NR)	5.6 (NR)
HR (95% CI)	0.41 (0.17 to 0.97)		0.43 (0.22 to 0.81)		0.60 (0.30 to 1.20)	
TNBC patients						
N	52	26	50	21	28	13
Number of events, n (%)	NR	NR	NR	NR	NR	NR
Median, months (95% CI)	7.3 (NR)	5.5 (NR)	5.4 (NR)	3.5 (NR)	4.3 (NR)	1.5 (NR)
HR (95% CI)	0.67 (0.65 to 1.27)		0.58 (0.29 to 1.12)		0.46 (0.21 to 1.03)	
Final OS [b]						
HR+/HER2- BC patients						
N	59	28	57	33	41	23
Number of events, n (%)	36 (61.0)	17 (60.7)	45 (78.9)	27 (81.8)	33 (80.5)	17 (73.9)
Median, months (95% CI)	NR	NR	NR	NR	NR	NR
HR (95% CI)*	0.87 (0.47 to 1.60)		0.62 (0.37 to 1.04)		1.32 (0.72 to 2.45)	
TNBC patients						
N	52	26	50	21	28	13
Number of events, n (%)	38 (73.1)	16 (61.5)	40 (80.0)	20 (95.2)	24 (85.7)	11 (84.6)
Median, months (95% CI)	NR	NR	NR	NR	NR	NR
HR (95% CI)	0.97 (0.53 to 1.77)		0.84 (0.48 to 1.45)		0.78 (0.38 to 1.63)	

* Highlighted cell shows that result favours PCT
[a] The data cut-off date for PFS was 15 September 2017
[b] The data cut-off date for final OS was 30 September 2019
aBC=advanced stage breast cancer; CI=confidence interval; HER2-=human epidermal growth factor receptor 2 negative; HR=hazard ratio; HR+=hormone receptor positive; IRF=independent radiology facility; NR=not reported; OS=overall survival; PCT=physician's choice treatment; PFS=progression-free survival
Source: CS, Figure 16; CS, Appendix D, Table 12

3.3.1 Progression-free survival

The EAG notes that:

- results for PFS by independent radiology facility (IRF) favour talazoparib over PCT for:
    - the whole trial population (Table 9)
    - subgroups defined only by hormone receptor status (Table 9)
    - subgroups defined only by number of prior regimens of cytotoxic chemotherapy for aBC (Table 10)
    - subgroups defined by hormone receptor status and by number of prior regimens of cytotoxic chemotherapy for aBC (Table 11)
- compared to all patients with TNBC, median PFS (in both arms) was higher for patients with HR+/HER2- BC ; similarly, when comparing patients who had received the same number of prior cytotoxic regimens for aBC (0, 1 or ≥2), median PFS was also higher for patients with HR+/HER2- BC than for patients with TNBC
- median PFS decreased as number of previous lines of treatment increased
- HRs between treatment arms were relatively similar for the ITT population, for subgroups defined only by hormone receptor status and for subgroups defined by hormone receptor status and number of prior regimens of cytotoxic chemotherapy for aBC.

It is noted in the EPAR, p102/140 (CS, Appendix C) that, when comparing PFS by IRF and PFS by investigator, discrepancy rates were high (40%) and that censoring rates were 'higher based on IRF and led, as expected, to prolonged medians to event'. Investigator assessment of PFS was therefore the CHMP preferred metric. The PFS by investigator HR for the whole trial population (0.54, 95% CI: 0.42 to 0.69) was very similar to the PFS by IRF HR. Median PFS was shorter in both treatment arms when assessments were made by the investigator (talazoparib, 7.0 months, 95% CI: 5.7 to 7.6; PCT, 4.4 months, 95% CI: 2.9 to 5.6) rather than by the IRF.

PFS subgroup analyses results are presented in the CS (Figures 14 to 15) by baseline characteristics. Reported PFS HRs favoured talazoparib in comparison to PCT for all subgroups considered. The difference in PFS between EMBRACA trial arms was statistically significant for the subgroup of patients who had not received prior platinum chemotherapy (HR=0.52, 95% CI: 0.39 to 0.71), not for the subgroup who had received prior platinum chemotherapy (HR=0.76, 95% CI: 0.40 to 1.45). The EAG highlights that subgroup analyses were not powered to detect statistically significant differences.

3.3.2 Overall survival

In the EMBRACA trial ITT population, median OS was similar for patients in the two treatment arms and the OS HR did not indicate a statistically significant difference. Considering the K-M plot (CS, Figure 9), the EAG highlights that the survival curves cross twice, with similar OS

rates (CS, Table 10) observed at 12 months in both treatment arms, and higher OS rates in the talazoparib arm than in the PCT arm during the later stages of the trial (i.e., at 24, 36 and 48 months). This supports the EAG's conclusion that the PH assumption is likely to be violated and that the OS HR may not be an appropriate measure of treatment effect for the ITT population. The EAG considers that the size and direction of the OS treatment effect of talazoparib versus PCT for the ITT population is uncertain.

Subgroups defined by hormone receptor status

In the hormone receptor status OS subgroups, the EAG considers that the reported data demonstrate the unsuitability of using HRs to represent the treatment effect (talazoparib versus PCT). In particular, in the TNBC subgroup, median OS was 5.2 months longer for patients treated with PCT compared to patients treated with talazoparib, while the OS HR numerically favoured treatment with talazoparib. In this instance, the OS HR does not provide an accurate representation of the treatment effect of talazoparib versus PCT for the whole trial follow-up period. Although median OS is also not able to fully capture treatment effect for the whole trial follow-up period, clinical advice to the EAG is that the difference in median OS of 5.2 months (favouring PCT) is a clinically meaningful result.

In line with the EMBRACA trial PFS data, the median OS results suggest that patients in the HR+/HER2- BC subgroup are likely to have a better prognosis than patients in the TNBC subgroup. Relative treatment effects (i.e., HRs) were comparable between subgroups defined by hormone receptor status. There is no evidence to demonstrate whether the PH assumption holds/is violated for OS subgroups.

Subgroups defined by number of prior regimens of cytotoxic chemotherapy for aBC (EAG proxy for line of treatment)

In line with the EMBRACA trial PFS data, the median OS results suggest that patients who had received fewer prior regimens of cytotoxic chemotherapy for aBC are likely to have a better prognosis than patients who had received more prior regimens. For the ITT population and all subgroups, median OS results were lower in the talazoparib arm than in the PCT arm.

HRs varied between subgroups defined by number of prior regimens of cytotoxic chemotherapy for aBC. For patients who had received 2 or more prior regimens of cytotoxic chemotherapy for aBC, the HR favoured treatment with PCT over treatment with talazoparib. There is no evidence to demonstrate whether the PH assumption holds/is violated for OS subgroups.

Subgroups defined by both hormone receptor status and number of prior regimens of cytotoxic chemotherapy for aBC (EAG proxy for line of treatment)

The EAG notes that within subgroups defined by hormone receptor status and number of prior regimens of cytotoxic chemotherapy for aBC, OS HRs varied (0.62 to 1.32). There is no evidence to demonstrate whether the OS PH assumption holds/is violated for these subgroups. In addition, the small numbers of patients and events contributing to subgroup results, and the absence of reported medians, mean that it is difficult to draw any conclusions about how hormone receptor status and number of prior regimens of cytotoxic chemotherapy for aBC interact to impact the treatment effect of talazoparib in comparison to PCT.

Subgroup defined by prior platinum chemotherapy

OS subgroup analyses results are presented in the CS (Figure 16) by prior platinum chemotherapy in any setting (yes/no) or neo(adjuvant) therapy (yes only) . In all three subgroups, the results numerically favoured the talazoparib arm (HR=0.73, 95% CI: 0.42 to 1.28 and HR=0.60, 95% CI: 0.24 to 1.49 for those who had received platinum chemotherapy in any or the neoadjuvant setting, respectively; HR=0.89, 95% CI: 0.99 to 1.16 for those who had not received platinum chemotherapy)The EAG highlights that subgroup analyses were not powered to detect statistically significant differences.

Other subgroup analyses

Results for OS subgroup analyses are presented in the CS (Figure 16) by baseline characteristics. OS HRs were generally consistent across subgroups and mostly favoured talazoparib. However, there were four subgroups for whom the reported OS HR numerically favoured PCT in comparison to talazoparib. Results for two of the subgroups favouring PCT (prior regimens of cytotoxic chemotherapy for aBC ≥2, and prior regimens of cytotoxic chemotherapy for aBC in HR+/HER2- patients ≥2) are presented in Table 10 and Table 11 of this EAG report, respectively. The two remaining subgroups favouring PCT are race=other (HR=1.28, 95% CI: 0.76 to 2.16) and age <50 years (HR=1.04, 95% CI: 0.74 to 1.45). There is no evidence to demonstrate whether the OS PH assumption holds or is violated for these subgroups. In addition, the small treatment effect for the age <50 years subgroup, and small numbers of patients and events contributing to the 'other' race subgroup, means that it is difficult to draw conclusions about the OS treatment effect for patients in these subgroups.

3.3.3 Adjusted OS estimates for subsequent treatment

Following disease progression, patients in the EMBRACA trial could receive subsequent treatment. Litton et al 2020[26] reported that a high proportion of patients in both arms received a subsequent treatment (talazoparib: 232/287, 80.8%; PCT: 110/144, 76.4%). The EAG notes that 13/287 (4.5%) patients in the talazoparib arm and 47/144 (32.6%) patients in the PCT

arm received a PARPi (mostly olaparib: 8/287 [2.8%] in the talazoparib arm and 36/144 [25.0%] in the PCT arm) as subsequent treatment. Subsequent treatment with platinum chemotherapy was common in both arms (talazoparib: 133/287, 46.3%; PCT: 60/144, 41.7%).

The company carried out two analyses using the rank-preserving structural failure time model (RPSFTM) method to estimate the OS treatment effect by adjusting for (i) subsequent treatment with a PARPi (HR=0.82, 95% CI: 0.62 to 1.05), and (ii) subsequent PARPi and/or platinum chemotherapy use (HR=0.76, 95% CI: 0.50 to 1.03). In line with the unadjusted OS analysis, the adjusted analyses did not demonstrate a statistically significant OS advantage for talazoparib in comparison to PCT.

Clinical advice to the EAG is that subsequent platinum chemotherapy in the EMBRACA trial reflects NHS clinical practice. Therefore, the RPSFTM method should only be used to adjust OS for subsequent PARPi treatment.

The RPSFTM method was developed to adjust for patients in the control arm of a trial switching to receive treatment that was given to patients in the experimental arm of the trial (and/or vice versa). The RPSFTM method incorporates data on how long each individual spent "on treatment" (i.e., received the experimental treatment) and "off treatment" (i.e., received the control treatment). However, the company has attempted to use the RPSFTM method to adjust for patients in the control arm switching to a non-study treatment (olaparib, veliparib, platinum chemotherapy).

The EAG asked the company to justify using the RPSFTM method to estimate the OS treatment effect adjusting for non-study treatment; however, no justification for using the RPSFTM method was provided (Clarification Response, Question A2). The EAG considers that, if the PARPi options used in the EMBRACA trial (olaparib, talazoparib, veliparib) can be considered equivalent (see Appendix 4, Section 8.4), then an RPSFTM analysis which only adjusts for subsequent therapy with a PARPi is appropriate, as all patients would either be "on treatment" (i.e., receiving a PARPi) or "off treatment" (i.e. not receiving a PARPi).

The company used an OS HR to summarise treatment effect in the RPSFTM analysis. To assess the assumption of PH for the RPSFTM-adjusted OS data set (adjusting for subsequent PARPi use only), the EAG digitised the K-M data presented in the CS (Figure 10), generated a log-log plot and performed the Grambsch-Therneau test of Schoenfeld residuals. The EAG assessments indicate that the PH assumption is violated for the RPSFTM-adjusted OS data set as the log-log plots showed unparallel survival curves (Appendix 2, Section 8.2.2), and the test of Schoenfeld residuals was statistically significant (p=0.0322). The EAG therefore

considers that this analysis does not provide a valid estimate of OS treatment effect that accounts for subsequent treatment with a PARPi, and that the impact of subsequent treatment with a PARPi on OS results in the EMBRACA trial is unknown.

3.3.4 Objective response rate

The EAG notes that:

- ORRs were much higher for patients in the talazoparib arm than for patients in the PCT arm, for the ITT population, for subgroups defined by hormone receptor status and for subgroups defined by number of prior regimens of cytotoxic chemotherapy for aBC
- for patients receiving PCT, the ORR was considerably lower for patients with TNBC compared to patients with HR+/HER2- BC (and to the ITT population)
- the only patients to achieve a CR were in the talazoparib arm
- ORs for ORR suggested a greater treatment benefit for patients in the TNBC subgroup than patients in the HR+/HER2- BC subgroup (likely due to a very low ORR for patients in the PCT arm), and for patients who had received 0 or 1 lines of previous cytotoxic chemotherapy for aBC, in comparison to patients who had received ≥2 lines of previous cytotoxic chemotherapy for aBC.

ORR subgroup analyses were also performed. In all instances, the results were found to favour talazoparib over PCT (EPAR, Table 48, CS Appendix C). Based on the OR subgroup results for talazoparib versus PCT, the CHMP highlighted a number of subgroup analyses (in addition to hormone receptor status and line of treatment, see Section 3.3.1 of this report) that demonstrated considerably different ORR benefits between subgroups (EPAR p103/140, CS, Appendix C). These subgroup analyses included *BRCA* status (*BRCA1/ BRCA2*), ECOG PS (0/>0), history of CNS metastasis (yes/no), prior platinum chemotherapy (yes/no) and time from initial diagnosis to initial diagnosis of advanced disease (<12 months/≥12 months). These results are summarised in Appendix 3 (Section 8.3, Table 35). Of note, pre-specified EMBRACA subgroup analyses showed that ORR was greater in the talazoparib and PCT arms for patients not previously treated with platinum chemotherapy (65% versus 28%) than for those who were previously treated with platinum (50% versus 24%). The OR for ORR between arms was higher for patients not previously treated with platinum chemotherapy (OR=5.36, 95% CI: 2.89 to 9.89) than for patients who were previously treated with platinum (OR=3.16, 95% CI: 0.88 to 15.67).

3.3.5 Exploratory endpoints

The company also presented results for the following exploratory endpoints (CS, Sections B.2.4.4 to B.2.4.5): duration of response, clinical benefit rate, and time to the end of first post-study therapy. Results for these exploratory endpoints all indicated at least a numerical treatment benefit for talazoparib in comparison to PCT (statistical tests were not reported except for time to the end of first post-study therapy: HR=0.68, (95% CI: 0.51 to 0.91).

It is stated by the CHMP (EPAR, p135/140, CS, Appendix C) that duration of response in the talazoparib arm (5.4 months versus 3.1 months in those who received PCT) was considered to be shorter than expected given the high ORR in the talazoparib arm.

3.4 EMBRACA trial patient reported outcomes

The company presented (CS, Section B.2.4.6) health-related quality of life (HRQoL) data that were collected as part of the EMBRACA trial using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) and EORTC QLQ breast cancer module (EORTC QLQ-BR23). The company reported change from baseline (CFB) and differences between groups for all EORTC QLQ-C30 and EORTC QLQ-BR23 subscales, however, it was not clear at which timepoint CFB was calculated and the company did not specify what they considered to be a clinically meaningful improvement in EORTC QLQ-C30 and EORTC QLQ-BR23 subscale scores.[27]

The EAG extracted additional data from the published HRQoL report by Ettl (2018).[25] In summary:

- overall, patients in the talazoparib arm had improved HRQoL compared to patients in the PCT arm (Table 12)
- median time to clinically meaningful deterioration (≥10 point decrease) in global health status (GHS)/QoL was statistically significantly longer for patients in the talazoparib arm (24.3 months, 95% CI: 13.8 months to NR [not reached]) than for patients in the PCT arm (6.3 months, 95% CI: 4.9 to 12.2)[25]
- median time to clinically meaningful deterioration (death, first occurrence of progression or ≥10 point increase) in breast symptoms was statistically significantly longer for patients in the talazoparib arm than for patients in the PCT arm (HR=0.392, 95% CI: 0.20 to 0.78; p=0.0053), however, median time to clinically meaningful deterioration was not reached in either treatment arm.[25]

The company highlighted (CS, p81) that ≥81% of patients in the talazoparib arm and ≥73% of patients in the PCT arm completed at least one question in the EORTC QLQ-C30 and EORTC QLQ-BR23 questionnaires for every cycle from baseline to Cycle 13. However, patients only completed the questionnaires while on treatment, i.e., patients who progressed and discontinued study drug did not complete questionnaires. The patient reported outcome results may therefore be biased by responses from patients who remained progression-free on study drug.

Table 12 EMBRACA EORTC QLQ-C30 and EORTC QLQ-BR23 results

		Score numerically improved versus baseline		Score statistically significantly improved versus baseline		Difference in CFB between groups numerically favoured talazoparib over PCT	Difference in CFB between groups statistically significantly favoured talazoparib over PCT
		Talazoparib	PCT [a]	Talazoparib	PCT [b]		
EORTC QLQ-C30	GHS/QoL	Yes		Yes		Yes	Yes
EORTC QLQ-C30 functional scales	Physical functioning	Yes		Yes		Yes	Yes
	Role functioning	Yes				Yes	Yes
	Emotional functioning	Yes		Yes		Yes	Yes
	Cognitive functioning					Yes	Yes
	Social functioning	Yes				Yes	Yes
EORTC QLQ-C30 symptom scales	Fatigue	Yes		Yes		Yes	Yes
	Nausea/vomiting	Yes				Yes	
	Pain	Yes		Yes		Yes	Yes
	Dyspnoea	Yes				Yes	
	Insomnia	Yes		Yes		Yes	Yes
	Appetite loss	Yes		Yes		Yes	Yes
	Constipation	Yes		Yes		Yes	
	Diarrhoea	Yes				Yes	
EORTC QLQ-BR23 functional scales	Body image	Yes		Yes		Yes	Yes
	Sexual functioning					Yes	
	Sexual enjoyment [c]					Yes	
	Future perspective	Yes	Yes	Yes	Yes	Yes	
EORTC QLQ-BR23 symptom scales	Systemic therapy side-effects					Yes	Yes
	Breast symptoms	Yes		Yes		Yes	Yes
	Arm symptoms	Yes		Yes		Yes	Yes
	Upset by hair loss [d]	Yes	Yes		Yes		

[a] Patients in the PCT arm had numerically worse scores versus baselines for all EORTC QLQ-C30 subscale scores and all EORTC QLQ-BR23 subscales but 'future perspective' and 'upset by hair loss'.
[b] Patients in the PCT arm has a statistically significant deterioration in 5/6 EORTC QLQ-C30 functional subscales, 3/8 EORTC QLQ-C30 symptom subscales and in the EORTC QLQ-B23 systemic therapy side-effects subscale.
[c] Patients in the talazoparib arm had a statistically significant deterioration in sexual enjoyment versus baseline.
[d] Patients in the PCT arm had greater improvement in the EORTC QLQ-BR23 'upset by hair loss' symptom scale score compared to patients in the talazoparib arm but the difference was not statistically significant.
CFB=change from baseline; EORTC QLQ-BR23=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Breast Cancer module; EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; GHS=global health status; PCT=physician's choice treatment; QoL=quality of life
Source: Ettl (2018)[25]

3.5 EMBRACA trial safety and tolerability results

The company presented adverse event (AE) data from the EMBRACA trial (CS, Section 2.8) from the 22 March 2021 data cut.[46] The data provided in the CS included: extent of drug exposure (CS, Table 17), summary of AEs (CS, Table 18), the proportions of patients who experienced treatment-emergent adverse events (TEAEs; CS, Table 19), Grade 3 or 4 TEAEs (CS, Table 20) and serious adverse events (SAEs; CS, Table 21). The EAG highlights that:

- median duration of exposure was longer for patients in the talazoparib arm ([redacted] months; range: [redacted]) than for patients in the PCT arm ([redacted] months; range: [redacted])
- similar proportions of patients in the talazoparib arm (256/286, 89.5%) and PCT arm (112/126, 88.9%) experienced at least one treatment-related adverse event (TRAE)
- the TRAEs most frequently (≥20%) experienced by patients in the talazoparib arm were [redacted][46]
- the TRAEs most frequently (≥20%) experienced by patients in the PCT arm were [redacted] the EAG notes that the frequency of TRAEs varied across the PCT drugs (see Table 13), e.g., [redacted][46]
- in the talazoparib arm (31/286, 10.8%) a slightly higher proportion of patients experienced at least one serious TRAE than in the PCT arm (11/126, 8.7%)
- the most frequent serious TRAE experienced by patients in the talazoparib arm was [redacted] ([redacted], [redacted]) and the most frequent serious TRAE experienced by patients in the PCT arm was [redacted] ([redacted], [redacted])[46]
- in the talazoparib arm (167/286, 58.4%) a higher proportion of patients experienced at least one Grade 3 or Grade 4 TRAE than in the PCT arm (62/126, 49.2%)
- the Grade 3 or 4 TRAEs most frequently (≥5%) experienced by patients in the talazoparib arm were [redacted][46]
- the Grade 3 or 4 TRAEs most frequently (≥5%) experienced by patients in the PCT arm were [redacted][46]
- similar proportions of patients in the talazoparib arm (15/286, 5.2%) and PCT arm (7/126, 5.6%) discontinued treatment due to AEs; the most common AE associated with permanent study drug discontinuation was [redacted] which occurred in [redacted]
- in the talazoparib arm (112/286, 39.2%) a higher proportion of patients received RBC transfusions during the study period than in the PCT arm (7/126, 5.6%);[47] however, the company considered (CS, 108) that the frequency of RBC transfusions was higher than would be seen in the NHS (see Section 6.3 for more details)

[redacted]

[redacted]

Table 13 EMBRACA treatment-related adverse events experienced by ≥20% of EMBRACA trial patients

TRAE	Talazoparib (N=286)	PCT (N=126)	Capecitabine (n=55)	Eribulin (n=50)	Gemcitabine (n=12)	Vinorelbine (n=9)
[redacted]						

Source: supplemental safety clinical study report,[46] Section 12.2.2.3

3.5.1 Adverse events of special interest in the EMBRACA trial

Adverse events of special interest (AEOSIs) included acute myeloid leukaemia (AML), myelodysplastic syndrome (MDS) and hepatotoxicity. The frequencies of AEOSIs in the EMBRACA trial were reported in the supplemental safety CSR.[46]

[redacted]

[redacted]

3.5.2 Adverse events associated with death

AEs associated with death were reported for [redacted] in the talazoparib arm and [redacted] in the PCT arm. The investigator considered that [redacted].[46]

3.6 EAG critique of the talazoparib supporting evidence

Supporting information for talazoparib is available from the ABRAZO study[38] (CS, Appendix M and Turner 2019[38]) and four RWE studies[41-43,48] (CS, Section B.2.4.7). The company did not provide quality assessments for any of these studies.[38,41-43,48] The EAG highlights that this supporting evidence may be of lower quality than evidence from the EMBRACA trial (e.g., due to smaller patient numbers, lack of randomisation [increasing the risk of selection bias] or a control arm). Furthermore, the RWE studies have either only been reported as conference posters,[41,42,48] so are not peer-reviewed publications or, in one case, published in Russian.[43] The company did not systematically search for RWE of talazoparib and instead included RWE studies that were known to the company (company response to clarification C6), therefore, there is a risk of selective reporting of results. Nonetheless, the EAG considers that this supporting evidence provides additional insight into the clinical effectiveness of talazoparib.

3.6.1 Supporting evidence: study and baseline characteristics

ABRAZO study characteristics

The ABRAZO study[38] was a multicentre, two-stage, open-label study with a two-cohort design (see Table 6 for cohort details). Turner (2019)[38] highlighted that the ABRAZO study enrolment was halted after an amendment to the EMBRACA trial protocol (dated 14 December 2015) led to an overlap in enrolment between the ABRAZO study[38] and the EMBRACA trial. Patients were enrolled into the ABRAZO study[38] between May 2014 and February 2016.

Real-world evidence study characteristics

Mahtani (2022)[41] carried out a retrospective chart review of medical records of patients (N=84) treated with talazoparib by nine community practice oncologists in the US between August and October 2021. Loirat (2022)[48] presented evidence from one of two cohorts in the ambispective, multicentre, longitudinal, phase IV ViTAL study; this cohort included patients (N=86) treated with talazoparib through the French Early Access Program from November

2018 to September 2019. Sendur (2021)[42] retrospectively analysed data from patients (N=47) treated with talazoparib in 24 different oncology centres via a Turkish Early Access Program (dates not reported). Semiglazova (2020)[43] reported on a multicentre Russian Compassionate Use Program (sponsored by the company) of patients (N=24) treated with talazoparib between March 2018 and June 2022. Patients recruited to all studies[41-43,48] had g*BRCA*m aBC; the phase IV ViTAL[48] study also included patients with somatic *BRCA*m (n=5).

The company highlights that the studies described by Mahtani (2022)[41] and Loirat (2022)[48] are ongoing (CS, Section B2.9).

Baseline characteristics: ABRAZO study and studies providing RWE

Baseline characteristics of the studies[38,41-43,48] providing supporting evidence are summarised in Appendix 5, Section 8.5.1 (Table 37), alongside the characteristics of the EMBRACA trial ITT population (for comparison). The characteristics of the study populations differ between and within studies and the populations are heterogeneous. All studies[41-43,48] included proportionately more heavily pre-treated patients than the EMBRACA trial (5% of patients received ≥3 prior cytotoxic chemotherapies for aBC). The Mahtani 2022[41] study included a relatively high proportion of patients with ECOG PS ≥2 (as would be expected in NHS clinical practice).

3.6.2 Supporting evidence: efficacy, HRQoL and safety results

Supporting evidence: efficacy

Efficacy results from the studies[38,41-43,48] providing supporting evidence are summarised in Appendix 5, Section 8.5.2 (Table 38), alongside EMBRACA trial ITT results (for comparison). All five studies[38,41-43,48] included subgroup analyses based on hormone receptor status[38,41-43,48] and/or prior lines of treatment[38,42,43,48] and/or prior platinum chemotherapy.[38,43] However, the EAG has only presented the subgroup absolute results from the Mahtani (2022)[41] and Loirat (2022)[48] studies; the EAG considers that subgroup analyses for cohort 1 and cohort 2 of the ABRAZO study[38] and from the other two studies[42,43] providing RWE are very small.

Compared with EMBRACA trial results, ABRAZO study[38] median PFS, median OS and ORR (in particular) were lower; this is not unexpected as the ABRAZO study[38] population was more heavily pre-treated than the EMBRACA trial population.

The company argued that the RWE study results[41-43,48] were consistent with the results from the EMBRACA trial. However, the EAG notes the following RWE study results:

- median PFS ranged from 6.5 months[42,43] to just over 8.5 months[41,48]

- median OS data were only available from an updated analysis of OS in cohort 1 of in the ViTAL study Loirat (2022[48]) provided by the company during clarification (company response to clarification question C6);[41] median OS was 25.2 months in the study population, 25.6 months in the HR+/HER2- BC subgroup and was not estimable in the TNBC subgroup
- the ORRs were 29%,[43] 33%[42] and 63%;[41] patients in the Mahtani (2022)[41] study had the highest ORR and the lowest proportion of patients previously treated with prior platinum chemotherapy.

In all these RWE studies,[41-43,48] patients were more heavily pre-treated than the EMBRACA trial population. The EAG also highlights that the proportions of patients with HR+/HER2- BC and TNBC varied across the RWE studies.[41-43,48] The EAG therefore considers that it is inappropriate to formally compare results across studies.

Supporting evidence: health-related quality of life

HRQoL results from the ABRAZO study[38] are summarised in Appendix 5, Section 8.5.3. The EAG highlights that cohort HRQoL results were not consistent and were based on responses from small numbers of patients.

Supporting evidence: safety

Safety outcomes from the studies[38,41-43,48] providing supporting evidence are summarised in Appendix 5, Section 8.5.4 (Table 39), alongside EMBRACA trial results (for comparison). While the actual frequencies varied, generally the talazoparib safety profile appears to be consistent across the studies.

3.7 Studies of platinum chemotherapy

The company presented data from two platinum chemotherapy studies[31,40] for patients with HER2- aBC (CS, Appendix D). The EAG identified one an additional study.[49] None of the studies[31,40,49] reported HRQoL data. The three studies were:

- TNT phase III trial (carboplatin versus docetaxel; however, the company extracted data from the platinum chemotherapy arm only, N=188)[31]
- TBCRC009 phase II study (cisplatin or carboplatin [PCT]; N=86)[40]
- A phase II, open-label study registered as NCT01611727 (cisplatin; N=20).[49]

3.7.1 Baseline characteristics of the studies of platinum chemotherapy

In the studies,[31,40,49] most or all patients treated with platinum chemotherapy had TNBC: 174/188 (92.4%),[31] 86/86 (100%) [40] and 15/20 (75%).[49] However, there were only 56/294 patients with aBC who had been treated with platinum chemotherapy and who had a g*BRCA*m: 11/86 (12.8%) in the TNT trial,[31] 25/188 (13.3%) in the TBCRC009 study[40] and 20/20 (100%) in the study registered as NCT01611727.[49]

For patients with aBC who had a g*BRCA*m:

- all patients (20/20, 100%) in the study registered as NCT01611727,[49] and most patients (16/25, 64%) in the TNT trial,[31] had g*BRCA1*m; the type of g*BRCA*m was not reported in the TBCRC009 study[40]
- all patients in the TNT trial[31] had received at least one prior regimen of cytotoxic therapy for aBC, compared to only 27% and 40% of patients in the TBCRC009 study[40] and NCT01611727[49] respectively.

3.7.2 Results from the platinum chemotherapy studies

ORR was the primary efficacy outcome in all three studies[31,40,49] and results show:

- ORR was greater in the subgroup of patients with g*BRCA*m aBC than all patients with aBC treated with platinum chemotherapy in the TNT trial[31] (68% versus 31%) and TBCRC009 study[40] (55% versus 26%); in the study registered as NCT01611727,[49] ORR was 80% in patients with both HR+/HER2- BC and TNBC but proportionately more patients with TNBC had a CR (53% versus 20%)
- median PFS was greater in the subgroup of patients with g*BRCA*m aBC than all patients with aBC treated with platinum chemotherapy in the TNT trial[31] (6.8 months versus 3.1 months) and TBCRC009 study[40] (3.3 months versus 2.9 months); time to progression (TTP) was 12 months in the study registered as NCT01611727[49] and varied by response to treatment, TTP was 17 months for those with a CR, 8 months for those with a PR and 3 months for those with stable disease
- median OS was greater in the subgroup of patients with g*BRCA*m aBC than all patients with aBC treated with platinum chemotherapy in the TNT trial[31] (not reached versus 12.8 months) and TBCRC009 study[40] (13.7 months versus 11 months); in the study registered as NCT01611727,[49] median OS was 30 months with OS rates of 80% at 12 months, 60% at 24 months, 25% at 36 months
- AEs for patients with g*BRCA*m aBC were only reported in the study registered as NCT01611727;[49] most commonly, nausea (10/20, 50%), neutropenia (7/20, 35%) and anaemia (1/20, 5%), with only 2/20 (10%) experiencing a Grade ≥3 AE (these patients being were reported to be receiving third-line platinum chemotherapy).

The EAG considers that it is difficult to draw conclusions from studies that include small numbers of patients but notes the high ORRs in all three studies.[31,40,49] Clinical advice to the EAG is that the TNT trial[31] results led to platinum chemotherapy being the preferred type of chemotherapy delivered in NHS clinical practice (i.e., as opposed to non-platinum chemotherapy) for patients with g*BRCA*m aBC.

3.8 EAG clinical effectiveness evidence conclusions

The EMBRACA trial is a high quality RCT that compares the effectiveness of talazoparib versus PCT for patients with HER2- aBC. Trial results show that compared with PCT, treatment with talazoparib improves PFS and ORR for the ITT population, and for subgroups of interest to the EAG (i.e., hormone receptor status and prior regimens of cytotoxic chemotherapy for aBC). The EAG considers that EMBRACA trial ITT OS results are uncertain as EAG statistical test results suggest that the PH assumption is likely to be violated (for some analyses, the OS HR numerically favours the talazoparib arm when the median OS favours the PCT arm and this is most noticeable for patients with TNBC). EMBRACA trial data show that treatment with talazoparib appears to deliver HRQoL benefits when patients are on treatment. Most AEs associated with talazoparib are haematological, and anaemia was the most common AE. Clinical advice to the EAG is that the safety profile of talazoparib is manageable.

The EMBRACA trial recruited a heterogeneous group of patients (different hormone receptor status and different lines of treatment) with HER2- aBC. Although the EMBRACA trial was not powered to show differences between subgroups, the evidence appears to suggest that patients with HR+/HER2- BC had better outcomes (in absolute terms as measured by median PFS, median OS and ORR) than patients with TNBC and that patients who had received fewer regimens of cytotoxic chemotherapy for aBC had better outcomes than patients who were more heavily pre-treated. Results for subgroups by **both** hormone receptor status and line of treatment show that for HR+/HER2- BC patients treated with talazoparib, only patients who had received <2 prior cytotoxic regimens for aBC achieved numerically better OS results than patients treated with PCT. For patients with TNBC, however, patients who had received ≥2 prior cytotoxic regimens for aBC appear to achieve numerically better OS than patients who had received <2 prior cytotoxic regimens for aBC.

The ABRAZO study[38] and RWE studies[41-43,48] included populations that differed by hormone receptor status and number of prior lines of treatment. Results from these studies[38,41-43,48] show that median PFS, median OS and ORR varied. Therefore, the EAG considers that it is inappropriate to formally compare results across studies.

While the evidence presented in the CS is in line with the final scope issued by NICE, clinical advice to the EAG and the options shown in the treatment pathways presented in the CS (Figures 1 to 3), the EAG considers that evidence should also have been presented for talazoparib versus platinum chemotherapy. The EAG notes that this is a view that was also expressed by the CHMP and SAG in the EPAR (CS, Appendix C), and was also suggested by the company at the scoping stage.

4 COST EFFECTIVENESS EVIDENCE

This section provides a structured critique of the economic evidence submitted by the company in support of the use of talazoparib as an option for treating adults with g*BRCA*m, HER2- aBC who have been treated with an anthracycline and/or taxane in the (neo)adjuvant, adjuvant, or metastatic setting. The two key components of the economic evidence presented in the CS are (i) a systematic review of the relevant literature and (ii) a report of the company's de novo economic evaluation. The company has provided an electronic copy of their economic model, which was developed in Microsoft Excel.

4.1 Published cost effectiveness evidence

4.1.1 Objective of the company's literature searches

The company undertook a SLR to identify cost effectiveness studies that could potentially be used to inform the development of the company's economic model. The database searches were designed to retrieve articles published between January 2012 and August 2022. The company also searched conference proceedings (last 3 years), the NICE website (2012-2022), and bibliographies of recent systematic reviews (2020-2022).

The company's search identified 30 unique relevant models (described in 34 publications); however, none of these studies evaluated the cost effectiveness of the intervention or the indication that are the focus of this appraisal. Full details of the company systematic review are provided in the CS, Appendix G.

4.1.2 EAG critique of the company's literature review

A summary of the EAG's critique of the company's literature review methods is provided in Table 14.

Table 14 EAG appraisal of systematic review methods (cost effectiveness)

Review process	EAG response
Was the review question clearly defined in terms of population, interventions, comparators, outcomes and study designs?	Yes
Were appropriate sources searched?	Yes
Was the timespan of the searches appropriate?	Yes
Were appropriate search terms used?	Yes
Were the eligibility criteria appropriate to the decision problem?	Yes
Was study selection applied by two or more reviewers independently?	Yes
Were data extracted by two or more reviewers independently?	Data were extracted by a single reviewer and checked by a second reviewer
Were appropriate criteria used to assess the quality of the primary studies?	Yes
Was the quality assessment conducted by two or more reviewers independently?	Undertaken by one reviewer and checked by a second reviewer
Were any relevant studies identified?	30 unique models were identified; however, none considered the intervention or indication that are the focus of this appraisal

EAG=External Assessment Group

4.2 EAG conclusions: company systematic literature review

The EAG has no concerns about the methods used by the company to identify cost effectiveness studies. No published models exploring the cost effectiveness of interventions to treat patients with g*BRCA*m, HER2- aBC were identified by the company review.

4.3 Summary of the company's submitted economic evaluation

4.3.1 NICE Reference Case checklist

Table 15 NICE Reference Case checklist completed by EAG

Element of health technology assessment	Reference case	EAG comment on company submission
Defining the decision problem	The scope developed by NICE	Yes
Comparator(s)	As listed in the scope developed by NICE	Yes
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes
Perspective on costs	NHS and PSS	Yes
Type of economic evaluation	Cost utility analysis with fully incremental analysis Cost comparison analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes
Synthesis of evidence on health effects	Based on systematic review	NA. Direct evidence from the EMBRACA trial was available
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults	**PFS health state** The company mapped EMBRACA trial EORTC QLQ-30 data to EQ-5D-3L data using a published algorithm **PD health state** Published data were used
Source of data for measurement of health-related quality of life	Reported directly by patients or carers, or both	Yes
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Yes
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit, except in specific circumstances	Yes
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes

EAG=External Assessment Group; EORTC-QLQ C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core30; EQ-5D-3L=EuroQol-5 Dimension 3-Levels; PD=progressed disease; PFS=progression-free survival; PSS=Personal Social Services; QALY=quality adjusted life year
Source: NICE Reference Case[23]

Table 16 Drummond and Jefferson critical appraisal checklist completed by the EAG

Question	Critical appraisal	EAG comment
Was a well-defined question posed in answerable form?	Yes	
Was a comprehensive description of the competing alternatives given?	Yes	
Was the effectiveness of the programme or services established?	Unclear	Subgroup clinical effectiveness data by **both** hormone receptor status and line of treatment requires further exploration
Were all the important and relevant costs and consequences for each alternative identified?	Mostly	The EAG re-estimated the cost of treating neutropenia
Were costs and consequences measured accurately in appropriate physical units?	Yes	
Were the cost and consequences valued credibly?	Yes	
Were costs and consequences adjusted for differential timing?	Yes	
Was an incremental analysis of costs and consequences of alternatives performed?	Yes	
Was allowance made for uncertainty in the estimates of costs and consequences?	Yes	
Did the presentation and discussion of study results include all issues of concern to users?	No	Both hormone receptor status and line of treatment subgroups should have been considered

EAG=External Assessment Group
Source: Drummond and Jefferson (1996)[50]

4.3.2 Company model structure

The company developed a cohort partitioned-survival model. This approach is in line with that used in previous NICE breast cancer appraisals.[21,32,33,51,52]

The three health states modelled were progression-free (PFS), post-progression survival (PPS) and death. In the PFS health state, for the purpose of estimating costs associated with resource use, patients were sub-divided by response (CR/PR and stable disease). In the post-progression survival (PPS) health state, patients were treated until death. A schematic showing the different possible patient pathways is shown in Figure 1. Costs and QALYs were assigned to each health state and QALYs varied depending on type of treatment received.

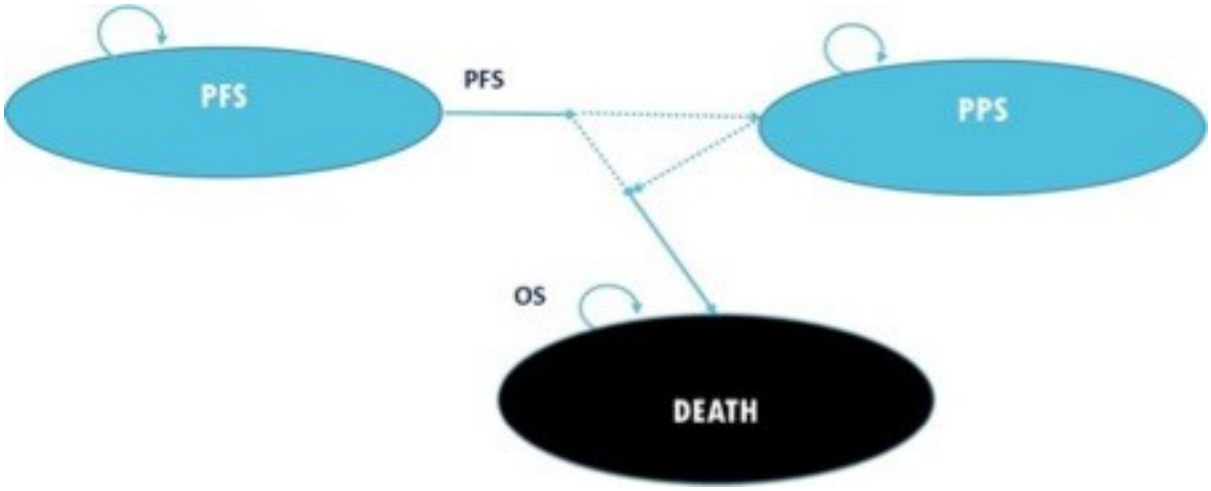

Figure 1 Company model schematic

CS=company submission; PFS=progression-free survival; PPS=post-progression survival
Source: CS, Figure 17

4.3.3 Population

The company analysis focused on the EMBRACA trial population, i.e., adults with deleterious or suspected deleterious g*BRCA*m, HER2- aBC who have been previously treated with an anthracycline and/or a taxane in the (neo)adjuvant, locally advanced or metastatic setting. Model baseline characteristics are those of the EMBRACA trial baseline population.

Table 17 Model baseline population characteristics (EMBRACA trial, ITT population)

Baseline characteristic	Mean value
Age, years (SD)	[redacted]
Weight, kg (SD)	[redacted]
Body surface area, m^2	[redacted]
Proportion male (%)	[redacted]

CSR=clinical study report; ITT=intention-to-treat; SD=standard deviation
Source: CS, Table 22

4.3.4 Interventions and comparators

The intervention is talazoparib. The recommended dose is 1mg daily, with or without food. Patients should be treated with talazoparib until disease progression or unacceptable toxicity occurs.

The comparator is PCT. PCT treatment options permitted in the EMBRACA trial were capecitabine, eribulin, gemcitabine and vinorelbine. Expert advice to the company was that these four treatments have equal efficacy. However, as gemcitabine was not an agent listed in the final scope issued by NICE, the proportions of patients in the EMBRACA trial who received the other three treatments were re-weighted as follows to exclude gemcitabine:

- capecitabine (48%)
- eribulin (44%)
- vinorelbine (8%)

The pooled efficacy of the four EMBRACA trial PCT treatments was assumed to reflect the efficacy of the three modelled treatments and thus the re-weighting only affected treatment cost calculations.

4.3.5 Perspective, time horizon and discounting

The model perspective was reported to be that of the NHS and PSS the cycle length was 3 weeks. The time horizon was 10 years, and costs and outcomes were discounted at a rate of 3.5% per annum. A half-cycle correction was applied to all costs and outcomes except first-line drug and administration costs which were assumed to be incurred at the start of each cycle.

4.3.6 Treatment effectiveness

Treatment efficacy estimates were sourced directly from the two arms (talazoparib and PCT) of the EMBRACA trial. Parametric distributions were fitted separately to EMBRACA trial talazoparib and PCT arm PFS, and to talazoparib arm OS K-M data. Goodness of fit was assessed using Akaike Information Criteria (AIC) and Bayesian Information Criteria (BIC) and curve selections were based on these statistics, visual inspection, an assessment of plausibility based on long-term hazard profiles and the extrapolated mean survival estimates, and clinical opinion.

PARPi subsequent treatments were received by 4.5% and 32.6% of patients in the talazoparib and PCT arms of the EMBRACA trial respectively. When the company carried out a RPSTFM analysis to adjust for subsequent PARPi use only, the cross-over adjusted OS HR was 0.820 (95% CI: 0.617 to 1.047). This HR estimate was used to adjust talazoparib arm OS K-M data to represent OS for patients receiving PCT. Company approaches to modelling PFS and OS are shown in Table 18.

Table 18 Company approaches to modelling progression-free and overall survival

Treatment	Progression-free survival	Overall survival
Talazoparib	Log-normal	Log-normal
PCT	Log-logistic	RPSFTM

PCT=physician's choice treatment; RPSFTM=rank preserving structural failure time model
Source: CS, Table 26, Table 29 and Section B.3.3.2.2

4.3.7 All-cause mortality

UK life table mortality rates,[53] chosen based on EMBRACA trial baseline age and gender data, were applied in the company model.

4.3.8 Treatment duration

EMBRACA trial median treatment duration data were used to model treatment duration.

4.3.9 Adverse events

The ten most frequently occurring treatment-related Grade ≥3 AEs were modelled as a one-off cost in the first cycle only. Each AE was associated with a specific cost (sourced from 2020/21 National Cost Collection data,[54] see CS, Table 42) and a utility decrement (sourced from TA819,[21] Lloyd 2006[55] or an assumption, e.g., thrombocytopenia had the same effect on HRQoL as neutropenia, see CS, Table 35).

4.3.10 Health-related quality of life

As EQ-5D data were not collected as part of the EMBRACA trial, the company mapped the collected EORTC QLQ-30 data to EQ-5D-3L data using a published algorithm[56] and used these values to estimate PFS health state utility values, regardless of response. The progressive disease health state utility value was assumed to be the average of two published estimates.[57,58]

Table 19 Company model health state utility values

Treatment	Progression-free survival	Overall survival
Talazoparib	[redacted]	[redacted]
PCT	[redacted]	

CS=company submission; PCT=physician's choice
Source: CS, Table 33

4.3.11 Treatment acquisition costs

When estimating costs, as NHS patients would not receive gemcitabine, the company re-weighted the proportions of patients who received the other three drugs (new weights: capecitabine=48%; eribulin=44%; vinorelbine= 8%). Dosing information for each treatment option was sourced from the EMBRACA trial and treatment SmPCs[59-61] and is shown in Table 20.

Table 20 Modelled drug doses

Treatment	Dosing	Source
Talazoparib	1mg once daily	EMBRACA trial
Capecitabine	1250mg/m^2 twice daily orally for 2 weeks followed by a 7-day rest period in 3-week cycles	Capecitabine SmPC[59]
Eribulin	1.23mg/m^2 IV over 2 to 5 minutes on Days 1 and 8 of a 21-day cycle	Halaven SmPC[60]
Vinorelbine	25 mg/m^2 IV day 1, weekly	Navelbine SmPC[62]

CS=company submission; IV=intravenous; SmPC=summary of product characteristics
Source: CS, Table 38

The company stated that, for all drugs, except for talazoparib, drug acquisition costs were sourced from the online British National Formulary (BNF) for talazoparib,[63] capecitabine[64] and eribulin[65] and from the online eMIT database for vinorelbine.[66] However, cost effectiveness results were generated using the talazoparib discounted PAS price.

Relative dose intensity multipliers were applied in the base case (Table 21). Subsequent treatment costs for all patients were assumed to equal PCT arm treatment costs.

Table 21 Relative dose intensity multipliers used in the company model

Drug	RDI
Talazoparib	[redacted]
Capecitabine	[redacted]
Eribulin	[redacted]
Vinorelbine	[redacted]

RDI=relative dose intensity
Source: Company model

4.3.12 Treatment administration costs

Modelled treatment administration costs are shown in Table 22.

Table 22 Treatment administration costs

Details	Mean value	Drug	Source
Exclusively oral at initiation	£215.80	Talazoparib and capecitabine	2020/21 National Cost Collection data[54] - SB11Z
Infusion: ≤ 60 minutes, initial	£281.11	Eribulin and vinorelbine	2020/21 National Cost Collection data[54] - SB12Z
Infusion: Subsequent regimen	£438.38	Eribulin and vinorelbine	2020/21 National Cost Collection data[54] - SB15Z

CS=company submission
Source: CS, Table 37

4.3.13 Health state unit costs and resource use

Medical resource use costs were calculated by multiplying the unit cost of a resource (sourced from 2020/21 National Cost Collection data[54] or PSSRU[67]) by the frequency of use (varied by health state and, for PFS, response [CR/PR and stable disease]; estimates based on UK clinical advice) and the proportion of patients who used each resource (EMBRACA trial resource use data). Health state unit costs and resource use information are provided in the CS, Table 39 and Table 40.

The company highlights that, for patients on talazoparib who had had a dose interruption, the EMBRACA trial protocol required Hb values to recover to grade 1 or better (10g/dL) before resuming talazoparib and that a protocol amendment later changed this criterion to 9g/dL. However, NICE guidelines NG24[68] are less stringent (threshold of 70g/litre and an Hb concentration target of 70-90g/dL). Therefore, the company chose to use a value of 8.3% (source: US retrospective chart review by Mahtani (2022),[41] non-interventional final study report[69]) to represent the proportion of patients receiving a RBC transfusion, rather than the EMBRACA trial value of 38%.

4.3.14 Terminal care costs

Terminal care cost estimates include management, monitoring and resource use and are applied on entry to the death health state as a one-off cost. In line with the approach taken in TA639[51] and TA495.[70] The company has assumed the same proportions of patients in each setting (hospital: 40%; hospice: 10%; home: 50%) as were assumed in TA639.[51] Unit costs were sourced from PSSRU.[67] The weighted terminal care cost applied in the model is £7,952.60.

4.4 Severity modifier

Age (48.1 years) and sex (98.4% female) matched general population QALYs were estimated using age-related population utilities reported by Ara and Brazier (2010).[71] Results from the company QALY shortfall calculations are presented in Table 23.

Table 23 Company QALY shortfall calculation results

Outcome	Total QALYs	Shortfall	
		Absolute	Proportional
Expected total for the general population	16.026		
Disease specific	1.062	14.964	0.934
QALY multiplier		1.2	1.2
WTP threshold		£36,000	

CS=company submission; QALY=quality adjusted life year; WTP=willingness to pay threshold
Source: CS, Table 44

5 COST EFFECTIVENESS RESULTS

The company base case deterministic cost effectiveness results are presented in Table 24. These results have been generated using the PAS price for talazoparib. The modelled comparator (and subsequent treatment) drugs have been modelled using list prices. The EAG is aware that eribulin is available to the NHS at a confidential PAS price.

The EAG highlights that the cost effectiveness results generated by the company model do not match those reported in the CS (£33,016 versus £34,664 per QALY gained respectively); this is likely due to the company model not being set to show the base case ICER per QALY gained before the results were copied into the CS.

Table 24 Updated company deterministic base case cost effectiveness results (talazoparib PAS price)

Technologies	Total		Incremental		ICER (£/QALY)
	Costs	QALYs	Costs	QALYs	
Talazoparib	[redacted]	[redacted]			
PCT	[redacted]	[redacted]	[redacted]	[redacted]	£34,664

CS=company submission; ICER=incremental cost effectiveness ratio; PCT=physician's choice treatment; QALY=quality-adjusted life year
Source: CS, Table 47

The company probabilistic sensitivity analyses PSA (1,000 model iterations) are presented in Table 25. Results from the company analysis showed that, at a willingness to pay (WTP) threshold of £36,000, the probability of talazoparib being cost effective was approximately [redacted].

Table 25 Company probabilistic case cost effectiveness results (talazoparib PAS price)

Technologies	Total		Incremental		ICER (£/QALY)
	Costs	QALYs	Costs	QALYs	
Talazoparib	[redacted]	[redacted]			
PCT	[redacted]	[redacted]	[redacted]	[redacted]	£32,110

CS=company submission; ICER=incremental cost effectiveness ration; PCT=physician's choice treatment; QALY=quality-adjusted life year
Source: CS, Table 48

5.1 Deterministic sensitivity analyses

The company carried out a range of deterministic sensitivity analyses (n=30). Results from these analyses showed that the key cost effectiveness drivers were subsequent treatment costs, varying talazoparib CR/PR utility, acquisition cost of talazoparib and talazoparib median treatment duration (Table 26).

Table 26 Company key deterministic sensitivity analysis results (talazoparib PAS price)

Input name	Base case input	Lower bound input	Lower bound ICER/QALY	Upper bound input	Upper bound ICER/QALY
Subsequent treatment (average cost per cycle aggregate)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Varying talazoparib CR/PR utility	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Acquisition cost per pack - talazoparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median treatment duration - talazoparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CR=complete response; PR=partial response; ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year
Source: Company model

5.2 Scenario analyses

Company carried out nine scenario analyses (CS, Table 50) exploring six different areas:

- PFS for talazoparib and PCT (HER2-)
- OS for talazoparib and PCT (HER2-)
- impact of response
- relative dose intensity
- treatment duration
- societal perspective

The lowest ICER per QALY gained (£30,545) was generated when PFS was modelled using a log-logistic distribution for talazoparib and a log-logistic distribution for PCT. The three highest ICERs per QALY gained were generated when treatment duration was set equal to PFS (£43,068), when RDI was set to zero (£40,248) and when impact of no response was considered (£39,975).

5.3 Subgroup analyses

The EMBRACA trial did not provide sufficient data for subgroup analyses to be run.

5.4 Validation of the cost effectiveness analyses

The company carried out the following checks:

- a technical review of the model was conducted by an independent economist
- the relevance of assumptions was validated by UK clinicians
- a cell-by-cell verification process was carried out to check all input calculation, formulae and visual basic code
- company compared medians generated by OS survival extrapolations for talazoparib and PCT with published data reporting median OS for a mixture of treated or untreated HR+/HER2- BC or TNBC patients across different treatments and found that the modelled medians fell within the range of median OS reported in the publications[49,72-83] (range: 12.9 months[82] to 38.4 months[72] [see CS, Table 60])
- compared median OS for patients receiving PCT with median OS reported in TA819[21] (sacituzumab govitecan for treating unresectable TNBC) and found that their extrapolation more closely matched the EAG extrapolation than the company extrapolation (current appraisal: 19.5 months; TA819 company: 6.9 months; EAG:14.8 months)
- Compared model output with EMBRACA trial data at 1, 2, 3, 5 years and an assumption that no patients were alive at 10 years (CS, Table 62) and concluded that the model output was a good match to trial data.

6 EAG CRITIQUE OF COMPANY ECONOMIC MODEL

6.1 Introduction

The EAG is satisfied that the company model algorithms are accurate and, except for the RDI multiplier applied to the talazoparib arm, that the parameter values used in the cost effectiveness model match those in the CS. However, the cost effectiveness results generated by the company model do not match those reported in the CS (£33,016 versus £34,664 per QALY gained respectively); this is likely due to the company model not being set to show the base case ICER per QALY before the results were copied into the CS.

Further, the EAG considers that the use of a partitioned survival model structure and the modelled pathway are appropriate, with the caveat that clinical advice to the EAG is that there are other relevant comparator treatments (for example, platinum chemotherapy) not considered by the company that may be more efficacious than those considered in the company model.

As discussed in Section 3.3.2, EMBRACA trial results show that median OS for patients in the talazoparib arm differed depending on hormone receptor status (HER2-/HR+ or TNBC). Additional evidence of a difference in OS by type of hormone receptor status is supplied by EMBRACA trial talazoparib arm OS K-M data (Figure 2).

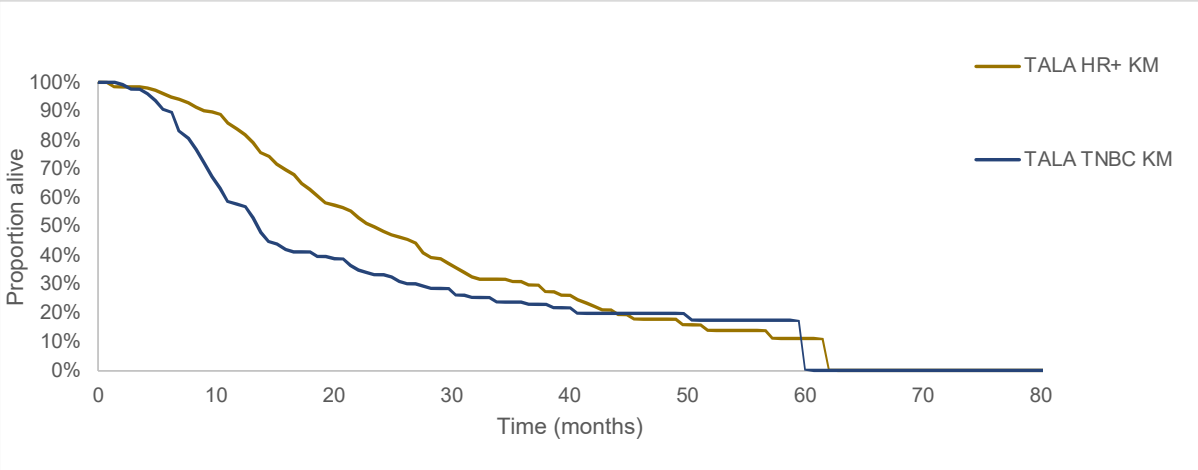

Figure 2 EMBRACA trial OS K-M data for HR+ and TNBC patients receiving talazoparib

HR+=hormone receptor positive; K-M=Kaplan-Meier; OS=overall survival; TNBC=triple-negative breast cancer
Source: Company model

Clinical advice to the EAG is that line of treatment is also likely to significantly affect OS. This advice is supported by EMBRACA trial OS K-M data for patients who received talazoparib in the first-line setting versus those who received it in the second-line or later setting (Figure 3). The company uses the descriptors 'first-line setting' and 'second-line or later-setting' but does not specify the type of prior treatments received.

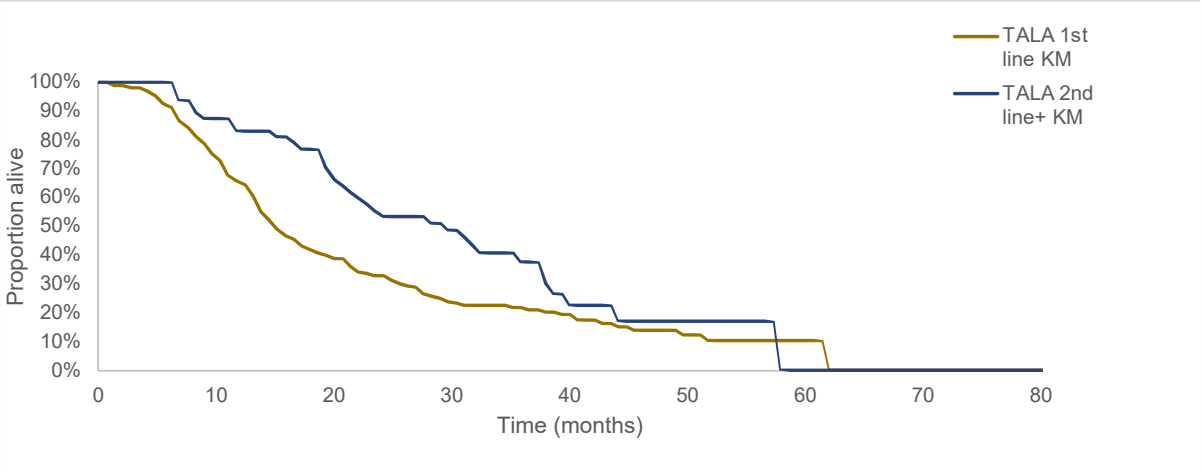

Figure 3 EMBRACA trial talazoparib OS K-M data

K-M=Kaplan-Meier; OS=overall survival
Source: Company model

Given the differences in OS by hormone receptor status and line of treatment, the EAG asked the company to run cost effectiveness analyses separately hormone receptor status and line of treatment (clarification question B1). The company did not supply these results. The company rationale for not supplying these results was that the EMBRACA trial was not powered to detect statistically significant differences by subgroup and that it would be inappropriate to assess cost effectiveness in these patient subgroups as talazoparib is efficacious in the ITT population.

The EAG considers that, given the differences in OS by **both** hormone receptor status and line of treatment for patients treated with talazoparib, company base case cost effectiveness results which do not consider these differences are unlikely to be generalisable to NHS patients. A summary of the other modelling issues considered by the EAG is shown in Table 27.

Table 27 Summary of EAG company model critique

Aspect considered	EAG comment	Section of EAG report
Model structure	• The model structure (partitioned survival approach) is appropriate for addressing the decision-problem	6.1
Population	• Cost effectiveness results presented by **both** hormone receptor status (HR+/HER2- BC and TNBC) and line of treatment would have been informative	NA
Comparators	• Clinical advice to the EAG is that, for some patients, platinum chemotherapy should be considered as a relevant comparator in the company model	6.1
Modelling OS and PFS	• The OS modelling approach for treatment with talazoparib was acceptable; however, rather than rely on an RPSFTM HR, a curve should have been fitted to the EMBRACA trial PCT OS K-M data • PFS modelling was acceptable	6.2
Blood transfusions	• The EMBRACA trial RBC transfusion rate for patients receiving talazoparib should have been used in the company base case	6.3
Time on treatment	• TTD should have been modelled using the EMBRACA trial TTD K-M data; it was inappropriate to use median TTD values	6.4
RDI	• The company approach to RDI for talazoparib is unclear	6.5
Resource use	• Resource use should not differ by response to treatment	6.6
Subsequent treatments	• Subsequent treatments should be re-weighted so that patients cannot receive more than one subsequent treatment at a time • The company's micro-costing approach should have been used in the company base case	6.7
Utility values	• The PFS utility value used by the company is acceptable for patients treated with talazoparib; however, utility values that differ by treatment (talazoparib/PCT) should not have been implemented in the company base case • The company base case PD utility value should have been derived from the best available evidence source, i.e., Lambert-Obry (2018)[57] only	6.8
Cost of treating neutropenia	• Cost of filgrastim should be included in the estimated cost of the treatment of neutropenia	6.9
Company severity modifier	• The EAG considers that the methods used to estimate the company severity modifier are appropriate	NA

AE=adverse event; EAG=External Assessment Group; HR=hazard ratio; K-M=Kaplan-Meier; NA=not applicable; OS=overall survival; PCT=physician's choice treatment; PD=progressed disease; PFS=progression-free survival; RPSFTM=rank preserving structural failure time model; RBC=red blood cell; RDI=relative dose intensity; TTD=time on treatment; QALY=quality adjusted life year
Source: EAG in-house checklist

6.2 Overall survival

In the CS, it is stated that OS for patients treated with talazoparib has been modelled using a log-normal distribution and PCT arm OS has been modelled by applying the RPSFTM HR adjusted for subsequent use of PARPi (0.820) to this log-normal distribution (CS, Table 31). The EAG considers that application of a HR should only be undertaken if the PH assumption holds; therefore, the EAG asked the company (clarification question A3) to assess whether the PH assumption holds for the comparison of EMBRACA trial talazoparib final OS and PCT final OS adjusted for use of subsequent PARPi. In response, the company stated that they did not need to test the PH assumption for this comparison as they used separate functions to model OS for patients treated with talazoparib and patients treated with PCT. However, as shown in Table 28, fitting separate functions is not the modelling approach described in the CS and/or used in the company base case analysis.

Table 28 Survival extrapolations applied in the company model (base case analysis)

	Talazoparib	PCT combined
OS	Parametric; log-normal	RPSFTM adjusted HR

OS=overall survival; PFS=progression-free survival
Source: CS, Table 31

Visual inspection of the EMBRACA trial OS K-M data adjusted for subsequent PARPi use provides evidence that the PH assumption does not hold, with the K-M data crossing twice over the first 24 months (Figure 4). Therefore, the EAG considers that separate functions should have been fitted to EMBRACA trial talazoparib and PCT OS data.

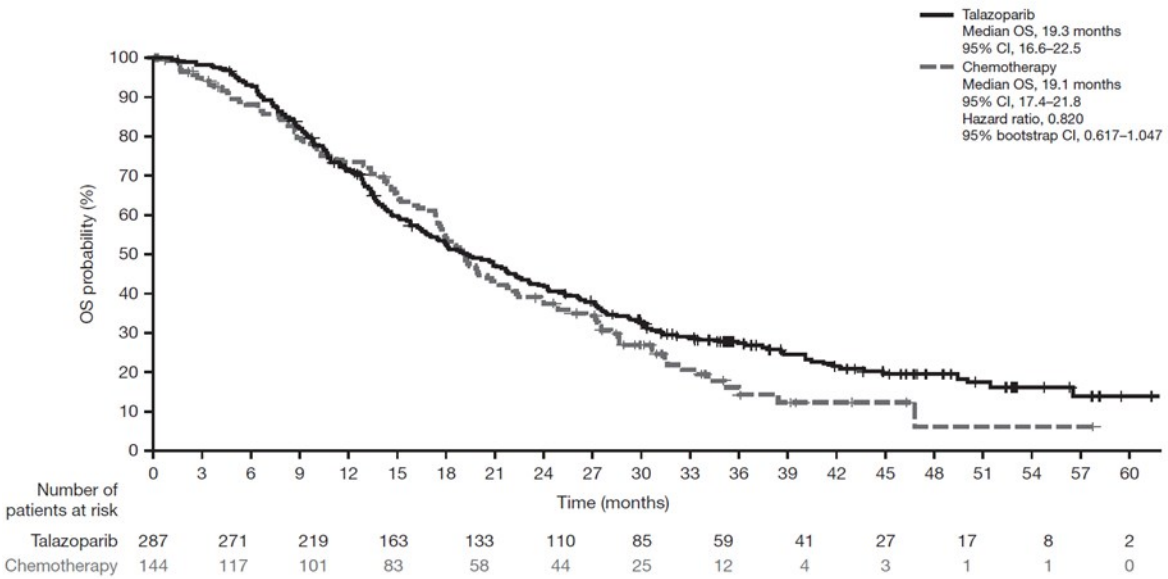

Figure 4 EMBRACA trial final OS adjusting for subsequent PARPi only
CI=confidence interval; OS=overall survival; PARPi=poly (ADP-ribose) polymerase inhibitor
Source: CS, Figure 10

The CS includes details of how the company identified the parametric function that best fitted EMBRACA trial PCT OS data (Weibull function). The EAG considers that using the log-normal function to model OS for patients treated with talazoparib and the Weibull function to model OS for patients treated with PCT is the most appropriate approach.

6.3 Red blood cell transfusions for patients with anaemia

The company considered that the RBC transfusion rate for EMBRACA trial patients treated with talazoparib (38.1%) was higher than would be seen if talazoparib were a routinely commissioned NHS treatment. The company's argument was that:

- High transfusion rates in EMBRACA are attributed to the protocol which required haemoglobin (Hb) values to recover to grade 1 or better (10 g/dL) before resuming talazoparib after a dosing interruption. A protocol amendment was made so that talazoparib could be resumed at Hb of 9 g/dL or greater, leading to lower transfusion rates. The rate of RBC transfusions declined by approximately 11% after the amendment
- NHS clinical guidelines state that transfusions should only be used when a patient's haemoglobin level falls below 7g/dL
- RWE from the US retrospective chart review by Mahtani (2022)[41] (the company states the US has similar guidelines to the UK) shows that the percentage of patients receiving talazoparib who required a transfusion was 8.3% (non-interventional final study report[69]).

In the talazoparib SmPC (CS, Appendix C), it is stated that talazoparib should be stopped if a patient's haemoglobin level falls below 8g/dL and not resumed (at a lower dose) until the patient's haemoglobin level increases to 9g/dL. The EAG considers that if, in the EMBRACA trial, RBC transfusions had not been offered until patients' haemoglobin levels fell below 7g/dL, then the following would have happened:

- a lower percentage of patients would have stopped treatment or had dose reductions, leading to unknown efficacy
- symptoms of anaemia would have been more pronounced, leading to a reduction in HRQoL gains for patients in the PFS health state treated with talazoparib.

As EMBRACA trial efficacy and HRQoL data for patients treated with talazoparib (and PCT) are dependent on trial RBC transfusion rate, the EAG considers that the EMBRACA trial talazoparib (and PCT) RBC transfusion rate should be used in the model.

6.4 Time on treatment

The company has used EMBRACA trial median TTD data to estimate treatment costs for patients treated with talazoparib and PCT; however, the rationale for using this approach rather than fitting a distribution to EMBRACA trial TTD K-M data or, given the maturity of the data, using the EMBRACA trial TTD K-M data directly, has not been presented in the CS. Estimating costs using EMBRACA trial TTD K-M data is a selectable option in the company

model but is not considered in the CS. As the EMBRACA trial TTD K-M data are not complete at the end of 5 years (PCT: no patients still on treatment; talazoparib: 4.4% of patients may still be receiving treatment) using EMBRACA trial TTD K-M data directly, without extrapolation, may underestimate the true cost of treatment with talazoparib and consequently underestimate the cost effectiveness of talazoparib versus PCT. Nevertheless, this is the EAG's preferred approach.

6.5 Relative dose intensity

The company has estimated RDI multipliers based on EMBRACA trial data; however, the methods used by the company have not been clearly described. The mean talazoparib RDI multiplier is stated, in the clinical section of the CS, as being 90.7% (CS, Table 17). However, this value has not been used in the model. Rather, it appears that the company has adjusted the estimated cost of talazoparib by the proportions of patients receiving specific doses of talazoparib (Table 29).

Table 29 Proportions of patients receiving different doses of talazoparib

Talazoparib	Proportion
1mg	[redacted]
0.75mg	[redacted]
0.5mg	[redacted]
0.25mg	[redacted]

Source: Company model

It is not clear whether the doses applied in the model relate to the total doses received at the time of the database lock of 22 March 2021 (given RDI for PCT was estimated at that database lock point) or the final recorded doses for each patient either before treatment stopped, death, or the time of the database lock.

The EAG asked the company to provide data showing talazoparib doses at the start of each model cycle (clarification question B2); however, the company stated that RDI data from the EMBRACA trial were not available by model cycle. Given the lack of information about RDI presented in the CS, the EAG's preferred scenario does not include talazoparib (or PCT) dose adjustments.

6.6 Health state resource use

The company has assumed that resource use in the PFS health state differs depending on whether patients have CR/PR or stable disease. The company states that this approach is based on "internal communication" (CS, p105) but no information has been provided about this communication. Further, no EMBRACA trial data were presented to support the assumption that resource use differs by response state. Given resource use by response state

has not been considered in the previous three most recently completed aBC Single Technology Appraisals (TA819,[21] TA836[84] and TA862[85]), there is no precedent for using this approach. In the absence of evidence to support using differential resource use by response state, the EAG has run a scenario in which resource use does not differ by response rate. The resource use values used in this scenario have been validated by clinical advice.

6.7 Subsequent therapies

The company has modelled two approaches to costing subsequent therapies. The first option, used in the company base case, is to apply the cost of PCT treatment in the PFS health state in the progressed disease (PD) health state to all patients. The second option is to use the EMBRACA trial subsequent treatment data, adjusted to only remove treatment with a PARPi ("micro-costing"). The EAG considers that the second option, i.e., modelling of trial subsequent treatments, should have been used in the company base case. However, as currently modelled, this approach is based on the percentage of patients receiving any treatment used at any point post-progression and applies drug costs to these percentages to estimate subsequent treatment cost per cycle. This is incorrect as the percentages add up to over 100% and so, effectively, all patients are receiving more than one subsequent treatment per cycle until death. In addition, not all patients will choose to have a subsequent treatment and it is unlikely that subsequent treatments will continue until death. The EAG considers that it would have been more appropriate to model subsequent treatments as a one-off cost applied at the time of progression. Whilst the company model could be adapted to accept a one-off cost on progression, there are insufficient data in the CS or CSR that allow the EAG to calculate this cost. Due to this limitation, the EAG has re-weighted the EMBRACA trial subsequent treatments to ensure that patients only receive one treatment at a time. The EAG and company (micro-costing approach) subsequent treatment baskets are presented in Table 30.

Table 30 Company and EAG subsequent treatment (micro-costing)

Treatment	Company micro-costing approach		EAG approach	
	Percentage of basket			
	Talazoparib	PCT	Talazoparib	PCT
Capecitabine	34.25%	17.70%	17.24%	10.25%
Eribulin	26.45%	20.93%	13.31%	12.12%
Gemcitabine	27.56%	29.72%	13.87%	17.21%
Vinorelbine	14.09%	10.41%	7.09%	6.03%
Talazoparib	0.00%	0.00%	0.00%	0.00%
Carboplatin	39.22%	39.32%	19.73%	22.77%
Cisplatin	10.23%	7.98%	5.15%	4.62%
Cyclophosphamide	8.82%	11.22%	4.44%	6.50%
Fulvestrant	12.36%	13.65%	6.22%	7.90%
Letrozole	10.23%	7.29%	5.15%	4.22%
Paclitaxel	15.50%	14.46%	7.80%	8.37%

EAG=External Assessment Group; PCT=physician's choice treatment
Source: Company model and EAG calculations

6.8 Utility values

The utility values used by the company to represent HRQoL in the PFS health state have been derived from EMBRACA trial EORTC QLQ-30 data. These utility values are broadly in line with published EQ-5D based utility values for advanced disease.[86] However, as the EMBRACA trial was an open-label trial, the potential for bias in response by treatment arm exists. The EAG, therefore, considers that it is inappropriate to use PFS health state utilities that differ depending on treatment in the company base case; the effect of this approach should only be explored in a scenario analysis.

The utility value used by the company (0.626) to represent HRQoL in the PD health state is the midpoint between the values reported by Huang (2020)[58] (0.601) and the values reported by Lambert-Obry (2018) (0.650).[57] The Huang (2020)[58] publication is a conference abstract reporting KEYNOTE-119 trial progressed disease state values; however, it is not clear whether patients were on or off treatment. The Lambert-Obry (2018)[57] publication is a peer-reviewed study that collected data from patients with HER-2- aBC who were receiving their first-line or later-line treatment and were in either the PFS or PD health state. The EAG considers that the Lambert-Obry (2018) paper[57] is a better source of utility values as this study has been peer reviewed and it is clear that all patients were on treatment (as is the case in the company PD health state). The Lambert-Obry (2018) study[57] utility value for patients in the later-line PD health state is 0.65; this is the value used in the EAG's preferred scenario.

The Lambert-Obry (2018) study[57] also reports utility values for first-line treatment. These are very similar to the Lambert-Obry (2018) study[57] values for patients receiving second-line or later treatment (PFS: 0.73 and 0.74 respectively; PD: 0.64 and 0.65 respectively).[57] The Lambert-Obry (2018) study[57] findings potentially make the description of the model PD health state, and the application of a relevant utility value to this health state, problematic. This is because patients in the PD health state will either be receiving 'subsequent active treatment PFS' (potentially with a utility value of 0.74) or be receiving best supportive care (potentially with a utility value of 0.65). Use of time to death utilities would solve this problem but this approach is not readily implementable in the company model. As patients in the PCT arm spend longer, on average, in the PD health state than patients in the talazoparib arm, this means that the company base case and EAG preferred ICERs per QALY gained for the comparison of talazoparib versus PCT are likely to be optimistic.

6.9 Cost of treating neutropenia

The company has modelled the cost of treating Grade ≥3 neutropenia using the cost associated with an NHS outpatient appointment. In addition, the company has included the cost of treatment with an immunostimulant (filgrastim) in the company model PFS health state as a treatment for neutropenia. The proportions of patients receiving filgrastim in the PFS health state are based on the proportions of patients in the talazoparib and PCT arms of the EMBRACA trial who had received filgrastim; the number of doses per month is based on clinical advice. This means that some patients receive daily filgrastim for the entire time that they are in the PFS health state. However, clinical advice to the EAG is that filgrastim posology is a daily dose for no more than 14 days.[87] The EAG's preferred approach is to remove the cost of filgrastim from the PFS health state and instead add the cost of a 14 days course of filgrastim to the cost of treating an episode of neutropenia.

6.10 Impact on the company base case results of EAG amendments

The EAG has made the following revisions to the company base case:

- Weibull function used to model OS for patients receiving PCT (R1)
- EMBRACA trial RBC transfusion rate used for patients receiving talazoparib (R2)
- EMBRACA trial TTD K-M data used to estimate treatment cost (R3)
- RDI removed from the model (R4)
- resource use in the PFS state set to not vary by response to treatment (R5)
- subsequent treatments re-weighted so that patients cannot receive more than one subsequent treatment at a time and the company's micro-costing approach used to estimate costs of subsequent treatments (R6)
- Lambert-Obry (2018) study[57] later line PD utility value used to estimate HRQoL in the PD health state (R7)

- PFS health state talazoparib utility value used in both treatment arms (R8)
- Cost of treating neutropenia removed from PFS state and add to neutropenia treatment cost (R9).

The EAG's revised deterministic ICERs per QALY gained and the EAG preferred scenario ICER per QALY gained are displayed in Table 31. The EAG's preferred scenario probabilistic ICER per QALY gained is displayed in Table 32. The EAG considers that the company's severity modifier estimate (1.2) is still appropriate. These results have been generated using the drug prices included in the company model/CS. In addition, the EAG has generated updated results using the eMIT prices listed in the NICE price tracker for this appraisal (Appendix 7, Section 8.7, Table 43 and Table 44). Company and EAG cost effectiveness results using all available discounted prices (and NICE price tracker eMIT prices) are presented in the confidential appendix.

Details of all Microsoft Excel revisions carried out by the EAG to the updated company model are provided in Appendix 8 (Section 8.8).

The EAG emphasises that the ICERs per QALY gained presented in Table 31 and Table 32 (and Table 43 and Table 44) may be of limited use to decision makers if the NICE Appraisal Committee (AC) concludes that EMBRACA trial ITT results are not generalisable to NHS patients.

Table 31 Deterministic results: EAG adjustments to company base case (talazoparib PAS price)

Scenario/EAG amendment	Talazoparib			PCT			Incremental			*ICER*	
	Cost	QALYs	Life Years	Cost	QALYs	Life years	Cost	QALYs	Life years	£/QALY	Change from base case
A. Company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	***£33,016***	
R1) Weibull function used to model OS for patients receiving PCT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£33,646	£630
R2) EMBRACA trial RBC transfusion rate used for patients receiving talazoparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£43,121	£10,105
R3) EMBRACA trial TTD K-M data used to estimate treatment costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£50,938	£17,922
R4) RDI removed from model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£38,412	£5,396
R5) Resource use in the PFS health state set to not vary by response to treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£38,328	£5,312
R6) Subsequent treatments reweighted and micro-costing approach applied	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£33,168	£152
R7) Lambert-Obry (2018) study later line PD utility value used to represent HRQoL in the PD health state	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£33,164	£148
R8) PFS health state talazoparib utility value used in both treatment arms	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£38,679	£5,663
R9) Cost of treating neutropenia removed from PFS state and add to neutropenia treatment cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£37,774	£4,758
B. EAG preferred scenario (R1-R8)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£85,911**	**£52,895**

EAG=External Assessment Group; HRQoL=health-related quality of life; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; PCT=physician's choice treatment; PD=progressed disease; QALYs=quality adjusted life years

Table 32 Probabilistic results: EAG preferred scenario results (talazoparib PAS price)

Scenario/EAG amendment	Talazoparib			PCT			Incremental			*ICER*	
	Cost	QALYs	Life Years	Cost	QALYs	Life years	Cost	QALYs	Life years	£/QALY	Change from base case
A. Company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	***£32,193***	
B. EAG preferred scenario	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£95,322**	**£63,129**

EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; PCT=physician choice of treatment; QALYs=quality adjusted life years

6.11 EAG cost effectiveness conclusions

The EAG considers that the efficacy of talazoparib is likely to be affected by hormone receptor status and line of treatment. However, the company has only submitted cost effective results for adults with g*BRCA*m who have HER2- aBC. Even if the NICE AC considers that the modelled population is appropriate, the EAG has concerns about the EMBRACA trial OS estimates used to populate the company model.

Further, the EAG has identified nine individual issues relating to the parameterisation of the company model. Following EAG revisions to address these issues, the EAG preferred scenario generates deterministic and probabilistic ICERs per QALY gained of £85,911 and £95,322 respectively.

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8 APPENDICES

8.1 Appendix 1: Quality assessment of the EMBRACA trial

Table 33 Quality assessment of the EMBRACA trial

Quality assessment item	Company	EAG	EAG comment
Was the randomisation method adequate?	Not clear	Yes	See CSR, Section 9.4.3: "[redacted]"
Was the allocation adequately concealed?	Yes	Yes	-
Were the groups similar at the outset of the study in terms of prognostic factors, for example severity of disease?	Not clear	Yes	Clinical advice to the EAG is that the baseline characteristics of patients in the EMBRACA trial (CS, Table 9) were well-balanced across the treatment arms
Were the care providers, participants and outcome assessors blind to treatment? If any of these people were not blind to treatment allocation, what might be the likely impact on the risk of bias (for each outcome)?	No	No	The EMBRACA trial was an open-label trial. However, the primary endpoint, PFS, was assessed by blinded independent central review and the secondary endpoints, OS and PK of talazoparib, are objective measures and therefore are not subject to bias. The secondary endpoints, ORR and safety, may have been subject to investigator and/or evaluation bias
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No	Yes	A higher proportion of patients in the PCT withdrew from the study before receiving study drug (18/144, 12.5%) than in the talazoparib arm (1/287, 0.3%). No adjustments were made in the analyses for these withdrawals
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	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	Yes	-
Did the authors of the study publication declare any conflicts of interest?	Yes	Yes	The company (manufacturer of talazoparib) sponsored the trial

CSR=clinical study report; EAG=External Assessment Group; ORR=objective response rate; OS=overall survival; PCT=physician treatment choice; PFS=progression-free survival; PK=pharmacokinetics
Source: CS, Table 16 and CS, Appendix D.3, Table 18

8.2 Appendix 2: EAG assessment of statistical approaches used to analyse EMBRACA trial data

8.2.1 Summary of statistical approach used to analyse EMBRACA trial data

Table 34 EAG assessment of statistical approaches used to analyse EMBRACA trial data

Item	EAG assessment	Statistical approach with EAG comments
Were all analysis populations clearly defined and pre-specified?	Yes	Analyses of PFS, OS, DoR, CBR and time to the end of first post-study therapy were carried out using data from the ITT population (all randomised patients). Analyses of ORR were carried out using data from the ITT with measurable disease population (patients in the ITT population who have ≥1 target lesion identified at baseline). Safety analyses were carried out using data from the safety population (all patients who receive any study drug). PRO analyses were carried out using data from the PRO-evaluable population (all patients who have completed the PRO questionnaire at baseline and at ≥1visit post baseline). The EAG is satisfied that these populations were clearly defined and pre-specified in the TSAP (p9)
Was an appropriate sample size calculation pre-specified?	Yes	A study sample size calculation was pre-specified in the TSAP (p8). This calculation determined that 288 PFS events would provide 90% power for a 2-sided log-rank test at a 0.05 significance level to detect a HR of 0.67. [redacted] At the time of the primary PFS analysis (data cut-off date:15 September 2017), 269 PFS events (93.4% of the planned 288 events) had occurred. The EAG is satisfied that the sample size calculation was appropriate
Were all changes in the conduct of the study or planned analysis made prior to analysis?	Partial	Changes in the conduct of the study or planned analyses are listed in the 2018 CSR (pp63-67), 2020 OS supplemental CSR (pp30-31) and 2021 safety supplemental CSR (pp13-14). [redacted] The EAG considers that all changes to the protocol and TSAP following the data cut-off date for the primary PFS analysis were reasonable and well justified
Were all primary and secondary efficacy outcomes pre-defined and analysed appropriately?	Partial	The primary, secondary and exploratory efficacy endpoints are listed in the CS (Table 13). Definitions and analysis approaches for these endpoints were pre-specified in the TSAP (pp17-27).

Item	EAG assessment	Statistical approach with EAG comments
		The company used a multiplicity adjustment schema to maintain the overall 2-sided type 1 error rate at 0.05. The company planned to perform formal hypothesis tests for OS only if the p-value for the primary PFS analysis was <0.05 and the HR favoured talazoparib. If these conditions were satisfied, the company planned to conduct an interim analysis of OS at a 0.0001 significance level at the time of the PFS analysis, and to conduct the final analysis of OS at a 0.04999 significance level. The company analysed PFS and OS using Cox PH models. This analysis approach requires the assumption of PH, i.e., the event hazards associated with the intervention and comparator data are proportional over time. The company did not provide PH assessment results for PFS and OS (response to clarification question A2) the EAG therefore used Kaplan-Meier (K-M) data provided as part of the company's economic model to generate log-log plots and perform Grambsch-Therneau tests of Schoenfeld residuals (Section 8.2.2). The EAG considered that the PH assumption likely to be violated for OS (log-log plots show the survival curves are not parallel), although the test of Schoenfeld residuals was not statistically significant (p=0.0835). The EAG considers that the HR may not be an appropriate measure of effect for OS
Was the analysis approach for PROs appropriate and pre-specified?	Yes	PROs were assessed as an exploratory efficacy endpoint using the EORTC QLQ-C30 and EORTC QLQ-BR23 at baseline, Day 1 of each cycle, and at the end of treatment. The EAG is satisfied that the analysis approaches pre-specified in the TSAP (pp27-31) were appropriate
Was the analysis approach for AEs appropriate and pre-specified?	Yes	Safety data presented in the CS included proportions of patients who experienced AEs, TEAEs and SAEs (Tables 18 to 21), information on discontinuation due to adverse events and the number of deaths (pp74-75). Safety analyses were descriptive only and were pre-specified in the TSAP (pp31-35)
Was a suitable approach employed for handling missing data?	Yes	The company's approach to handling missing data is outlined in the TSAP (p12). The EAG is satisfied that the approach described was appropriate
Were all subgroup and sensitivity analyses pre-specified?	No	The primary efficacy endpoint was PFS by IRF. Results were presented in the CS for the sensitivity analysis of PFS by investigator assessment (p44). This sensitivity analysis was pre-specified in the TSAP (p20). Subgroup analyses for PFS and OS are presented in the CS (Figures 14 to 16). Most of the subgroup analyses presented in the CS were pre-specified in the TSAP (pp25-26). However, the EAG notes that the subgroup analysis of PFS for patients with bone only disease (yes versus no), and the key subgroup analyses of OS for prior platinum chemotherapy in neoadjuvant/adjuvant setting (yes only), number of prior regimens of cytotoxic therapy for aBC in patients with TNBC (0, 1, or ≥2), and number of prior regimens of cytotoxic therapy for aBC in HR+ patients (0, 1, or ≥2) were not pre-specified in the TSAP, and should only be considered to be exploratory

AE=adverse event; CBR=clinical benefit rate; CS=company submission; CSR=clinical study report; DoR=duration of response; EAG=External Assessment Group; EORTC QLQ-BR23=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Breast Cancer Module; EORTC QLQ-C30=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30; HR=hazard ratio; HR+=hormone-receptor positive; IPD=individual patient data; IRF=independent radiology facility; ITT=intention-to-treat; K-M=Kaplan-Meier; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; PH=proportional hazards; PRO=patient-reported outcome; SAE=serious adverse event; TEAE=treatment-emergent adverse event; TNBC=triple-negative breast cancer; TSAP=trial statistical analysis plan
Source: CS, CSR[30] and supplemental CSR,[45] TSAP and trial protocol

8.2.2 Log-log plots generated by the EAG to assess the proportional hazards assumption in the EMBRACA trial

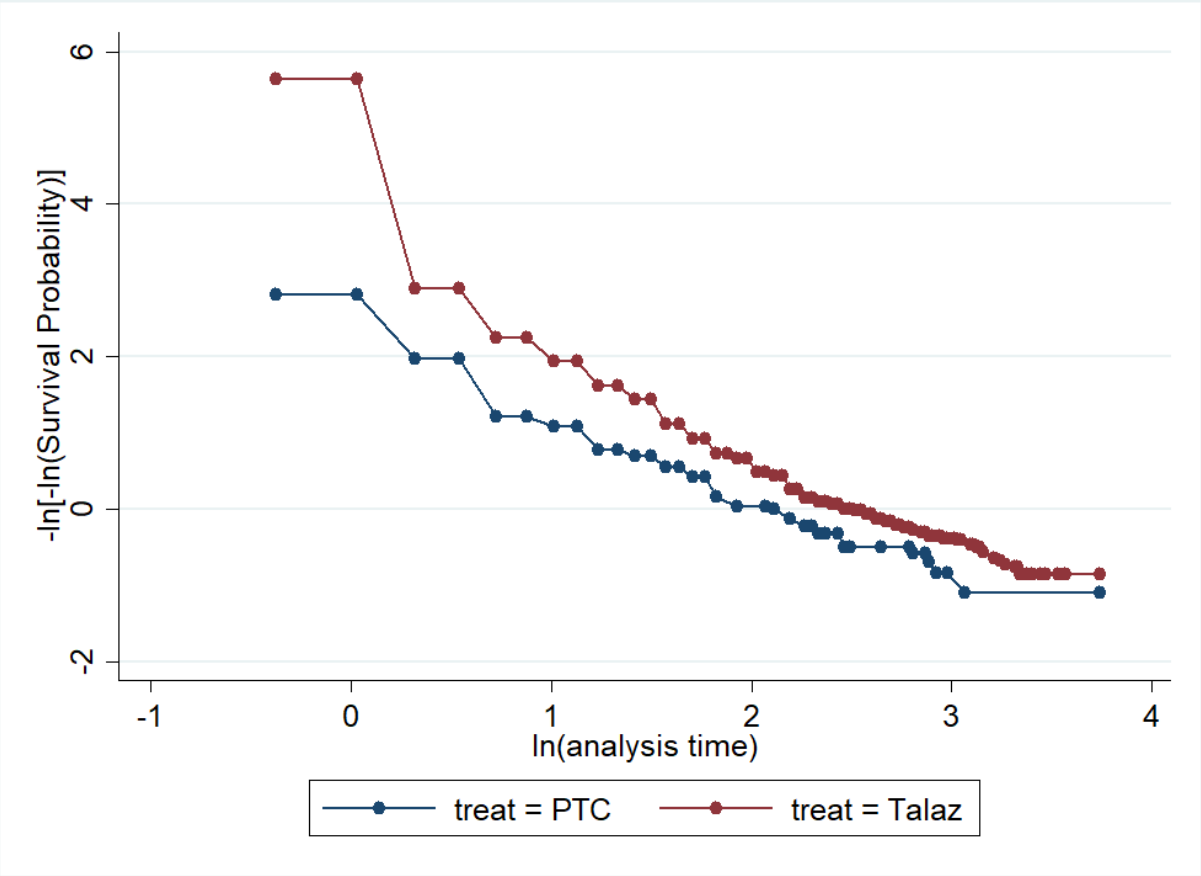


Figure 5 Log-log plot for PFS by IRF in the EMBRACA trial

The Grambsch-Therneau test of Schoenfeld residuals generated a p-value of 0.2092
IRF=independent radiology facility; PCT= physician's choice treatment; PFS=progression-free survival

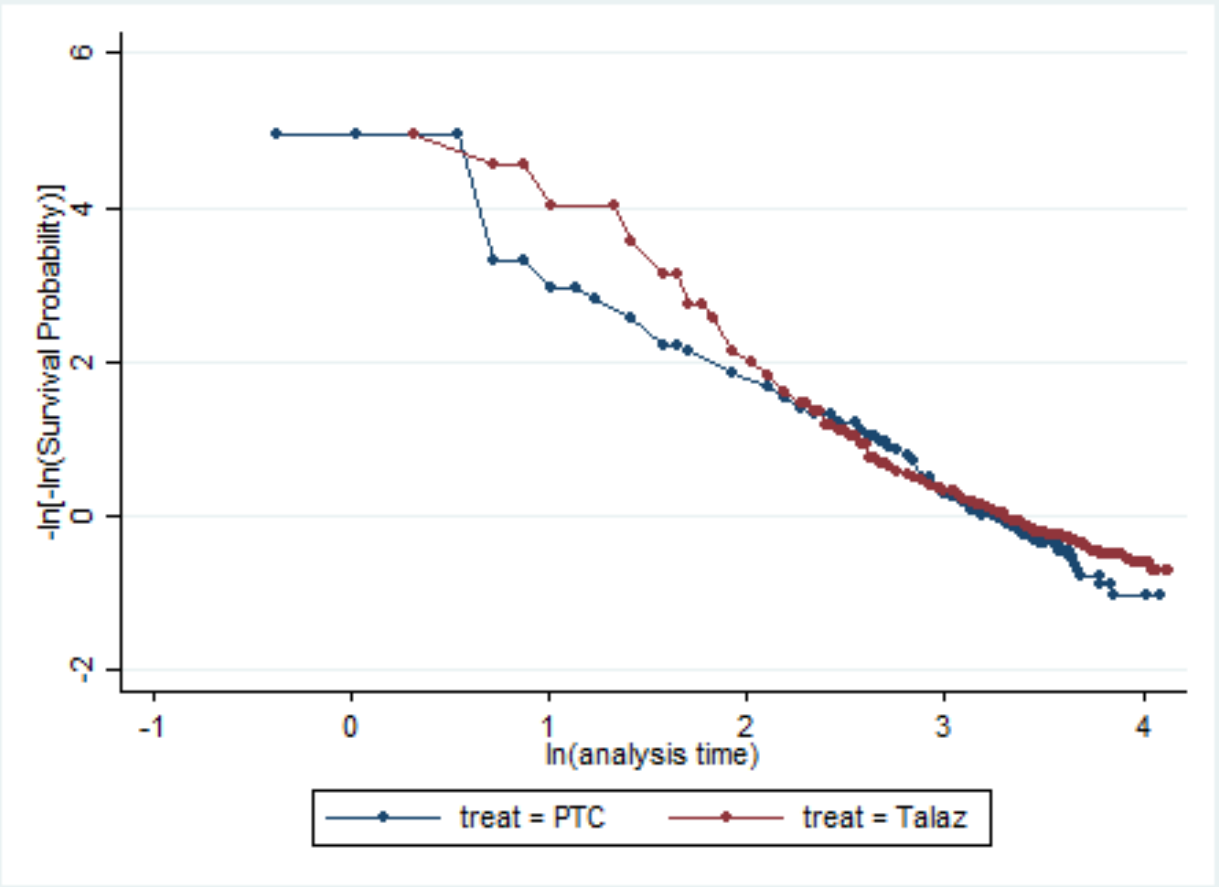


Figure 6 Log-log plot for OS in the EMBRACA trial

The Grambsch-Therneau test of Schoenfeld residuals generated a p-value of 0.0835
OS=overall survival; PCT= physician's choice treatment

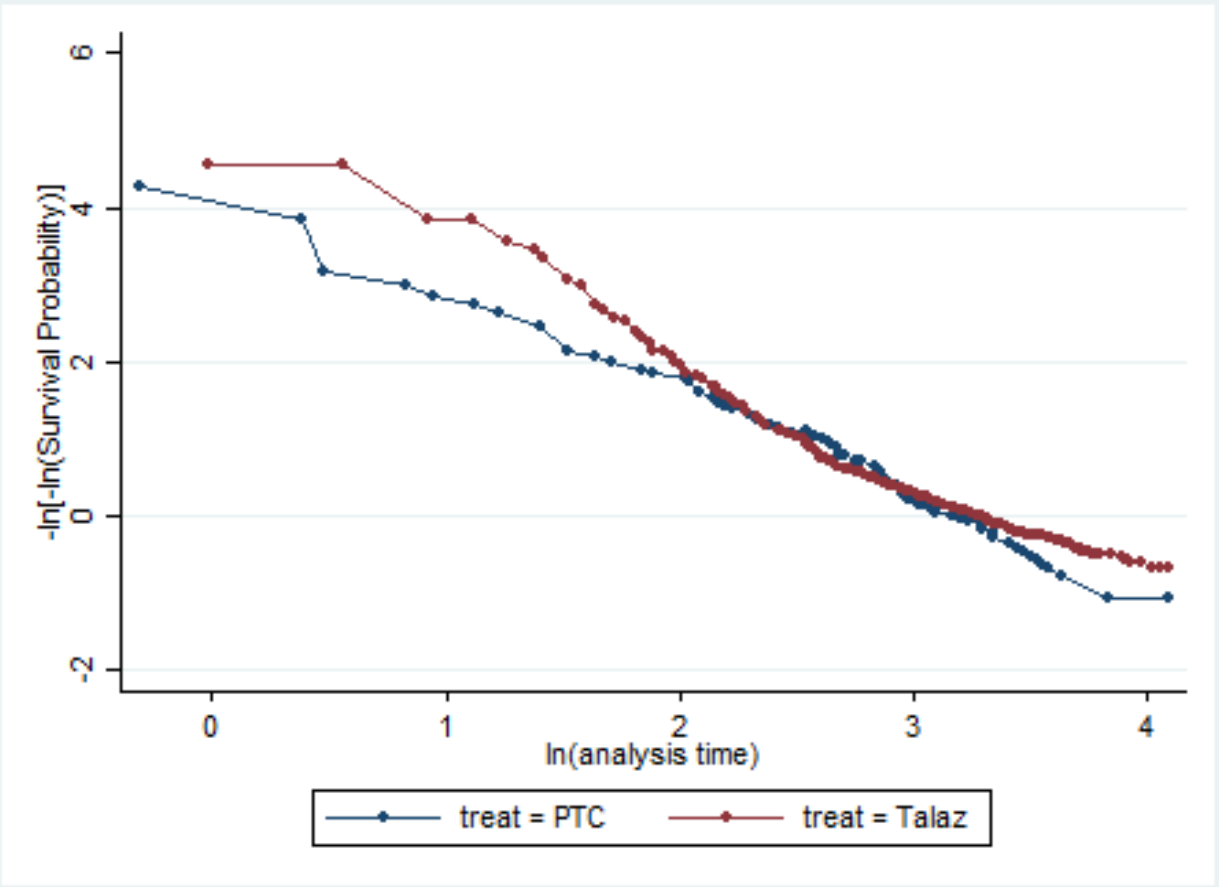


Figure 7 Log-log plot for RPSFTM-adjusted OS (adjusting for subsequent PARPi treatment only) in the EMBRACA trial

The Grambsch-Therneau test of Schoenfeld residuals generated a p-value of 0.0322
OS=overall survival; PCT= physician's choice treatment; RPSFTM=rank-preserving structural failure time model

8.3 Appendix 3: EMBRACA trial ORR subgroup results

Subgroup analyses for ORR referred to in Section 3.3.4 of this report are presented in Table 35.

Table 35 Subgroup analyses for ORR highlighted in the EPAR

Subgroup		ORR, n/N (%)		OR (95% CI) for talazoparib vs PCT
		Talazoparib	PCT	
BRCA status	*BRCA*1	59/92 (64.1)	11/50 (22.0)	7.01 (2.99 to 19.54)
	*BRCA*2	71/114 (62.3)	18/60 (30.0)	4.15 (1.90 to 8.52)
ECOG PS	0	77/120 (64.2)	14/64 (21.9)	6.06 (3.08 to 15.07)
	>0	60/98 (61.2)	17/49 (34.7)	3.32 (1.47 to 7.37)
History of CNS metastasis	Yes	24/38 (63.2)	3.19 (15.8)	8.95 (1.86 to 52.26)
	No	113/181 (62.4)	28/95 (29.5)	4.48 (2.53 to 8.43)
Prior platinum chemotherapy	Yes	19/38 (50.0)	6/25 (24.0)	3.16 (0.88 to 15.67)
	No	118/181 (65.2)	25/89 (28.1)	5.36 (2.89 to 9.89)
Time from initial diagnosis to initial diagnosis of advanced disease	<12 months	45/90 (50.0)	6/32 (18.8)	4.86 (1.85 to 19.71)
	≥12 months	92/129 (71.3)	25/82 (30.5)	6.33 (3.19 to 12.49)

Subgroup analyses for hormone receptor status and number of prior regimens of cytotoxic chemotherapy for aBC were also highlighted by the CHMP; results of these subgroup analyses are presented in Table 9 and Table 10 of this EAG report
CI=confidence interval; CNS=central nervous system; ECOG PS=Eastern Cooperative Oncology Group performance status; OR=odds ratio; ORR=objective response rate
Source: EPAR, Table 48 and p126/140 (CS, Appendix C)

8.4 Appendix 4: Evidence for olaparib

The company employed the RPSFTM for adjusting OS for subsequent treatment with a PARPi (which most commonly was olaparib). The EAG considers that the RPSFTM analysis which adjusts only for subsequent therapy with PARPi requires the assumption that the PARPi used in the EMBRACA trial (olaparib, talazoparib, veliparib) are of equivalent efficacy.

Evidence for olaparib is available from the OlympiAD trial.[88,89] The OlympiAD trial was a phase III, multicentre, international, open-label RCT of olaparib (N=205) versus PCT (N=97) for patients with HER2- mBC with g*BRCA*m and had very similar eligibility criteria to the EMBRACA trial. The drugs that were permitted in the PCT arm were capecitabine, eribulin and vinorelbine. In line with the EMBRACA trial, most patients either received capecitabine (41/97, 42.3%) or eribulin (34/97, 35.1%). The most notable differences, which were only small, were as follows:

- all eligible patients were required to have mBC whereas in the EMBRACA trial, 24/431 (5.6%) patients had LABC
- in the OlympiAD trial, prior platinum chemotherapy was permitted as long as disease progression had not occurred on treatment or, if given in the adjuvant/neoadjuvant setting, during a period of ≥12 months between last dose to study entry; in the EMBRACA trial this same criterion stipulated ≥6 months
- patients were only permitted to have ≤2 prior lines of chemotherapy for mBC; in the EMBRACA trial, patients were permitted to have had ≤3 prior cytotoxic regimens for aBC.

Generally patient characteristics were similar in the Olympiad trial and the EMBRACA trial. Small but notable differences included:

- hormone receptor status: there were fewer patients with HR+/HER2- BC (152/302, 50.3%) and more with TNBC (150/302, 49.7%) in the OlympiAD trial than in the EMBRACA trial (241/431, 55.9% and 190/431, 44.1%, respectively)
- ECOG PS: there were more patients with ECOG PS 0 (210/302, 69.5%) in the OlympiAD trial than in the EMBRACA trial (237/431, 55.0%)
- prior chemotherapy: although the EMBRACA trial permitted patients with more lines of prior chemotherapy for aBC than the OlympiAD trial, there were more patients who had not received any chemotherapy for aBC (165/431, 38.3%) in the EMBRACA trial than in the OlympiAD trial (87/302, 28.8%)
- prior platinum chemotherapy: more patients had received prior platinum chemotherapy (86/302, 28.5%) in the OlympiAD trial than in the EMBRACA trial (76/431, 17.6%)
- subsequent therapy following discontinuation of study drug: 2/205 (1.0%) of patients in the olaparib arm and 8/97 (8.2%) patients in the PCT arm received subsequent therapy with a PARPi and 88/205 (43.0%) patients and 44/97 (45.4%) patients, respectively, received subsequent platinum chemotherapy; the proportion receiving PARPi is lower than in the EMBRACA trial (talazoparib: 13/287, 4.5%; PCT: 47/144, 32.6%) but the proportion receiving platinum chemotherapy was similar (talazoparib: 133/287, 46.3%; PCT: 60/144, 41.7%).

As shown in Table 36, the results for PFS and, in particular, OS and ORR, were similar in the OlympiAD trial to the results in the EMBRACA trial, both in terms of relative and absolute effects. A naïve comparison would therefore suggest that olaparib and talazoparib are of similar efficacy. The hypothesis that both PARPi "can be declared equivalent therapeutic alternatives (ETA)" has been formally tested by Camean-Castillo et al 2019[90] who conducted an indirect treatment comparison (ITC) according to Bucher's method. The authors aimed to show ETA via a non-inferiority analysis of PFS. The maximum acceptable difference as a clinical criterion of no-inferiority was set at 0.650 (and its inverse, 1.538). The ITC results showed no statistically differences in PFS between olaparib and talazoparib, HR=1.074 (95% CI: 0.71 to 1.62). The authors therefore concluded "probable clinical equivalence between both drugs."

Table 36 Key EMBRACA and OlympiAD efficacy endpoints

Endpoint	Talazoparib	PCT [a]	Olaparib	TPC [a]
Blinded PFS [b]				
ITT population, N	287	144	205	97
Median, months (95% CI)	8.6 (7.2 to 9.3)	5.6 (4.2 to 6.7)	7.0 (5.7 to 8.3)	4.2 (2.8 to 4.3)
Hazard Ratio (95% CI)	0.54 (0.41 to 0.71)		0.58 (0.43 to 0.80)	
Final OS [c]				
ITT population, N	287	144	205	97
Median, months (95% CI)	19.3 (16.6 to 22.5)	19.5 (17.4 to 22.4)	19.3 (16.7 to 21.8)	19.6 (14.1 to 24.2)
HR (95% CI)	0.85 (0.67 to 1.07)		0.90 (0.63 to 1.29)	
ORR [d]				
ITT with measurable disease population, N	219	114	167	66
ORR, % (95% CI)	62.6 (55.8 to 69.0)	27.2 (19.3 to 36.3)	59.9 (52.0 to 67.4)	28.8 (18.3 to 41.3)
CR, %	5.5	0	9.0	1.5

[a] PCT/TPC in both trials included capecitabine, eribulin and vinorelbine; the EMBRACA trial also included patients who received gemcitabine
[b] The median length of follow-up was 11.2 months in the EMBRACA trial and 14.5 months (olaparib) and 14.1 months (TPC) in the OlympiAD trial
[c] The median length of follow-up was 44.9 months in the EMBRACA trial and 25.3 months (olaparib) and 26.3 months (TPC) in the OlympiAD trial. The EAG notes that the final OS results are reported differently at https://clinicaltrials.gov/ct2/show/results/NCT02000622:19.3 months with olaparib versus 17.1 months with PTC, HR 0.90 (95% CI 0.66 to 1.23). The reason for this discrepancy is unknown.
[d] Investigator assessed in the EMBRACA trial but assessed by blinded review in the OlympiAD trial
CI=confidence interval; CR=complete response; HR=hazard ratio; IRF=independent radiology facility; ITT=intention-to-treat; ORR=objective response rate; PCT=physician's choice treatment; PFS=progression-free survival; PR=partial response; SD=stable disease; TPC=treatment of physician's choice
Source: CS, Tables 9 to 11 (EMBRACA trial) and OlympiAD trial publications[88,91]

8.5 Appendix 5: Summary of evidence from studies of talazoparib

8.5.1 Talazoparib study and baseline characteristics

Table 37 Summary of evidence for talazoparib (and PCT, where appropriate): study and baseline characteristics

Characteristic	EMBRACA talazoparib (N=287) vs PCT (N=144)	ABRAZO Cohort 1 (N=49)	ABRAZO Cohort 2 (N=35)	Mahtani 2022 (N=84)	Loirat 2022 – ViTAL cohort 1 (N=86)	Sendur 2021 (N=47)	Semiglazova 2020 (N=24)
Location/type	Multicentre, open-label, phase III RCT	Multicentre, open-label, phase II cohort study	Multicentre, open-label, phase II cohort study	US retrospective chart review	France early access program	Turkey early access program	Russia compassionate use program
Population	g*BRCA*m HER2- aBC	g*BRCA*m HER2- aBC with prior response to platinum-containing regimen	g*BRCA*m HER2- aBC with ≥3 prior non-platinum cytotoxic regimens for aBC	g*BRCA*m HER2- mBC	g*BRCA*m / s*BRCA*m HER2- aBC	g*BRCA*m HER2- aBC	g*BRCA*m HER2- mBC
Median age (range), years	45 (27 to 84) vs 50 (24 to 88)	50 (31 to 74)	52 (33 to 75)	62 HR+/HER2-: 69 TNBC: 59	51 (26 to 85)	42	50 [mean]
HER2- HR+, %	55 vs 58	41	83	36	54	53 [64 known]	25
TNBC, %	45 vs 42	59	17	64	46	30 [36 known]	75
BRCA1-positive	46 vs 44	53	43	64	48	43	Not reported
BRCA2-positive	54 vs 56	45	57	36	52	49	Not reported
ECOG PS, %	0: 53 vs 58 1: 44 vs 40 2: 2 vs 1	0: 69 1: [redacted]	0: 43 1: [redacted]	≥2 all: 30 HR+/HER2-: 47 TNBC: 20	≥2: 6	Not reported	Not reported
CNS metastases, %	15 vs 14	16	3	19 [brain]	11	77	21 [brain]
Visceral metastases, %	70 vs 72	78	66	96	61	13	50

Characteristic	EMBRACA talazoparib (N=287) vs PCT (N=144)	ABRAZO Cohort 1 (N=49)	ABRAZO Cohort 2 (N=35)	Mahtani 2022 (N=84)	Loirat 2022 – ViTAL cohort 1 (N=86)	Sendur 2021 (N=47)	Semiglazova 2020 (N=24)
Line of treatment, %	Prior cytotoxic regimens for aBC: 0: 39 vs 38 1:37 vs 38 2:20 vs 19 ≥3: 4 vs 6 Median (range): 1 (0 to 10) vs 1 (0 to 3)	1L/2L: 53 3L/4L: 35 ≥ 5L: 12 Median (range): 2 (1 to 10)	1L/2L: 3 3L/4L: 63 ≥ 5L: 34 Median (range): 4 (1 to 9)	Line: all / HR+/HER2- / TNBC 1L: 14 / 3 / 20 2L: 41 / 30 / 46 3L: 35 / 43 / 30 4L: 11 / 23 / 4	Prior cytotoxic regimens for mBC: 0: 15 1: 33 ≥2: 52	≤3L: 49 ≥4L: 1	1L: 34 2L: 29 ≥3L: 34
Prior anthracycline, %	85	[redacted]	[redacted]	Not reported	Not reported	Not reported	Not reported
Prior taxane, %	91	[redacted]	[redacted]	Not reported	Not reported	Not reported	Not reported
Prior platinum chemotherapy, %	16 vs 21	100	0	All: 25 TNBC: 42	35	53	75
Prior immunotherapy, %	1 vs 1	[redacted]	[redacted]	Not reported	Not reported	Not reported	Not reported
Prior CDK4/6i, %	6 vs 4	[redacted]	[redacted]	HR+/HER2-: 90	HR+/HER2-: 74	Not reported	Not reported
Prior endocrine therapy, %	HR+/HER2- (any setting): 88	[redacted]	[redacted]	HR+/HER2- (advanced setting): Single agent: 28 Combination: 24	HR+/HER2- (any setting) 1: 26 ≥2: 63	Not reported	Not reported

aBC=advanced stage breast cancer; CNS=central nervous system; CDK4/6=cyclin-dependent kinase 4/6 inhibitor(s); CS=company submission; ECOG PS=Eastern Cooperative Oncology Group performance status; g*BRCA*m=germline BReast CAncer gene mutation(s); HR+/HER2-= hormone receptor-positive / human epidermal growth factor receptor 2 negative; LA=locally advanced; mBC=metastatic breast cancer; PCT=physician's choice treatment; PFS=progression-free survival; RCT=randomised controlled trial; s*BRCA*m=somatic BReast CAncer gene mutation(s); TNBC=triple-negative breast cancer

Source: CS Table 14, EPAR, Table 37 (CS, Appendix C), Litton 2020[26] and company response to clarification question A1 (EMBRACA trial); CS, Appendix M, Table 6 and ABRAZO CSR,[92] Section 11.2.2 and Table 14.1.5.2 (ABRAZO study); conference posters[41,42,48] and abstract and materials and methods sections to published paper (the full text of which was in Russian)[43] supplemented by information in CS, Section B.2.4.7 (all other studies)

8.5.2 Talazoparib efficacy results

Table 38 Summary of evidence for talazoparib (and PCT, where appropriate): efficacy results

Endpoint	EMBRACA talazoparib (N=287) vs PCT (N=144)	ABRAZO Cohort 1 (N=49)	ABRAZO Cohort 2 (N=35)	Mahtani 2022 (N=84)	Loirat 2022 – ViTAL cohort 1 (N=86)	Sendur 2021 (N=47)	Semiglazova 2020 (N=24)
Median follow up, months	11.2 Final OS: 44.9 vs 38.8	13.7 Updated OS: Not reported	13.7 Updated OS: Not reported	8.2	17.8 OS update: Not reported	13.6	Not reported
PFS, months (95% CI)	8.6 (7.2 to 9.3) vs 5.6 (4.2 to 6.7)	4.0 (2.8 to 5.4)	5.6 (5.5 to 7.8)	All: 8.7 (8.0 to 9.9) HR+/HER2-: 8.5 (8.0 to 10.6) TNBC: 9.0 (7.5 to 10.1)	TTD, all: 8.6 (6.0 to 10.9) HR+/HER2-: 8.7 (5.6 to 11.5) TNBC: 8.0 (5.0 to 12.2)	6.5 (5.0 to 8.1)	6.5 (3 to 10)
OS, months (95% CI)	19.3 (16.6 to 22.5) vs 19.5 (17.4 to 22.4)	12.7 (9.6, 15.8)	14.7 (11.0, 24.4)	"immature"	OS update: 25.6 (20.8 to NE) HR+/HER2-: 25.2 (18.9 to NE) TNBC: NE (15.0 to NE)	Not reached	Not reported
OS rates (months: %)	12: 71 vs 74 24: 42 vs 38 36: 27 vs 21 48: 19 vs 7	Not reported	Not reported	Not reported	Original: 24: 82 OS update: not reported	12: 74	Not reported
ORR, % (95% CI)	63 (56 to 69) vs 27 (19 to 36)	21	37	All: 63 (52 to 74) HR+/HER2-: 70 TNBC: 59	Not reported	32	29

CS=company submission; HR+/HER2-= hormone receptor-positive / human epidermal growth factor receptor 2 negative; ORR=objective response rate; OS=overall survival; PCT=physician's choice treatment; PFS=progression-free survival; TNBC=triple-negative breast cancer; TTD=time to treatment discontinuation

Source: CS, Figure 15, CS, Appendix D, Tables 11 to 13 and EPAR, Table 48 (CS, Appendix C) (EMBRACA trial); CS, Appendix M, Tables 8, 11, and 12 (ABRAZO study); conference posters[41,42,48] and abstract to published paper (in Russian)[43] supplemented by information in CS, Section B.2.4.7 and company response to clarification question C6 (all other studies)

8.5.3 Patient reported outcomes in the ABRAZO study of talazoparib

In the ABRAZO study,[38] following examination of data in the CS, Appendix M, Table 13, the EAG highlights that in terms of change from baseline:

- unlike in the talazoparib arm of the EMBRACA trial, the estimated overall change from baseline in GHS/QoL scores did not achieve statistical significance; in cohort 1 the median value was suggestive of a deterioration whereas in cohort 2 it was suggestive of an improvement
- there was statistically significant and a clinically meaningful deterioration in role functioning in cohort 1 but in cohort 2 there was a statistically significant improvement; the change from baseline in the talazoparib arm of the EMBRACA trial was neither statistically significant nor clinically meaningful (i.e., change from baseline score ≥10 points)
- there was a statistically significant and a clinically meaningful deterioration in dyspnoea in cohort 2 whereas in cohort 1 the change from baseline was not statistically significant; the change from baseline in the talazoparib arm of the EMBRACA trial was neither statistically significant nor clinically meaningful
- there was a statistically significant and a clinically meaningful improvement in future perspective in cohort 1 and in cohort 2 there was a statistically significant but not clinically meaningful improvement; the change from baseline in the talazoparib arm of the EMBRACA trial was statistically significant but not clinically meaningful
- in addition to the above, there were statistically significant, but not clinically meaningful, improvements in:
    - EORTC QLQ-C30 functional scales: role functioning and social functioning in cohort 2 only; changes were not statistically different from baseline in the talazoparib arm of the EMBRACA trial
    - EORTC QLQ-C30 symptom scales: nausea/vomiting, pain and insomnia in cohort 2 and diarrhoea in cohort 1; changes from baseline in pain and insomnia were also statistically significant in the talazoparib arm of the EMBRACA trial
    - EORTC QLQ-BR23 functional scales: sexual enjoyment in cohort 2 and future perspective in both cohorts); changes were not statistically different from baseline in the talazoparib arm of the EMBRACA trial
    - EORTC QLQ-BR23 symptom scales: breast and arm symptoms in both cohorts; changes from baseline in both of these symptoms were also statistically significant in the talazoparib arm of the EMBRACA trial.

8.5.4 Talazoparib safety results

Table 39 Summary of evidence for talazoparib (and PCT, where appropriate): adverse events

Endpoint	EMBRACA talazoparib (N=287) vs PCT (N=144)	ABRAZO Cohort 1 (N=49)	ABRAZO Cohort 2 (N=35)	Mahtani 2022 (N=84)	Loirat 2022 – ViTAL cohort 1 (N=86)	Sendur 2021 (N=47)	Semiglazova 2020 (N=24)
Any AE, %	99 vs 98	[redacted]	[redacted]	Not reported	71	62	Not reported
Most common AEs, %	[redacted] vs [redacted]	[redacted]	[redacted]	Not reported	Anaemia: 26 Thrombocytopenia: 9 Neutropenia: 8 Alopecia: 6% Asthenia: 5%	Haematologic cytotoxicity	Not reported
Any Grade ≥3 AE, %	70 vs 64	[redacted]	[redacted]	Not reported	Not reported	30	21
Most common Grade ≥3 AEs, %	[redacted] vs [redacted]	[redacted]	[redacted]	Not reported	Not reported	Not reported	Anaemia: 13 Thrombocytopenia: 1 Neutropenia: 1
Any SAE, %	36 vs 31	[redacted]	[redacted]	Not reported	10	Not reported	Not reported
Most common SAEs, %	[redacted] vs [redacted]	[redacted]	[redacted]	Not reported	Anaemia: 7	Not reported	Not reported
Dose interruptions, %	[redacted]	[redacted]	[redacted]	Not reported	38	Not reported	Not reported
Dose reductions, %	[redacted]	[redacted]	[redacted]	Not reported	19	Not reported	13
AEs leading to drug discontinuation, %	5 vs 6	[redacted]	[redacted]	Not reported	7 [c]	Not reported	Not reported
Blood transfusions	39 vs 6	[redacted]	[redacted]	8	Not reported	Not reported	13

AE=adverse event; CS=company submission; PCT=physician's choice treatment; SAE=serious adverse event
Source: CS, Section B.2.8.2, Litton 2020 and EMRACA trial supplementary safety clinical study report,[46] Tables 18 and 19 (EMBRACA trial); CS, Appendix M, Tables 16 and 17 and ABRAZO clinical study report,[92] Table 4.1.1 and ABRAZO supplemental clinical study report,[93] Table 13 (ABRAZO study); conference posters[41,42,48] and abstract to published paper (in Russian)[43] supplemented by information in CS, Section B.2.4.7 and CS, Table 40 (all other studies)

8.6 Appendix 6: Summary of evidence for platinum chemotherapy

8.6.1 Study baseline characteristics of studies of platinum chemotherapy

Table 40 Summary of evidence for platinum chemotherapy: study and baseline characteristics

Characteristic	TNT – all (N=188)	TNT – *BRCA*m (n=25)	TBCRC009 – all (N=86)	TBCRC009 – *BRCA*m (n=11)	NCT01611727 – *BRCA*m (N=20)
Drug	Carboplatin		Carboplatin/cisplatin		Cisplatin
Location/type	UK, multicentre open-label RCT		US, multicentre open-label, single-arm, two-stage phase II clinical trial		Poland, phase II, open-label study
Population	Confirmed *BRCA*m carrier with any ER, PgR and HER2 mBC	g*BRCA*m mBC	LA/mTNBC	g*BRCA*m mBC	BRAC1m HER- mBC
Median age (range), years	55.7 (IQR: 47.6 to 62.9)	Not reported	52.0 (30.0 to 78.0)	Not reported	48.0 (32 to 70)
HER2- HR+, %	7	Not reported	0	Not reported	25
TNBC, %	93	Not reported	100	Not reported	75
BRCA1-positive	9	Not reported	Not reported	Not reported	100
BRCA2-positive	5	Not reported	Not reported	Not reported	0
ECOG PS, %	≤1: 93 2: 7	Not reported	≤1: 87 2:6	Not reported	≤1: 100
CNS metastases, %	Not reported	Not reported	Not reported	Not reported	Not reported
Visceral metastases, %	72	Not reported	Not reported	Not reported	Not reported
Line of treatment, %	≥2L: 100	≥2L: 100	Not reported	≥2L: 27	≥2L: 40
Prior (neo)adjuvant, %	Taxane: 35	Not reported	86	91	13
Prior anthracycline/ taxane, %	Adjuvant taxane: 35 Advanced anthracycline: 9	Not reported	Adjuvant: Anthracycline: 74 Taxane: 78	Not reported	Not reported

aBC=advanced stage breast cancer; *BRCA*m=BReast CAncer gene mutation(s) ; CNS=central nervous system; CS=company submission; ECOG PS=Eastern Cooperative Oncology Group performance status; ER=oestrogen receptor; g*BRCA*m=germline BReast CAncer gene mutation(s); HER2-= human epidermal growth factor receptor 2 negative; LA=locally advanced; mBC=metastatic breast cancer; PgR=progesterone receptor; PFS=progression-free survival; RCT=randomised controlled trial; TNBC=triple-negative breast cancer;
Source: CS, Appendix D, Table 10 supplemented by published papers[31,40,49]

8.6.2 Efficacy results from studies of platinum chemotherapy

Table 41 Summary of evidence for platinum chemotherapy: efficacy results

Endpoint	TNT – all (N=188)	TNT – *BRCA*m (n=25)	TBCRC009 – all (N=86)	TBCRC009 – *BRCA*m (n=11)	NCT01611727 – *BRCA*m (N=20)
Median follow up, months	Not reported	Not reported	49.9	49.9	Not reported
PFS, months (95% CI)	3.1	6.8	2.9	3.3	TTP: 12 (1 to 36) TTP varied by response: Complete: 17 Partial: 8 Stable:3 Progressive: 1
OS, months (95% CI)	12.8	Not reported	11	13.7	30
OS rates (months: %)	Not reported	Not reported	Not reported	Not reported	12: 80 24: 60 36: 25
ORR, % (95% CI)	31	68	25.6 (16.8 to 36.1) Complete response: 3.5	55 (23 to 83) Complete response: 0	80 HR+/HER2-: 80 TNBC: 80 Complete responders HR+/HER2-: 20 TNBC: 53

CS=company submission; HR+/HER2-= hormone receptor-positive / human epidermal growth factor receptor 2 negative; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; TNBC=triple-negative breast cancer; TTP=time to progression
Source: CS, Appendix D, Tables 11 to 13 supplemented by published papers[31,40,49]

8.6.3 Safety results from studies of platinum chemotherapy

Table 42 Summary of evidence for platinum chemotherapy: adverse events

Endpoint	TNT – all (N=188)	TNT – *BRCA*m (n=25)	TBCRC009 – all (N=86)	TBCRC009 – *BRCA*m (n=11)	NCT01611727 – *BRCA*m (N=20)
Any AE, %	Not reported	Not reported	Not reported	Not reported	Not reported
Most common AEs, %	Fatigue: 95 Nausea: 78 Constipation: 61 Haemoglobin decreased: 52 Vomiting: 47 Decreased appetite: 45 Mucosal inflammation: 38 Alopecia: 35 Neuropathy peripheral: 33 Platelet count decreased: 33	Not reported	Haemoglobin: 73 Fatigue: 66 Nausea: 66 Hyperglycaemia: 47 Neutrophils: 42 Leukocytes: 38 Neuropathy: 36 Thrombocytopenia: 33	Not reported	Nausea: 50 anaemia: 5 neutropenia: 35
Any Grade ≥3 AE, %	Not reported	Haematological: 36 Non-haematological: 48	Not reported	Not reported	10 “for both of these [patients], cisplatin was the third-line treatment“
Most common Grade ≥3 AEs, %	Fatigue: 16 Platelet count decreased: 7 Thrombocytopenia: 6 Dyspnoea: 6 Platelet disorder: 5 Nausea: 5 Vomiting: 5	Not reported	Fatigue: 8 Neutrophils: 7 Dyspnea: 6 Haemoglobin: 6 Hyperglycaemia: 6 Hyponatremia: 5	Not reported	Not reported
Any SAE, %	54	Not reported	Not reported	Not reported	Not reported
Most common SAEs, %	Not reported	Not reported	Not reported	Not reported	Not reported
Dose modification (interruption or adjustment), %	Not reported	Not reported	Not reported	Not reported	20 (anaemia or neutropenia)
AEs leading to drug discontinuation, %	7	Not reported	12	Not reported	5 (Neutropenia)

AE=adverse event; CS=company submission; PCT=physician’s choice treatment; SAE=serious adverse event
Source: CS, Appendix D, Table 14 supplemented by published papers[31,40,49]

8.7 Appendix 7: EAG results using the eMIT prices listed in the NICE price tracker for this appraisal

Table 43 Deterministic results: EAG adjustments to company base case (talazoparib PAS price, updated eMIT prices)

Scenario/EAG amendment	Talazoparib			PCT			Incremental			*ICER*	
	Cost	**QALYs**	**Life Years**	**Cost**	**QALYs**	**Life years**	**Cost**	**QALYs**	**Life years**	**£/QALY**	**Change from base case**
A. Company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	***£35,259***	
R1) Weibull function used to model OS for patients receiving PCT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£35,544	£285
R2) EMBRACA trial RBC transfusion rate used for patients receiving talazoparib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£45,365	£10,106
R3) EMBRACA trial TTD K-M data used to estimate treatment costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£52,915	£17,655
R4) RDI removed from model	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£41,111	£5,851
R5) Resource use in the PFS health state set to not vary by response to treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£40,571	£5,312
R6) Subsequent treatments reweighted and micro-costing approach applied	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£37,000	£1,741
R7) Lambert-Obry (2018) study later line PD utility value used to represent HRQoL in the PD health state	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£35,414	£155
R8) PFS health state talazoparib utility value used in both treatment arms	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£41,308	£6,048
R9) Cost of treating neutropenia removed from PFS state and add to neutropenia treatment cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£40,018	£4,759
B. EAG preferred scenario (R1-R9)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	***£89,626***	***£54,366***

EAG=External Assessment Group; HRQoL=health-related quality of life; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; PCT=physician's choice treatment; PD=progressed disease; QALYs=quality adjusted life years

Table 44 Probabilistic results: EAG adjustments to company base case (talazoparib PAS price, updated eMIT prices)

Scenario/EAG amendment	Talazoparib			PCT			Incremental			*ICER*	
	Cost	QALYs	Life Years	Cost	QALYs	Life years	Cost	QALYs	Life years	£/QALY	Change from base case
A. Company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	***£34,748***	
B. EAG preferred scenario	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	***£99,743***	***£64,995***

EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; PCT=physician choice of treatment; QALYs=quality adjusted life year

8.8 Appendix 8: EAG revisions to the company model

Table 45 Microsoft EXCEL revisions made to the company model by the EAG

EAG revision number and description (see Section 6.10)	Implementation instructions
R1) Weibull function to model OS for the patients receiving PCT	In Sheet 'Clinical Inputs' In cell F40 select "Best Fit Parametric"
R2) EMBRACA trial RBC transfusion rate for talazoparib	**Insert Sheet named "EAG Revisions"** In cell B3 enter text "R2" Set value in cell C3=1 In Sheet 'Resource Use' Set value in cell G27=IF('EAG Revisions'!C3=1,38.1%,8.3%) Set value in cell G43=IF('EAG Revisions'!C3=1,38.1%,8.3%) Set value in cell G59=IF('EAG Revisions'!C3=1,38.1%,8.3%)
R3) EMBRACA trial TTD K-M data	In Sheet 'Treatment Costs' In cell F134 select "Trial KM"
R4) RDI removed from model	In Sheet 'Treatment Costs' In cell F22 select "No"
R5) Resource use in PFS independent of response to treatment	In Sheet 'Clinical Inputs' In cell F93 select "No"
R6) Reweighted subsequent therapies and applied micro-costing	In Sheet "EAG Revisions" In cell B4 enter text "R6" Set value in cell C4=1 In Sheet 'Treatment Costs' In cell F79 select "Micro Costing" In Sheet 'Settings' Copy range E52:F64 Paste to range E90:F102 Set value in cell E70=E52/SUM(E$52:E$64)

EAG revision number and description (see Section 6.10)	Implementation instructions
	Copy cell E70 Paste to range E70:F82 Copy range E70:F82 Paste values to range E70:F82 Set value in cell E52=IF('EAG Revisions'!C4=1,E70,E90) Copy cell E52 Paste to range E52:F64
R7) Utility values in PD state based on Lambert (2018)	In Sheet "EAG Revisions" In cell B5 enter text "R7" Set value in cell C5=1 In Sheet 'Utility' Set value in cell E17=IF('EAG Revisions'!C5=1,0.65,0.6255)
R8) Utility values in PFS independent of treatment arm	In Sheet "EAG Revisions" In cell B6 enter text "R8" Set value in cell C6=1 In Sheet 'Utility' Set value in cell F12=IF('EAG Revisions'!C$6=1,0.750,0.687) Copy cell F12 Paste to range F14:F15
R9) Cost of treating neutropenia removed from PFS state and included in AE cost	In Sheet "EAG Revisions" In cell B7 enter text "R9" Set value in cell C7=1 In Sheet 'Resource Use' Set value in cell F45=IF('EAG Revisions'!C7=1,0,24.35) Set value in cell F61=IF('EAG Revisions'!C7=1,0,36.525)

EAG revision number and description (see Section 6.10)	Implementation instructions
	Set value in cell F29=IF('EAG Revisions'!C7=1,0,30.4375) In Sheet 'Adverse Events' Set value in cell F18=IF('EAG Revisions'!C7=1,F34+'Resource Use'!E29*14,F34)

Single Technology Appraisal

Talazoparib for treating HER2-negative locally advanced or metastatic breast cancer with germline BRCA1/2-mutations

EAG report – factual accuracy check and confidential information check

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

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

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on 24 March** 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 separately highlight information that is submitted as 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

Issue 1 Description of treatment pathway (page 13)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The company's treatment pathways for patients with gBRCAm aBC show that platinum chemotherapy is: 1. an option for patients with HR+/HER2- BC (CS, Figure 1) 2. an option for newly diagnosed patients with TNBC and is the preferred option for PD-L1- patients (CS, Figure 2) 3. the preferred option for previously treated patients with TNBC who have not previously received platinum chemotherapy (CS, Figure 3).	The company's treatment pathways for patients with gBRCAm aBC show that platinum chemotherapy is: 1. an option for patients with HR+/HER2- BC (CS, Figure 1) 2. an option for newly diagnosed patients with TNBC and is the preferred option for ***gBRCAm***- patients (CS, Figure 2) 3. the preferred option for previously treated patients with ***gBRCAm*** TNBC who have not previously received platinum chemotherapy (CS, Figure 3).	Accurate description of treatment pathway.	The focus of the appraisal is treatment of aBC with *gBRCAm* and hence this is implied by the EAG's original statement. All of the figures in the CS show that these are treatment options for patients who test positive for *gBRCAm*. CS, Figure 2, shows that the choice of first-line treatment depends on PD-L1 status; platinum chemotherapy is only the preferred option for patients who test negative for PD-L1. Therefore, the EAG considers no changes are necessary.

Issue 2 Year of Litton publication (page 26)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Table 3; Litton (2022)[26]	Table 3; Litton (2020)[26]	Correct year of Litton publication is 2020.	Thank you for highlighting this typographical error. Text in Table 3 has been amended.

Issue 3 Prior treatment regimens (page 31)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The EAG considers that the number of prior regimens of cytotoxic chemotherapy for aBC can be a proxy for line of treatment.	N/a	This is not a good proxy, there are other treatments that are not cytotoxic chemotherapy e.g. CDK 4/6i.	The EAG acknowledges there are non-cytotoxic regimens available for patients with HR+/HER2- aBC (EAG report, p31). See also response to Issue 4.

Issue 4 Prior treatment regimens (page 31)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Number of prior regimens of cytotoxic chemotherapy for aBC is a proxy for line of treatment because there are non-cytotoxic treatment options for patients with HR+/HER2- aBC (see CS, Figure 1).	N/a	This is believed to be a typo, however there are CDK 4/6i, ET options which are not cytotoxic chemotherapy.	Thank you for highlighting this unclear wording. Text amended for clarity as follows: Number of prior regimens of cytotoxic chemotherapy for aBC is *only* a proxy for line of treatment because there are non-cytotoxic treatment options for patients with HR+/HER2- aBC (*endocrine-based therapy with or without CDK4/6i, everolimus or alpelisib*, see CS, Figure 1).

Issue 5 Talazoparib PAS (page 33)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Talazoparib and eribulin are available to the NHS at (confidential) Patient Access Scheme (PAS) prices.	Eribulin is available to the NHSE at a (confidential) Patient Access Scheme (PAS) price. Talazoparib is not reimbursed for any indication by the NHS yet, however a confidential PAS offer has been made, which would be available on the condition that talazoparib is reimbursed for the indication under consideration with NICE (ID1342).	Talazoparib is not yet reimbursed, but a confidential PAS offer has been made.	Thank you for highlighting this error. Text amended as follows: *The company has submitted a confidential Patient Access Scheme (PAS) application for talazoparib. The company has used the anticipated talazoparib PAS price to generate the company base cost effectiveness results presented in the CS.* *Eribulin has a confidential PAS price and filgrastim (an immunostimulant which may be used alongside talazoparib or chemotherapy for treating neutropenia) has a Commercial Medicines Unit (CMU) price. Company and EAG cost effectiveness results using all available discounted prices (and NICE price tracker eMIT prices) are presented in the confidential appendix.*

Issue 6 RBC transfusion rate (page 79)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
The company considered that the RBC transfusion rate for EMBRACA trial patients treated with talazoparib (38.1%) was higher than would be seen if talazoparib were a routinely commissioned NHS treatment. The company's argument was that: • NHS clinical guidelines state that transfusions should only be used when a patient's haemoglobin level falls below 7g/dL • RWE from the US (the company states the US has similar guidelines to the UK) shows that the percentage of patients receiving talazoparib who required a transfusion was 8.3% (the EAG was unable to identify the source of this figure from the references provided by the company).	The company considered that the RBC transfusion rate for EMBRACA trial patients treated with talazoparib (38.1%) was higher than would be seen if talazoparib were a routinely commissioned NHS treatment. The company's argument was that: • *High transfusion rates in EMBRACA are attributed to the protocol which required haemoglobin (Hb) values to recover to grade 1 or better (10 g/dL) before resuming talazoparib after a dosing interruption. A protocol amendment was made so that talazoparib could be resumed at Hb of 9 g/dL or greater, leading to lower transfusion rates. The rate of RBC transfusions declined by approximately 11% after the amendment*	To accurately reflect the justification for including real-world transfusion rates. Reference has been provided with this response (Page 97 of data on file).	Thank you for providing this reference. Text amended (and reference added) as follows: • *High transfusion rates in EMBRACA are attributed to the protocol which required haemoglobin (Hb) values to recover to grade 1 or better (10 g/dL) before resuming talazoparib after a dosing interruption. A protocol amendment was made so that talazoparib could be resumed at Hb of 9 g/dL or greater, leading to lower transfusion rates. The rate of RBC transfusions declined by approximately 11% after the amendment* • NHS clinical guidelines state that transfusions should only be used when a patient's haemoglobin level falls below 7g/dL

	• NHS clinical guidelines state that transfusions should only be used when a patient's haemoglobin level falls below 7g/dL • RWE from the US (the company states the US has similar guidelines to the UK) shows that the percentage of patients receiving talazoparib who required a transfusion was 8.3% (the EAG was unable to identify the source of this figure from the references provided by the company).		• RWE from the *US retrospective chart review by Mahtani (2022)*[41] (the company states the US has similar guidelines to the UK) shows that the percentage of patients receiving talazoparib who required a transfusion was 8.3% *(non-interventional final study report*[69]*).* Reference to non-interventional final study report also now made on page 70.

Location of incorrect marking	**Description of incorrect marking**	**Amended marking**
Give full details of inaccurate marking - document title and page number	Give details of incorrect confidential marking	Please copy the impacted section here, with your amended marking.

(Please add further lines to the table as necessary)

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Talazoparib for treating HER2-negative locally advanced or metastatic breast cancer with germline BRCA1/2 -mutations (ID1342)

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

The deadline for comments is **5pm** on **<insert deadline>**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we

received, and are not endorsed by NICE, its officers or advisory committees.

About you

Table 1 About you

Your name	Hannah Lawless Keon Yi
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Pfizer UK
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.] Please state the name of the company, amount, and purpose of funding.	**N/a**
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	**N/a**

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

We thank the EAG for their thoughtful interrogation of our submission and whilst we acknowledge there are some key areas of uncertainty, we wish to avoid creating inequity between subgroups of HER2- BC, without the trial being powered to do so. We do accept that there is uncertainty around platinum chemotherapy, red blood cell transfusion rates and dose intensity and we have attempted to adjust for these leading to revised ICERs of £30,586, £35,366 and £33,854 respectively, compared to our deterministic base-case of £27,316. Probabilistic scenario analysis was conducted to account for parameter uncertainty in the model, generating a probabilistic base-case ICER of £25,181 (Figure 4).

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
EMBRACA trial included a heterogeneous population	No	We also thank Breast Cancer Now, METUPUK and NCRI-ACP-RCP-RCR for their submissions in this appraisal. Breast Cancer Now have highlighted the unmet need for both TNBC and HR+/HER2-negative patients, as for TNBC patients, for many years chemotherapy was the mainstay of treatment and there have been significantly limited treatments for this group of patients. There is also an unmet need for the HR+/HER2- population for new and effective treatment options post CDK/46 inhibitor as patients become resistant to these treatments. Additionally, TNBC can be more aggressive and harder to treat than other types of breast cancer, resulting in potentially poorer outcomes and short prognoses, as described by Breast Cancer Now and METUPUK.

		The scope of the submission covers the ITT population as assessed in EMBRACA. As provided in the company clarification question response, the EMBRACA trial was designed with adequate power to detect 90% and 80% effect sizes for PFS and OS in the ITT population. Any analyses across subgroups would not be powered to detect significant differences, and therefore it is inappropriate to explore analyses of the data within sub-populations of the trial. We wish to avoid inequity in access of talazoparib by subgrouping the ITT population, given the unmet need and clinical benefit in PFS and HRQoL that talazoparib has demonstrated in EMBRACA.
Platinum chemotherapy is not included as a comparator	Yes	Whilst it is recognised that platinum chemotherapy is a relevant comparator for patients with BRCAm triple negative breast cancer (TNBC), there are several limitations associated with the inclusion of platinum chemotherapy in the economic model. As highlighted by the EAG, there are no trials directly comparing physician's choice of treatment (PCT) and platinum chemotherapy and therefore we have no common comparator. Additionally, there are huge trial population differences. 90% of patients in the TNT platinum chemotherapy trial had no known BRCA1/2 mutations, whereas 100% of patients in the EMBRACA trial had a BRCA1/2 mutation. Although we do not believe it is appropriate to compare platinum chemotherapy with talazoparib given the limitations, we have attempted to run a scenario including this comparator. In the absence of data, we have made the following assumptions: - Efficacy and safety of platinum chemotherapy is the same as PCT - 15% of patients receive platinum chemotherapy (TNBC patients only) - 90:10 split between carboplatin and cisplatin, - Administration costs including EDTA testing for carboplatin are included

		The base case ICER excluding platinum chemotherapy is £27,316, and the revised ICER including platinum chemotherapy is £30,586. Therefore, the impact on the ICER of including platinum chemotherapy is +£3,270, although we reiterate that we do not feel this is the most appropriate ICER on which to base decision making, and in practice we expect significantly fewer than 15% of patients to be platinum chemotherapy eligible.
Is it appropriate to assume that the effectiveness of the individual EMBRACA trial physician's choice of treatment (PCT) arm drugs have similar efficacy?	No	We acknowledge that there is a gap in the evidence base of trials comparing the efficacy of individual treatments in the PCT arm of EMBRACA, in patients with gBRCAm and advanced/metastatic breast cancer. Clinical advice received by the company is that it is reasonable to assume equivalent efficacy for all treatments in the PCT arm of EMBRACA in the economic model, in the absence of head-to-head data. However, clinical input to further validate this assumption in the committee meeting will be valuable.
Prior treatments received by EMBRACA trial patients may not reflect prior treatments received by NHS patients	No	EMBRACA was a global trial which was initiated in 2013 and completed in 2021. Given the evolving treatment landscape for advanced/metastatic breast cancer patients, some prior treatments received by patients enrolled in EMBRACA are not reflective of treatments received in NHS clinical practice.
Interpretation of EMBRACA trial overall survival (OS) results is problematic	No	The EAG highlights that, for the TNBC subgroup, the OS results require explanation, as median overall survival favours PCT, whilst the HR favours talazoparib (not statistically significant). The same trend is seen in the ITT population. Crossover in the OS K-M curves for TNBC patients occurs after month 9, and again at month 21, as shown in Figure 3. The hazard ratio and the median difference provide different contrasts of 2 time-to-event distributions, and a difference via the hazard ratio does not imply a difference in medians or vice versa. This difference is not explainable with the current evidence base, due to the smaller patient numbers and lack of statistical power to detect differences in OS in the TNBC subgroup, however the observed difference in median OS may be driven by subsequent treatments received by patients treated with PCT.

		Whilst we do understand that these results are challenging to interpret, we are reassured by the statistically significant PFS and Quality of Life results favouring talazoparib over PCT. Indeed, feedback from patients and clinicians is that PFS is a clinically meaningful outcome for advanced/metastatic breast cancer patients, and statistically significant improvement in PFS for talazoparib was observed in EMBRACA. As emphasised by Breast Cancer Now: *"As patients' time is limited, people tell us that quality of life is just as important to take into account as length of life, as this enables them to spend quality time with their loved ones."*
Appropriateness of using EMBRACA trial intention-to-treat (ITT) data in the company model	No	The scope of this submission is aligned with the population enrolled in EMBRACA, and includes HR+/HER2-negative and TNBC patients. Drawing conclusions about the efficacy and cost-effectiveness of talazoparib within subgroups would be inappropriate due to smaller and lack of statistical power in the trial. As discussed above, patient groups have highlighted the unmet need in both HR+/HER2-negative, and TNBC patient populations, and we wish to avoid inequity in access by subgrouping the EMBRACA population.
EMBRACA trial talazoparib red blood cell (RBC) transfusion rates were not used in the model and the relationship between transfusion rates, dose modifications/reductions and efficacy is unknown	No	We received strong clinical advice that transfusion rates are far lower in the UK than seen in the trial (38.1%) and much closer to the US RWD rates of 8.3%. This is partly because of the difference in RBC transfusion thresholds between the EMBRACA threshold for transfusion (10 g/dL pre protocol amendment; 9 g/dL post protocol amendment) and UK/US guidelines for transfusion (7 g/dL), but also the decision to transfuse Is a clinical decision factoring in not just guidelines but also patient symptoms. However, we do understand the concerns about using RW transfusion rates instead of trial rates and the question as to whether lower transfusion rates seen in the RW (in the USA) would lead to (more dose interruptions and/or) different outcomes. The correlation between transfusion rates, dose modifications/reductions and efficacy observed in EMBRACA is unknown but we do welcome a Committee discussion and further clinical input on this assumption. The median PFS of talazoparib observed in the US real-world study was 8.7 months (95% CI 8.0-9.9)[1],

		which is consistent with EMBRACA in which median PFS for talazoparib was 8.6 months (95% CI 7.2-9.3), despite the higher transfusion rates noted above. Nonetheless, it is plausible that lower transfusion rates impact upon quality of life. Unfortunately, we do not have any data on the link between transfusion and utility and so we have explored the impact of modifying the utility of talazoparib to be equal to that of PCT (0.687), where the transfusion rate in EMBRACA was 6% (i.e. comparable to the US RWD transfusion rate for talazoparib). Using the RW transfusion rate (8.3%) and reduced utility rate (0.687) for talazoparib results in a revised ICER is £35,366. We believe this is a pessimistic approach because quality of life is impacted by more than just the transfusion rate – however we hope this gives an upper bound to explore the uncertainty around more realistic transfusion rates. As above, we welcome the Committee and clinical input to explore the best way of accurately representing the true cost to the NHS of introducing talazoparib.
The derivation of the relative dose intensity multipliers used in the model are not clearly described	Yes	Detailed dosing from EMBRACA have been provided to provide an accurate representation of actual doses received by patients. However, it is acknowledged that this may not accurately reflect the whole duration of the trial. Therefore, an updated model is provided with this response, in which it is assumed that 100% of patients receive the 1 mg dose of talazoparib, with a relative dose intensity of 90.8% as observed in EMBRACA. The revised ICER is £33,854 (an increase of £6,538 compared to the deterministic base case ICER).
Other issues identified by NICE technical team (not included in the EAR): **QALY multiplier – Please apply the multiplier to QALYs, not ICERs**	Yes	An updated model is provided with this response, with the 1.2 multiplier applied to incremental QALYs, rather than the ICER threshold. In the company base case, the incremental QALYs increase from [redacted] with the 1.2 severity modifier applied. Updated cost-effectiveness analysis results are presented in Table 5.

1. Zimmerman Savill, K. M., Ivanova, J., Asgarisabet, P., Falkenstein, A., Balanean, A., Niyazov, A., ... & Mahtani, R. L. (2023). Characteristics, Treatment, and Outcomes of Real-World Talazoparib-Treated Patients With Germline BRCA-Mutated Advanced HER2-Negative Breast Cancer. The Oncologist, oyad021.

Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

Table 3 Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: KM treatment duration	Section 6.4 of EAG report	Yes	As the EMBRACA trial time to treatment discontinuation (TTD) K-M data are not complete at the end of 5 years (PCT: no patients still on treatment; talazoparib: 4.4% of patients may still be receiving treatment), parametric survival curves have been fitted to the trial TTD KM data to align with PFS approach and to estimate the costs of talazoparib more accurately. AIC and BIC for the talazoparib and PCT extrapolations are presented in Figure 1 and Figure 2 respectively. The AIC and BIC values are presented in Table 4. Based on AIC/BIC values, the generalised gamma distribution is a good fit to the talazoparib and PCT data. However, based on visual inspection, it may be more appropriate to use the lognormal distribution for the PCT arm.

Table 4. AIC/BIC and ICERs for parametric survival curves fitted to KM data for treatment duration

	Talazoparib		PCT	
Distribution	AIC	BIC	AIC	BIC
Exponential	1482.1	1485.759	595.8143	598.7842
GenGamma	**1418.825**	**1429.803**	**547.0365**	**555.9459**
Gompertz	1484.099	1491.418	591.1438	597.0834
Log-normal	1422.72	1430.039	551.9063	557.8459
Weibull	1469.265	1476.584	574.7606	580.7003

Figure 1. Parametric distributions fitted to Kaplan-Meier treatment duration for talazoparib

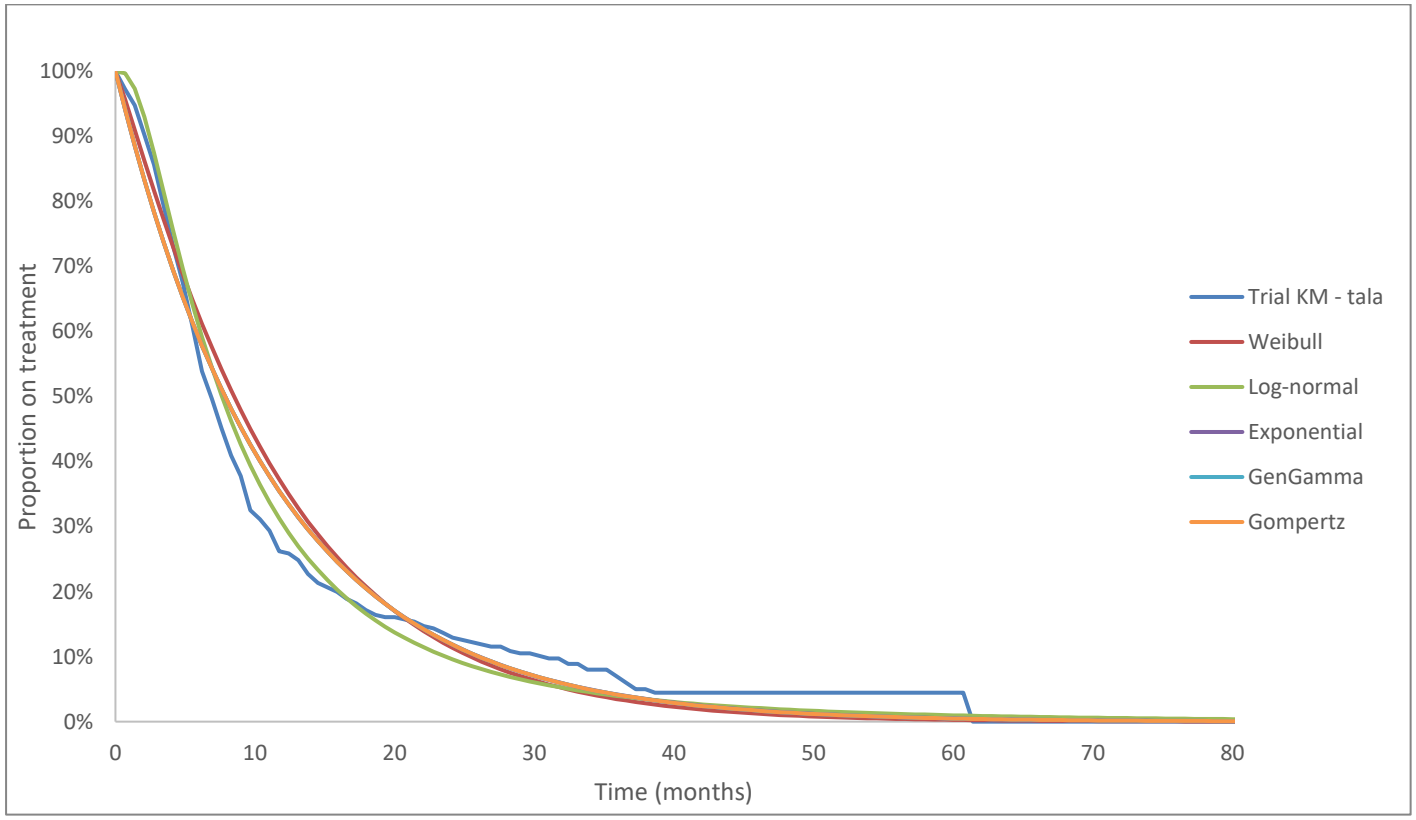


Figure 2. Parametric distributions fitted to Kaplan-Meier treatment duration for PCT

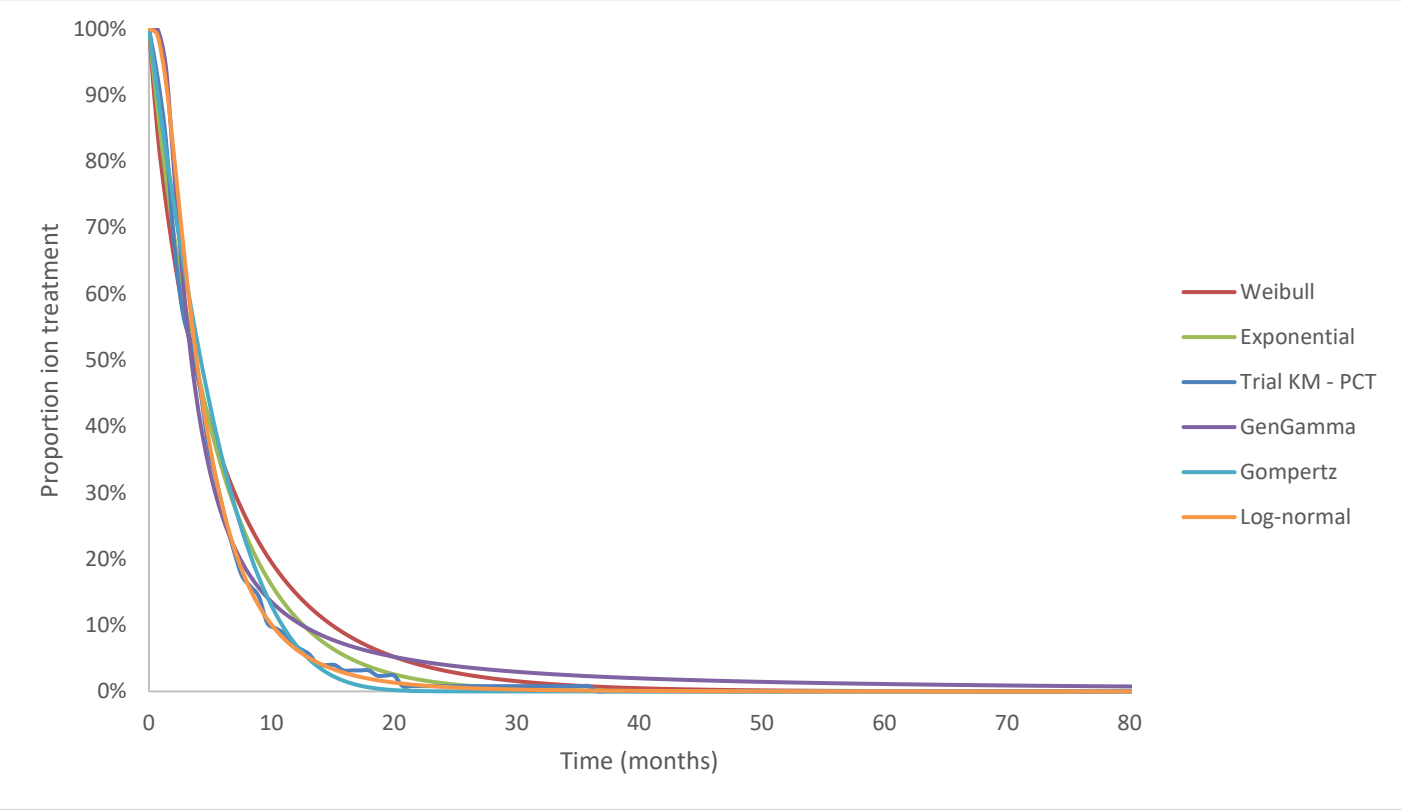
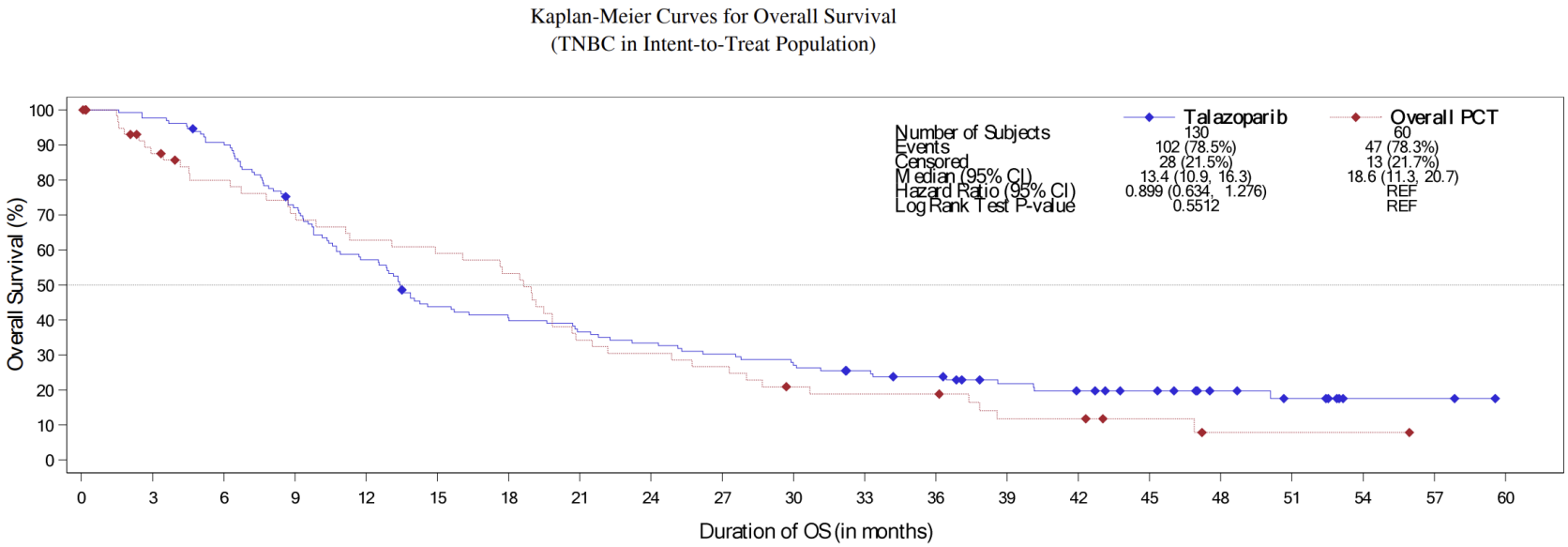


Figure 3. Kaplan-Meier curve for Overall Survival in TNBC



Talazoparib: Evt/Cum.	0/0	3/3	9/12	24/36	19/55	17/72	4/76	5/81	4/85	4/89	4/93	2/95	2/97	2/99	2/101	0/101	0/101	1/102	0/102	0/102	0/102
Patients at Risk	130	127	117	92	73	55	51	46	42	38	34	30	27	21	18	15	10	7	2	2	0
Overall PCT: Evt/Cum.	0/0	7/7	4/11	5/16	4/20	2/22	3/25	10/35	2/37	2/39	3/42	1/43	0/43	3/46	0/46	0/46	1/47	0/47	0/47	0/47	0/47
Patients at Risk	60	48	42	37	33	31	28	18	16	14	10	9	9	5	5	3	1	1	1	0	0

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base

Technical engagement response form

Talazoparib for treating HER2-negative locally advanced or metastatic breast cancer with germline BRCA1/2 -mutations (ID1342)

case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

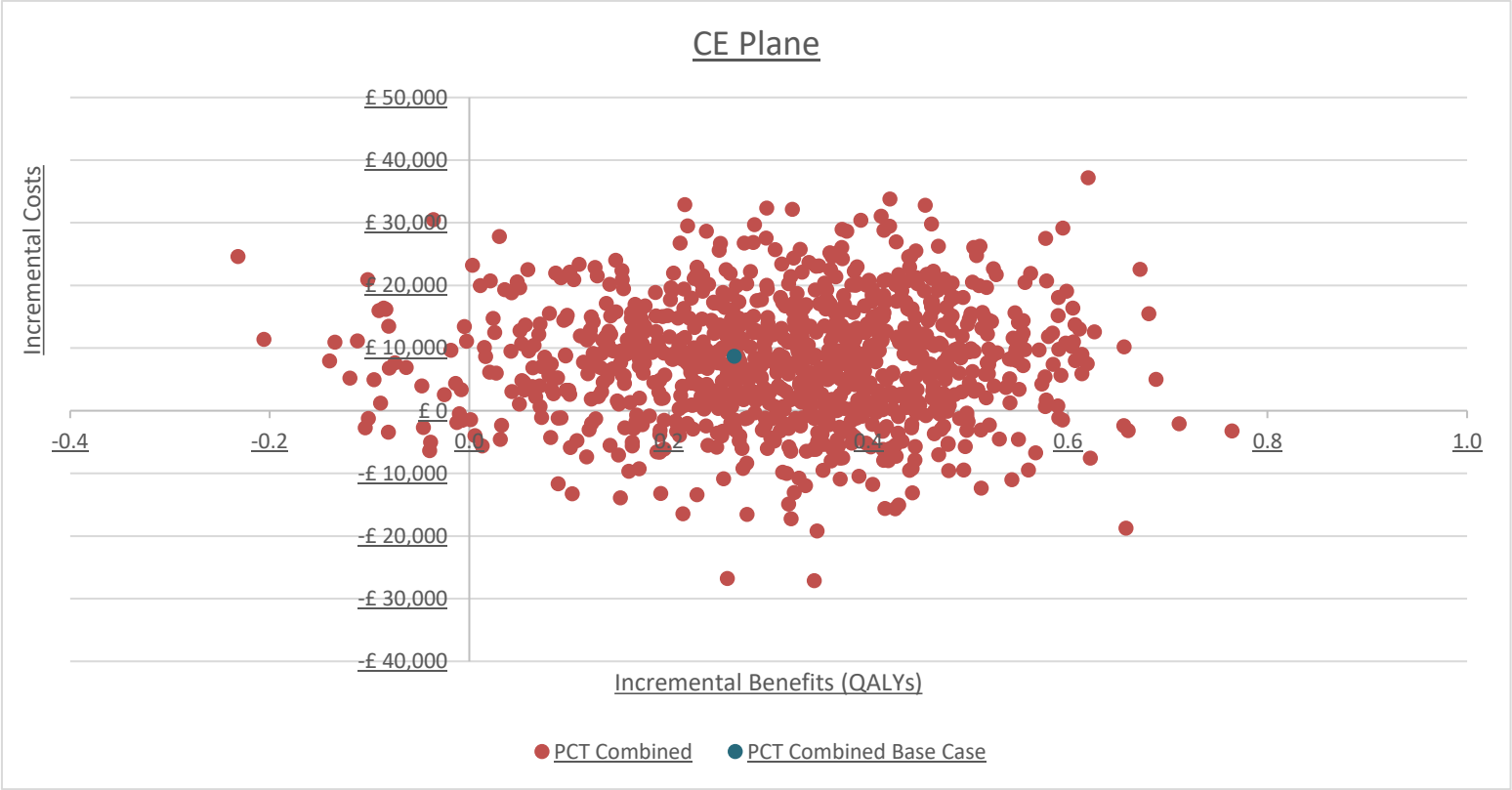
The revised base case ICER, when the severity modifier is applied to incremental QALYs, is £27,316. Scenario analyses based on the key issues identified by the EAG are presented in Table 5.Table 5 Changes to the company's cost-effectiveness estimate

Table 5 Changes to the company's cost-effectiveness estimate

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Additional issue identified by NICE	Severity modifier applied to WTP threshold	Severity modifier applied to incremental QALYs	The incremental QALYs increase from [redacted] with the severity modifier of 1.2 applied. The revised base case ICER is **£27,316.**
Key issue 2	Platinum chemotherapy is not included as a comparator	Platinum chemotherapy is included within the basket of comparators for TNBC patients (15% of all patients)	£30,586 (+£3,270)
Key issue 7	RBC transfusion rate from US RWD, which is expected to be more reflective of transfusion rates in UK clinical practice	Scenario analysis presented exploring the impact of lower transfusion rates on utility, in which the utility of talazoparib is assumed to be equal to PCT (0.687).	£35,366 (+£8,050)
Key issue 8	The derivation of the relative dose intensity multipliers used in the model are not clearly described	Relative dose intensity of 90.8% as observed in EMBRACA	£33,854 (+£6,538)

Probabilistic sensitivity analyses around the revised base case are presented in Figure 1Figure 4 below. The base case probabilistic ICER for talazoparib compared to PCT is £25,181.

Figure 4. Probabilistic sensitivity analyses



NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Talazoparib for treating HER2-negative locally advanced or metastatic breast cancer with germline BRCA1/2 -mutations (ID1342)

Clinical expert statement and technical engagement response form

Thank you for agreeing to comment on the external assessment report (EAR) for this evaluation, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The EAR and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR (section1). You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

The deadline for your response is **5pm** on **<insert deadline>.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

Clinical expert statement

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

Part 1: Treating HER2-negative locally advanced or metastatic breast cancer with germline BRCA1/2 -mutations (including triple-negative breast cancer) and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Andrew Tutt
2. Name of organisation	The Institute of Cancer Research London and Kings College London
3. Job title or position	Professor of Breast Oncology, Professor of Clinical Oncology
4. Are you (please tick all that apply)	☒ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with HER2-negative locally advanced or metastatic breast cancer with germline BRCA1/2 -mutations ? ☐ A specialist in the clinical evidence base for HER2-negative locally advanced or metastatic breast cancer with germline BRCA1/2 -mutations or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ Yes, I agree with it ☐ No, I disagree with it ☒ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here.	☐ Yes

(If you tick this box, the rest of this form will be deleted after submission)	
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	NA
8. What is the main aim of treatment for **HER2-negative locally advanced or metastatic breast cancer with germline BRCA1/2 -mutations?** (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	To prevent progression and improve and/or preserve quality of life in comparison to alternative available treatments or best supportive care
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	a median delay of progression of disease of greater 3 months with preservation of quality of life when compared to other treatment choices available at the time that comparisons made in a relevant randomised trial and that remain relevant in practice.
10. In your view, is there an unmet need for patients and healthcare professionals in HER2-negative locally advanced or metastatic breast cancer with germline BRCA1/2 -mutations ?	Yes. Patients need oral therapy that improves PFS and has manageable toxicity and lower impact on quality of life than other standard of care oral therapies and that intravenous therapies that require multiple episodes hospital attendance and blood testing.
11. How is HER2-negative locally advanced or metastatic breast cancer with germline BRCA1/2 -mutations currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	I agree with the guidelines quoted by the EAP and would point out that the current NICE guidelines do not specifically address the special situation of germline BRCA1/2 mutation associated breast cancer. These are however better addressed in the NCCN and ESMO guidelines are broadly used in the UK practice. These guidelines include the use of all therapies relevant for HER2-negative locally advanced or metastatic breast cancer **without** germline BRCA1/2 -mutations but add to these the treatment options of carboplatin chemotherapy as a treatment option at or beyond diagnosis of diagnosis of advanced disease. The use of PARP inhibitors Olaparib or Talazoparib are also options in this setting

• What impact would the technology have on the current pathway of care?	but have never been compared as the relevant trials were run in parallel and so neither PARPi or platinum were considered a comparator standard of care in the relevant trials. (TNT, EMBRACA, OlympiAD). The technology would align the NHS practice with the ESMO and NCCN guidelines for this group of patients and add an oral SACT option for treatment for the patients with germline BRCA1/2 -mutations and would likely replace a line of intravenous therapy option such as intravenous taxane therapy rechallenge (in PDL1 -ve patients) and intravenous vinorelbine or eribulin that require weekly or 2/3 weekly hospital attendance and chemotherapy day unit care and or have a more TAE / side effect and quality of life impact profile. It would also likely replace capecitabine completely as a SACT line as EMBRACA trial shows clear evidence of improved PFS and QOL preservation.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	This would reduce the use of intravenous therapy and attendances and impacts of intravenous therapy and chemotherapy day units and blood monitoring services. It would be used in secondary specialist care as must be supervised by an oncologist as with all other current treatment options. No investment needed. Genetic testing is already funded by relevant test directories in early breast cancer or familial risk settings.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	The evidence of effects on overall survival are not statistically significant in the ITT population. I would expect differences in OS if the first / second line metastatic TNBC setting especially in PDL1 -ve patients but these data do not exist simply because standards of care move on during the conduct of phase III trials of new interventions and do not focus on discrete targetable biological subgroups such as those with HER2-negative locally advanced or metastatic breast cancer with germline BRCA1/2 -mutations

	Yes I expect the technology to increase health-related quality of life more than current care based on efficacy measured by PFS and by lower impact on TeAEs and requirement for blood tests and hospital attendances for care.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No. This is already targeted at those with the technology to increase health-related quality of life more than current care. Focus on the absence of data in comparison with platinum, while true, cannot be answered with evidence and misses the advantage of replacing an intravenous therapy requiring multiple hospital attendances and chemotherapy day unit impacts for delivery and an adverse side effect profile, accepting cross limitations of cross trial comparisons.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	Much easier No chemo day unit attendance vs 2/3 weeks or weekly Bloods 1 per 28 days vs weekly or 2/3 weekly for several current SOC regimen comparitors
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Standard assessments of response by imaging and blood monitoring (see comment above)
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen	Yes. The benefits in terms of time away from hospital and economic impact of patients and carers of current SOC intravenous or weekly attendance therapies. Less blood testing required

may be more easily administered (such as an oral tablet or home treatment) than current standard of care	
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	Yes as this a therapy that is based on individual germline genetics assessment and may be influenced by germline genetics results funded by NHS England.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The side effect profile is largely favourable compared to many current standards of care. Anaemia is the main TEAE that is of concern but is also a very significant impact of more recently identified standards of care such as platinum and Sacituzumab Govitecan in TNBC. The rates of neutropaenia are largely facvourable compared to other options in both ER+ve HER2 -ve and TNBC disease. New agents such as alpelisib have a significantly adverse TEAE / side effect profile compared to the technology.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Yes excepting that as always practice has move on internationally based on concurrently run phase III studies in non-germline BRCA1/2 carriers with HER2 -ve BC.

21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	There is emerging evidence of relative lack of efficacy of CDK4/6 inhibitors in BRCA2 mutation carriers with ER+ HER2 negative breast cancer from the MSKCC group (Safanov et al abstract 2021/22).
22. How do data on real-world experience compare with the trial data?	They are consistent
23. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why.	Germline BRCA1/2 mutation associated advanced breast cancer is more prevalent in young women within the BC community. These women are often young mothers and the time and economic impact of current multiple attendance therapy regimens for HER2-ve breast cancer which are often intravenous is very significant. These women are specifically disadvantaged by lack of access to this oral licensed therapy option associated with fewer hospital attendances, in my view.

More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the EAR, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

EMBRACA trial included a heterogeneous population • **Are there any groups of people with HER2-negative locally advanced or metastatic breast cancer with germline BRCA1/2-mutations that should be considered separately? For example, subgroups stratified by line of treatment, by hormone receptor status, or by both?**	I believe efficacy results should only be analysed in this way if one is seeking to see if the subgroup confidence interval excludes the ITT group point estimate of effect for the end point of interest. It should not seek evidence that Cis exclude the zero effect line. This is supported by many statistical experts and has been explained by Professor Jack Cuzick who I would recommend consulting in this matter. In EMBRACA I believe that there is no evidence that subgroup confidence interval excludes the ITT group point estimate of effect for the end points of interest. It believe therefore that the HR for treatment effects from the ITT population could in general be applied across subgroups. There is a rationale based on the ABRAZO trial and preclinical data

	that the HR effect may be less in patients previously treated with a platinum but I do not believe these data are of sufficient level of evidence weight to influence the assessment
Platinum chemotherapy is not included as a comparator • **Is platinum chemotherapy currently used for treating HER2-negative locally advanced or metastatic breast cancer with germline BRCA1/2-mutations in the NHS? And if so, for which patients?**	Yes it is based on the TNT trial cited. Please see comments above.
Is it appropriate to assume that the effectiveness of the individual EMBRACA trial physician's choice of treatment (PCT) arm drugs (including eribulin, capecitabine, vinorelbine and gemcitabine) have similar efficacy?	No but they are unlikely to be substantially different.
Prior treatments received by EMBRACA trial patients may not reflect prior treatments received by NHS patients • **Very few people, had CDK4/6 inhibitors (<6%),**	No with the possible exception of platinum. There is a rationale based on the ABRAZO trial and preclinical data that the HR effect may be less in patients previously treated with a platinum but I do not believe these data are of sufficient level of evidence weight to influence the assessment

immunotherapy (<1%) or platinum chemotherapy (<21%) before entering EMBRACA trial. Are these treatments currently used in the NHS? • **Is the treatment effect of talazoparib likely to differ because not many people had these treatments?**	
Interpretation of EMBRACA trial overall survival (OS) results is problematic • **Please comment on the OS results as reported by hormone receptor status or by line of therapy.** • **Should results by both hormone receptor status and line of therapy be also considered?**	I believe efficacy results should only be analysed in this way if one is seeking to see if the subgroup confidence interval excludes the ITT group point estimate of effect for the end point of interest. It should not seek evidence that Cis exclude the zero effect line. This is supported by many statistical experts and has been explained by Professor Jack Cuzick who I would recommend consulting in this matter. In EMBRACA I believe that there is no evidence that subgroup confidence interval excludes the ITT group point estimate of effect for the end points of interest.
Appropriateness of using EMBRACA trial intention-to-treat (ITT) data in the company model • **Is the treatment effect of talazoparib likely to differ by patient subgroups?**	I believe efficacy results should only be analysed in this way if one is seeking to see if the subgroup confidence interval excludes the ITT group point estimate of effect for the end point of interest. It should not seek evidence that Cis exclude the zero effect line. This is supported by many statistical experts and has been explained by Professor Jack Cuzick who I would recommend consulting in this matter.

For example, subgroups stratified by line of treatment, by hormone receptor status, or by both?	In EMBRACA I believe that there is no evidence that subgroup confidence interval excludes the ITT group point estimate of effect for the end points of interest.
EMBRACA trial talazoparib red blood cell (RBC) transfusion rates were not used in the model • **Which RBC transfusion rate (38.1% versus 8.3%) would reflect the clinical practice more closely?**	38.1%
The derivation of the relative dose intensity multipliers used in the model are not clearly described	
Are there any important issues that have been missed in the external assessment report (EAR)?	I am not sure that the patient benefit of the availability of a new oral therapy associated with fewer hospital visits and NHS chemotherapy day unit and phlebotomy and blood analysis impacts on both patients and the NHS has been assessed. I believe this technology has significant advantages here. I believe that NHS England funded testing now identifies this group of patients for whom there are licensed options with PARPi (Olaparib and Talazoparib) but these are currently unavailable despite advantages in PFS, QOL and NHS chemotherapy day unit impacts. This seems counterintuitive.

	I believe efficacy results should only be analysed in this way if one is seeking to see if the subgroup confidence interval excludes the ITT group point estimate of effect for the end point of interest. It should not seek evidence that Cis exclude the zero effect line. This is supported by many statistical experts and has been explained by Professor Jack Cuzick who I would recommend consulting in this matter. In EMBRACA I believe that there is no evidence that subgroup confidence interval excludes the ITT group point estimate of effect for the end points of interest.

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

The technology has level 1 evidence of clinically and statistically important improvements of important PFS and QOL endpoints in a relevant ITT population of genetic breast cancer patients identified by NHS England test directories.
Subgroup analyses in the key trial EMBRACA have confidence intervals that include the ITT population treatment effect are in my view are consistent with application of the HR of the ITT population across subgroups in the absence of level I from trials conducted specifically in those subgroups.
Platinum is a relevant treatment option after the use of which there may be effects on expectation of PARPi treatment effect but there is no level I breast cancer evidence to support this.
There may be for which there is no comparative data for platinums with the technology in the relevant population but this is because it was not a guideline indicated standard of care at the time the EMBRACA trial was designed.

New NICE approved standard of care do exist that can be used in the same population but I would expect the same HR for relevant endpoints for the technology to apply in the setting in which these therapies would also apply or after they have been applied. There are significant benefits to patients and to NHS resource use gained by the alternative use of an oral therapy requiring one Outpatient visit and phlebotomy session per 28 days compared to SOCs requiring multiple visits and use of intravenous therapy chemotherapy resources.

Thank you for your time.

Your privacy

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

☐ **Please tick this box** if you would like to receive information about other NICE topics.

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

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Talazoparib for treating HER2-negative locally advanced or metastatic breast cancer with germline BRCA1/2 -mutations (ID1342)

Clinical expert statement and technical engagement response form

Thank you for agreeing to comment on the external assessment report (EAR) for this evaluation, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The EAR and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR (section1). You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

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Clinical expert statement

NICE National Institute for Health and Care Excellence

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NICE National Institute for Health and Care Excellence

Part 1: Treating HER2-negative locally advanced or metastatic breast cancer with germline BRCA1/2 -mutations (including triple-negative breast cancer) and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Dr Jennifer Glendenning
2. Name of organisation	Kent Oncology centre
3. Job title or position	Consultant Clinical Oncologist, breast cancer
4. Are you (please tick all that apply)	☒ An employee or representative of a healthcare professional organisation that represents clinicians. ☐ A specialist in the treatment of people with HER2-negative locally advanced or metastatic breast cancer with germline BRCA1/2 -mutations ? ☐ A specialist in the clinical evidence base for HER2-negative locally advanced or metastatic breast cancer with germline BRCA1/2 -mutations or technology? ☒ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it (duplicated below) ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here.	☒ Yes

(If you tick this box, the rest of this form will be deleted after submission)	
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Nil
8. What is the main aim of treatment for **HER2-negative locally advanced or metastatic breast cancer with germline BRCA1/2 -mutations?** (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	To improve survival and quality of life in patients with metastatic Her2 negative germline BRCA1/2 positive breast cance
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Delaying time to progression using a therapy which maintains quality of life and function
10. In your view, is there an unmet need for patients and healthcare professionals in HER2-negative locally advanced or metastatic breast cancer with germline BRCA1/2 -mutations ?	Yes. Currently there are no BRCA specific treatments available for use in this cohort of patients with metastatic breast cancer
11. How is HER2-negative locally advanced or metastatic breast cancer with germline BRCA1/2 -mutations currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	ER+ Her2 negative BRCA metastatic breast cancer: Options comprise standardly available chemotherapy/endocrine therapy approaches. ER-, PR- Her2 negative BRCA metastatic breast cancer: Options comprise standardly available chemotherapy Approaches to management of metastatic ER+ HER2 negative and Triple negative breast cancer are well defined and in my experience, there is very little discordance in approach between professionals across the UK NICE CG81 provides UK advanced breast cancer management however this was last updated August 2017 so is somewhat outdated. For example, the guidance does not describe the place in ER+ve disease for CD4/6 inhibitors (where there is a mutation) PIK3CA inhibitor (alpelisib) and in TNBC the place of check point

	inhibitors for PDL1 positive disease and second line Sacituzumab govitecan. These agents are supported by NICE (TA816, TA819, TA836, TA801, TA725, TA639) and available in the UK via CDF funding. However none have specific role in the 5% of BRCA associated breast cancer. Germline mutations in breast cancer susceptibility genes 1 and 2 (BRCA1 and BRCA2) are present in around 5 percent of patients with metastatic breast cancer. PARP inhibitors have demonstrated single agent activity in BRCA associated metastatic breast cancer. FDA approval for Talazoparib based on the the EMBRACA trial data was secured in 2018. However absence of funding means currently clinicians are not able to offer this option to UK patients on the NHS.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	In line with the results from the EMBRACA trial talazoparib would be used in preference to current options (capecitabine, eribulin, gemcitabine, or vinorelbine chemotherapies) for gBRCAm HER2-negative locally advanced or metastatic breast cancer treated with no more than 3 lines of therapy including endocrine for ER+. Compared to current standard of care alternatives there will be no change in imaging monitoring procedures. Chemotherapy unit chair/nursing/pharmacy time will be reduced compared to intravenous chemotherapy comparators (eribulin, gemcitabine) Delivery of Talazoparib will be in secondary care specialist oncology metastatic breast cancer clinics and chemotherapy units. Funding for talazoparib will be required as this is not currently available on the NHS. Would not expect significant training investment as oral agent

	with very manageable side effect profile. Compared to the current standard of care alternatives there will be no change in imaging response procedures Chemotherapy unit chair/nursing/pharmacy time will be reduced compared to chemotherapy comparators (capecitabine, eribulin, gemcitabine, or vinorelbine) which may have capacity benefits for treatment units.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Yes. The phase 3 EMBRACA trial met its primary endpoint demonstrating a progression free survival advantage (median 8.6 versus 5.6 months; HR 0.54, 95% CI 0.41-0.71). The PFS benefit with talazoparib was seen across all predetermined patient subgroups (BRCA1, BRCA2, ER status, history of CNS metastasis, visceral disease, prior platinum treatment and number of prior lines of treatment). At 1 year 37% of patients in the talazoparib group compared to 20% in the standard therapy group were free from disease progression or death. Overall Survival (OS), evaluated as a secondary endpoint in the EMBRACA trial, was not significantly improved with talazoparib compared with chemotherapy (HR 0.848; 95% CI 0.670-1.073; P = 0.17). Adjusting for post-study treatment reduced the hazard ratio and lowered the upper bound of the confidence interval. The difference in median OS still did not reach statistical significance compared with chemotherapy in patients who received subsequent PARP inhibitor and/or platinum therapy (19.3 vs 17.4 months, respectively; HR, 0.756; 95% bootstrap CI, 0.503-1.029). However, these data suggest subsequent treatments may have impacted the OS results, potentially underestimating the talazoparib benefit. The 2021 Cochrane systematic review evaluating PARP inhibitors (PARPi) for locally advances metastatic breast cancer confirm that PARPi offer

	improvements in PFS. Pooled analysis from the 4 studies reporting overall survival (singe agent PARPi vs chemo in EMBRACA and OLYMPIAD; chemo-PARPi vs chemo in BROCADE 1 and 2) support overall survival (HR 0.87 (95% CI 0.760-1.00; p=0.05; high certainty evidence with no significant heterogeneity. The phase 3 EMBRACA trial demonstrated significant improvements in quality of life and compared to standard therapy resulted in significant delay in onset of clinically meaningful deterioration
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	This treatment is very specifically for the subset of metastatic breast cancer patients with germline mutations in breast cancer susceptibility genes 1 and 2 (BRCA1 and BRCA2). It is not being considered for the more general metastatic breast cancer population where it would be expected to be less efficacious
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	This oral agent will be easier for patient and health professional than standard of care chemotherapy options which consume greater pharmacy and day unit chair time than talazoparib which is an oral fixed dose agent
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Currently most patients diagnosed with TNBC (and all those under 60 years) will be offered testing for germline mutations in breast cancer susceptibility genes 1 and 2 (BRCA1 and BRCA2). There may be a subset of patients with ER+ Her2 negative breast cancer who don't currently qualify for testing and miss out of this agent if undetected underlying BRCA mutation. Considering the current technology appraisal

	AND the adjuvant Olaparib data they may be need to expand criteria for BRCA testing beyond the scope currently defined by NICE (CG164).
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	The emotional burden of BRCA mutation on patients and their families will likely be beneficially impacted by availability of treatment options more specific to their genetic susceptibility
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	Yes This technology specifically addresses the needs of the metastatic breast cancer subset who carry germline BRCA mutation
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The AE profile and QOL date from EMBRACA is extremely reassuring in this regard, clearly demonstrating significant clinical benefit to talazoparib and no increase in toxicity compared to physicians choice chemotherapy. Within this trial only 3.6% of patients discontinued treatment due to side effects supporting good tolerability with this agent.
20. Do the clinical trials on the technology reflect current UK clinical practice?	Yes, reflects current UK practice

• If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Given the lines of treatment options in the clinic for metastatic HER2 negative breast cancer choosing PFS rather than OS as the primary outcome measure was appropriate in the EMBRACA trial Surrogate outcomes were not used There are no unexpected adverse effects that have since come to light. Experience from their use in other settings for example ovarian cancer populations reassures that single agent PARPi are consistently well tolerated and manageable
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. How do data on real-world experience compare with the trial data?	Mahtani et al have published real world data reporting for 543 patents treated for BRCAm metastatic breast cancer using physician's choice across the spectrum of platinum and non-platinum containing chemotherapy, chemo- immunotherapy, PARPI monotherapy, endocrine based therapy Of the cohort n=79 received PARPi monotherapy using talazoparib or olaparib. The real-world study population were overall older and less likely to be PS0 than the phase 3 EMBRACA or OlympiAD study participants. Reassuringly the real world PARPI experience described less frequent AE rates than were seen in the EMBRACA study and high levels of physical satisfaction with PARPi treatment option and therefore complement the phase 3 data
23. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this	No

treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the EAR, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

EMBRACA trial included a heterogeneous population • **Are there any groups of people with HER2-negative locally advanced or metastatic breast cancer with germline BRCA1/2-mutations that should be considered separately? For example, subgroups stratified by line of treatment, by hormone receptor status, or by both?**	EMBRACA trial population were uniform defined by presence of gBRCA1/2 mutation and overwhelmingly metastatic disease. PFS benefit was demonstrated across clinically relevant subgroups defined by BRCA1 vs 2; hormone receptor status, CNS metastasis, and prior treatment lines.

Clinical expert statement

Platinum chemotherapy is not included as a comparator • **Is platinum chemotherapy currently used for treating HER2-negative locally advanced or metastatic breast cancer with germline BRCA1/2-mutations in the NHS? And if so, for which patients?**	In the context of BRCA mutation UK oncologists now generally use platinum in the adjuvant/neoadjuvant setting, adding carboplatin alongside the taxane component of sequential anthracycline- taxane based regimen. For TNBC irrespective of BRCA status carboplatin is incorporated into standard early breast cancer treatment and is specified where immunotherapy is used on the neoadjuvant setting (TA851). In the context of prior exposure carboplatin rechallenge would not be recommended at metastatic recurrence unless other options had been exhausted. Therefore specification of no preceding progression on carboplatin within the EMBRACA physicians choice comparator group is reflective of the UK practice at metastatic relapse. Within EMBRACA, 76 (17%) patients had received prior platinum including in the early breast cancer setting. Analysis relating to platinum sensitivity and prior platinum exposure is provided in the 2018 supplementary appendix. Sensitivity to platinum as assessed by duration of platinum free interval (>6/12, <6/12, no use) did not significantly influence effect of talazoparib treatment. Similarly prior use of platinum (>3 cycles, <3 cycles or none) did not influence treatment effect of talazoparib.
Is it appropriate to assume that the effectiveness of the individual EMBRACA trial physician's choice of treatment (PCT) arm drugs (including eribulin, capecitabine, vinorelbine and gemcitabine) have similar efficacy?	No specific data in gBRCA mutant breast cancer but in the EMBRACE trial eribulin conferred only very modest benefit over physicians choice options but sufficient to be adopted as a 3rd line option. Therefore these agents are all appropriate physicians choice options. Of the physician choice options eribulin and capecitabine were the most common agents (40% and 44% respectively) which is consistent with clinical practice. Sacituzumab govetican (Trodelvy) was not included in the PCT arm but since NICE approval is used for treating unresectable, triple-negative locally advanced or metastatic breast cancer in adults after 2 or more systemic therapies, at least 1 of which was for advanced disease. Available data does not suggest *BRCA* mutation status impacts efficacy (phase 3 ASCENT trial, PFS 4.6 months in *BRCA1/2* positive *vs.* 4.9 months in *BRCA1/2* negative)
Prior treatments received by EMBRACA trial patients may	How prior CDK4/6 inhibitor treatment would modify PARPi treatment effects remains unknown. However, for patients with germline BRCA mutation, PARP inhibitors remain a reasonable and

not reflect prior treatments received by NHS patients • **Very few people, had CDK4/6 inhibitors (<6%), immunotherapy (<1%) or platinum chemotherapy (<21%) before entering EMBRACA trial. Are these treatments currently used in the NHS?** • **Is the treatment effect of talazoparib likely to differ because not many people had these treatments?**	favoured second line alternative to chemotherapy beyond CDK4/6 inhibitors in the endocrine refractory setting (example review article summarising practical oncological approach to CDK4/6 inhibitor resistance https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10093251/). Immunotherapy is not applicable to ER+ve breast cancer (out side clinical trials). In TNBC immunotherapy has been a 1st line metastatic option for PDL1+ve relapse and more recently an option in the neoadjuvant setting for TNBC irrespective of PDL1 status (December 2022, NICE TA851). The available data does not suggest gBRCA1/2 carriers are more or less likely to carry PDL1 mutation than non carriers. In current UK practice platinum exposure for is likely to be higher and predominantly to have taken place within adjuvant/neoadjuvant settings. The available data does not suggest that historical prior platinum exposure is likely to impact talazoparib response. The EMBRACA trial protocol specifically excluded patients with objective disease progression on platinum. There is emerging data recognising somatic mutation reversal which may be a mechanism of resistance to platinum and PARPi in BRCAm tumour triggered by platinum or other DNA damaging agents which supports the chosen exclusion criteria and positioning of talazoparib ahead of platinum for gBRCA metasatic breast cancer.
Interpretation of EMBRACA trial overall survival (OS) results is problematic • **Please comment on the OS results as reported by hormone receptor status or by line of therapy.** • **Should results by both hormone receptor status and line of therapy be also considered?**	The phase 3 EMBRACA trial demonstrated significant improvements in quality of life and compared to standard therapy resulted in significant delay in onset of clinically meaningful deterioration. In the overall population talazoparib did not demonstrate OS benefit. Prespecifed OS subgroup analyses were consistent across TNBC, ER+ve, BRCA1 and BRCA2 subgroups. Subsequent treatment seems to be an important and clinically relevant confounder given the breadth of options available. Those receiving neither subsequent PARPi nor platinum demonstrated shorter OS and total treatment duration supporting the consideration of PARPi in metastatic BRCAm breast cancer..

Appropriateness of using EMBRACA trial intention-to-treat (ITT) data in the company model • **Is the treatment effect of talazoparib likely to differ by patient subgroups? For example, subgroups stratified by line of treatment, by hormone receptor status, or by both?**	Prespecified subgroup analyses suggests consistency of Talazoparib effect across TNBC, ER+ve, BRCA1 and BRCA2 subgroups. All patients were germline BRCAm and the practicalities of trial accrual in this niche subpopulation support the chosen ITT analyses.
EMBRACA trial talazoparib red blood cell (RBC) transfusion rates were not used in the model • **Which RBC transfusion rate (38.1% versus 8.3%) would reflect the clinical practice more closely?**	In UK practice transition would not be instigated unless Hb is 8g/dl or symptomatic anaemia and few patients with metastatic breast cancer have transfusions. This reflects the balance of transfusion risk and the paucity of evidence to support meaningful QOL benefit to higher threshold for instigating transfusion. Therefore 38.1 % transfusion rate feels high and level of 8.3% more reflective of day to day clinical practice. The EMBRACA trial protocol specified Hb levels for eligibility and resumption of talazoparib (Hb>9) which likely facilitated investigators to provide red blood cell transfusion at a higher haemoglobin level than recommended by current clinical practice and/or international clinical guidelines
The derivation of the relative dose intensity multipliers used in the model are not clearly described	
Are there any important issues that have been missed in the external assessment report (EAR)?	The gBRCA testing criteria are agreed at a national level and outlined in the NHSE national genomic test directory. All patients with TNBC under the age of 60 are eligible for testing. However there is very significant concern amongst breast oncologists that many women with ER

	positive HER2 negative breast ca will not qualify for testing based on current age/family history criteria (age ≤40 at diagnosis or family history supporting Manchester score of 15 or more. Thus a population with at least 4 involved Lymph nodes potentially already miss out on the option of adjuvant Olaparib (NICE approved TA886) and would also miss out on talazoparib in the metastatic setting even if this is approved through this appraisal process

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- For patients with BRCA associated metastatic breast cancer Talazoparib has demonstrated significant progression free survival benefit compared to standard therapy
- For patients with BRCA associated metastatic breast cancer Talazoparib has demonstrated significant improvements in quality of life and compared to standard therapy resulted in significant delay in onset of clinically meaningful deterioration
- Talazoparib benefits are seen in both triple negative and ER+ Her2 negative BRCAm subsets
- The Talazoparib AE profile and QOL data supports significant clinical benefit to talazoparib and no increase in toxicity compared to physicians choice chemotherapy

Click or tap here to enter text.

Click or tap here to enter text.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Talazoparib for treating HER2-negative locally advanced or metastatic breast cancer with germline BRCA1/2 -mutations (ID1342)

Patient expert statement and technical engagement response form

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments and feedback on the key issues below are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources. The external assessment report (EAR) and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking you about living with HER2-negative locally advanced or metastatic breast cancer with germline BRCA1/2 -mutations (including triple-negative breast cancer) or caring for a patient with HER2-negative locally advanced or metastatic breast cancer with germline BRCA1/2 -mutations (including triple-negative breast cancer). The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR (section 1).

A patient perspective could help either:

Patient expert statement

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise. We have given guidance on the issues in which we expect this to be the case and advice on what you could consider when giving your response.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

Patient expert statement

Please note, **part 1** can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

The deadline for your response is **5pm** on **<insert deadline>.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Part 1: Living with or caring for a patient with HER2-negative locally advanced or metastatic breast cancer with germline BRCA1/2 -mutations (including triple-negative breast cancer)

Table 1 About you, HER2-negative locally advanced or metastatic breast cancer with germline BRCA1/2 -mutations current treatments and equality

1. Your name	Helen Stewart
2. Are you (please tick all that apply)	X A patient with HER2-negative locally advanced or metastatic breast cancer with germline BRCA1/2 -mutations (including triple-negative breast cancer)? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with HER2-negative locally advanced or metastatic breast cancer with germline BRCA1/2 -mutations (including triple-negative breast cancer)?? ☐ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	MetUpUK
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement

	X I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	X I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference x I have not completed part 2 of the statement
6. What is your experience of living with HER2-negative locally advanced or metastatic breast cancer with germline BRCA1/2 -mutations (including triple-negative breast cancer)? **If you are a carer (for someone with HER2-negative locally advanced or metastatic breast cancer with germline BRCA1/2 -mutations) please share your experience of caring for them**	**MY DIAGNOSIS** I presented with a lump in my left breast in January 2020, aged 54, had a single mastectomy in February 2020 and was told that I had stage2 breast cancer (HR+/HER-) I had 6x sessions of EC chemotherapy starting in March 2020. Just before I started the chemotherapy I had bad sciatic pain, had a staging scan, and was then diagnosed with Stage 4 metastatic breast cancer with mets in my spine and also lung pleura. **MY TREATMENT** After the initial EC chemotherapy, I have been on a combination of Letrazole, Palbocicclib and Denosumab. I had a second mastectomy in 2021, for symmetry, and am currently considering removal of my ovaries sue to the higher risk of ovarian cancer. I have had CT/MRI scans every 6 months and so far have shown no sign of progression. **BRACA2** My younger sister, then aged 45, had been diagnosed with stage3 breast cancer 6

	weeks before me. We have a strong family history of breast cancer. Our mother had 3 primary breast cancer diagnoses, aged 40, 44 and 55. Our maternal grandmother died of stage4 breast cancer aged 60. Our maternal Grandmother died of stage4 breast cancer, I think in her 50's My sister and I have both been tested and have the BRACA2 gene mutation. We assume that it is from my maternal family history, although my mother was never tested and is now deceased. My maternal uncle also died of stage4 prostate cancer, and we assume he also inherited the BRACA2 gene mutation. The fact that I may have passed on the BRACA2 mutation to any of my 3 children is heartbreaking. One of my daughters has been tested, and is negative which was a huge relief to us all. My other two children have to decide whether to be tested, but the anxiety is overwhelming as the result of the test is lifechanging. I am aware that they could be diagnosed with breast cancer (or prostate cancer for my son) at an early age, they are currently 34,29 and 28 and it is causing me extreme anxiety that they too may have the BRACA2 mutation. I know that my mother suffered greatly when my sister and I found out about our BRACA2 mutation, she felt guilty and helpless that we were suffering. She died recently, aged 80 (having never developed metastases), knowing that I am likely to die at a much younger age that her. **THE EFFECTS OF STAGE4CANCER AND TREATMENT** Physically, I find that the present treatment is "doable". Although I do suffer with extreme fatigue for a few days in the 4 week cycle, also mouth ulcers, sores in my nose, back pain (due to the spine damage), hair thinning, hot sweats, extremely dry

	skin and nail problems. I am fortunate that I only have to attend the hospital for a 4weekly blood test and then 4weekly to collect my Palbo and have the denosumab injection. However, mentally, I find that the very fact that I have a life limiting condition with very limited treatment options has had a severe detrimental effect on my mental health and mental wellbeing. I find it difficult to plan any activities and events in the future, as i am unsure whether I will be well enough, on different (and more limiting) treatment. The knowledge that i will possibly not be around to see my children reach life events, such as marriage, children etc breaks my heart. Each routine scan causes me extreme anxiety (and also to my family) as I am very aware that there are limited lines of treatment available and my response to subsequent drugs may be poor.. When I have disease progression, and have chemotherapy as a treatment, my life will be severely affected as the frequency of hospital visits will increase, adverse effects to the treatment may increase, and quality of life will decrease. New drug lines are vital, my biggest hope is that there will be more available treatments in the near future, (particularly treatments specific to BRACA2 patients) to benefit my children and family members also affected by BRACA2 mutation, should they develop MBC.
7a. What do you think of the current treatments and care available for HER2-negative locally advanced or metastatic breast cancer with germline BRCA1/2 -mutations (including triple-negative breast cancer) on the NHS? **7b. How do your views on these current treatments**	

compare to those of other people that you may be aware of?	
8. If there are disadvantages for patients of current NHS treatments for HER2-negative locally advanced or metastatic breast cancer with germline BRCA1/2 -mutations (including triple-negative breast cancer). For example, how they are given or taken, side effects of treatment, and any others, please describe these.	The side effects to the current chemotherapy options can be brutal. I had severe fatigue, sickness, diarrhoea, vomiting, hair loss and nail loss. I also had to have daily injections after each does of chemo, had to attend hospital far more often. And I had a PICC line which severely restricted my ability to shower, swim, and do daily tasks. The IV infusion also meant that I was at the hospital half a day.
9a. If there are advantages of talazoparib over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does talazoparib help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	**I have not got experience of taking Talazoparib.** **But a daily tablet would be far preferable to chemotherapy**
10. If there are disadvantages of talazoparib over current treatments on the NHS please describe these. For example, are there any risks with talazoparib If you are concerned about any potential side effects you have heard about, please describe them and explain why	The only concern I would have is the risk of anaemia.
11. Are there any groups of patients who might benefit more from talazoparib or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other	\

health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	
12. Are there any potential equality issues that should be taken into account when considering HER2-negative locally advanced or metastatic breast cancer with germline BRCA1/2 -mutations (including triple-negative breast cancer) and talazoparib? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	

Part 2: Technical engagement questions for patient experts

Issues arising from technical engagement

The issues raised in the EAR are listed in table 2. We welcome your comments on the issues, but you do not have to provide a response to every issue, such as the ones that are technical, that is, cost effectiveness-related issues. We have added a comment to the issues where we consider a patient perspective would be most relevant and valuable. If you think an issue that is important to patients has been missed in the EAR, please let us know in the space provided at the end of this section.

For information: the patient organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR, the patient organisation responses will also be considered by the committee.

Table 2 Issues arising from technical engagement

EMBRACA trial included a heterogeneous population. • **Are there any groups of people with HER2-negative locally advanced or metastatic breast cancer with germline BRCA1/2-mutations that should be considered separately? For example, subgroups stratified by line of treatment, by hormone receptor status, or by both.**	

• **Is the treatment effect of talazoparib likely to differ by patient subgroups? For example, subgroups stratified by line of treatment, by hormone receptor status, or by both?** **We consider patient perspectives may particularly help to address this issue.**	
Platinum chemotherapy is not included as a comparator. • **Is platinum chemotherapy currently used for treating HER2-negative locally advanced or metastatic breast cancer with germline BRCA1/2-mutations (including triple-negative breast cancer) in the NHS? And if so, for which patients?** **We consider patient perspectives may particularly help to address this issue.**	
Is it appropriate to assume that the effectiveness of the individual EMBRACA trial	

physician choice treatment? (PCT) arm drugs have similar efficacy? • **Do you consider that eribulin, capecitabine, vinorelbine and gemcitabine are similarly good in treating HER2-negative locally advanced or metastatic breast cancer with germline BRCA1/2 -mutations (including triple-negative breast cancer)?** **We consider patient perspectives may particularly help to address this issue.**	
Prior treatments received by EMBRACA trial patients may not reflect prior treatments received by NHS patients • **Very few people, had CDK4/6 inhibitors (<6%), immunotherapy (<1%) or platinum chemotherapy (<21%) before entering EMBRACA trial. Are these treatments currently used in the NHS?** • **Is the treatment effect of talazoparib likely to differ**	

Patient expert statement

because not many people had these treatments? **We consider patient perspectives may particularly help to address this issue.**	
Interpretation of EMBRACA trial overall survival (OS) results is problematic	
Appropriateness of using EMBRACA trial intention-to-treat (ITT) data in the company model	
EMBRACA trial talazoparib red blood cell (RBC) transfusion rates were not used in the model • **Which RBC transfusion rate (38.1% versus 8.3%) would reflect the clinical practice more closely?** **We consider patient perspectives may particularly help to address this issue.**	
The derivation of the relative dose intensity multipliers used in the model are not clearly described	
Are there any important issues that have been missed in the	

Patient expert statement

external assessment report (EAR)?	

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- QOL would be much improved compared to chemotherapy, less side effects
- It is important to investigate new treatments that target specifically BRACA1/2
- QOL would be better as the treatment (daily tablets) is less intrusive than chemotherapy
- Fewer hospital appointments adds to increased QOL
- Click or tap here to enter text.

Thank you for your time.

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

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Single Technology Appraisal

Talazoparib for treating HER2-negative locally advanced or metastatic breast cancer with germline BRCA1/2 -mutations (ID1342)

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

The deadline for comments is **5pm** on **<insert deadline>**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we

received, and are not endorsed by NICE, its officers or advisory committees.

About you

Table 1 About you

Your name	LRiG
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	LRiG
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.] Please state the name of the company, amount, and purpose of funding.	**N/a**
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	**N/a**

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Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

We thank the EAG for their thoughtful interrogation of our submission and whilst we acknowledge there are some key areas of uncertainty, we wish to avoid creating inequity between subgroups of HER2- BC, without the trial being powered to do so. We do accept that there is uncertainty around platinum chemotherapy, red blood cell transfusion rates and dose intensity and we have attempted to adjust for these leading to revised ICERs of £30,586, £35,366 and £33,854 respectively, compared to our deterministic base-case of £27,316. Probabilistic scenario analysis was conducted to account for parameter uncertainty in the model, generating a probabilistic base-case ICER of £25,181 (Figure 4).

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response	EAG response
EMBRACA trial included a heterogeneous population	No	We also thank Breast Cancer Now, METUPUK and NCRI-ACP-RCP-RCR for their submissions in this appraisal. Breast Cancer Now have highlighted the unmet need for both TNBC and HR+/HER2-negative patients, as for TNBC patients, for many years chemotherapy was the mainstay of treatment and there have been significantly limited treatments for this group of patients. There is also an unmet need for the	The EAG notes subgroups have been used to inform NICE decision making in the past. Examples include technology appraisal (TA) 423,[1] TA515[2] and TA639.[3] In this appraisal, the EAG recognises that the EMBRACA trial ITT population matches the populations specified in the NICE scope and in the licensed indication. However, as detailed in the EAG report, according to the treatment

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		HR+/HER2- population for new and effective treatment options post CDK/46 inhibitor as patients become resistant to these treatments. Additionally, TNBC can be more aggressive and harder to treat than other types of breast cancer, resulting in potentially poorer outcomes and short prognoses, as described by Breast Cancer Now and METUPUK. The scope of the submission covers the ITT population as assessed in EMBRACA. As provided in the company clarification question response, the EMBRACA trial was designed with adequate power to detect 90% and 80% effect sizes for PFS and OS in the ITT population. Any analyses across subgroups would not be powered to detect significant differences, and therefore it is inappropriate to explore analyses of the data within sub-populations of the trial. We wish to avoid inequity in access of talazoparib by subgrouping the ITT population, given the unmet need and clinical benefit in PFS and HRQoL that talazoparib has demonstrated in	pathways presented by the company, some EMBRACA trial patients would not receive talazoparib in NHS clinical practice, i.e., patients with previously untreated HR+/HER2- aBC (see CS, Figure 1). These patients would receive talazoparib as a second- or third-line treatment, largely dependent on whether an anthracycline and/or taxane was received for early BC (second-line if yes, third-line if not). Given the improved PFS but not OS for patients treated with talazoparib versus PCT in the EMBRACA trial and given the heterogeneity of the EMBRACA trial population in terms of key characteristics (hormone receptor status **and** line of treatment), the EAG considers that subgroup data analysis results may improve understanding of ITT results. The EAG is concerned that for some subgroups, the OS hazard ratio numerically favours the talazoparib arm while the median OS favours the PCT arm. These results are challenging to interpret. One interpretation of median OS results is that OS is worse for some patient subgroups

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		EMBRACA.	treated with talazoparib than for the same patient subgroups treated with PCT. One interpretation of hazard ratio results is that OS is (numerically) worse for some patient subgroups treated with PCT than for the same patient subgroups treated with talazoparib. It is also likely that the EMBRACA trial ITT OS proportional hazards assumption is violated; the median favours one arm and the hazard ratio favours the other. This increases the complexity when interpreting ITT OS results. Hence, the EAG requested data at clarification for subgroups by hormone receptor status **and** line of treatment, including K-M data and the results of proportional hazards assessments. The EAG notes and welcomes the new evidence (K-M curves, description and possible interpretation of the data) provided by the company for the TNBC subgroup, albeit for all lines of treatment (see below).
Platinum chemotherapy is not included as a comparator	Yes	Whilst it is recognised that platinum chemotherapy is a relevant comparator for patients with BRCAm triple negative breast cancer (TNBC), there are several limitations	The EAG considers that running a scenario that includes platinum chemotherapy as a comparator for some patients is appropriate. However, the company has not provided any

Key issue	Does this response contain new evidence, data or analyses?	Response	EAG response
		associated with the inclusion of platinum chemotherapy in the economic model. As highlighted by the EAG, there are no trials directly comparing physician's choice of treatment (PCT) and platinum chemotherapy and therefore we have no common comparator. Additionally, there are huge trial population differences. 90% of patients in the TNT platinum chemotherapy trial had no known BRCA1/2 mutations, whereas 100% of patients in the EMBRACA trial had a BRCA1/2 mutation. Although we do not believe it is appropriate to compare platinum chemotherapy with talazoparib given the limitations, we have attempted to run a scenario including this comparator. In the absence of data, we have made the following assumptions: - Efficacy and safety of platinum chemotherapy is the same as PCT - 15% of patients receive platinum chemotherapy (TNBC patients only) - 90:10 split between carboplatin and	evidence to support the assumption that 15% of patients will be treated with platinum chemotherapy or why 15% is the upper bound. The company's positioning of talazoparib (CS, Figure 2) shows that single agent chemotherapy, preferably platinum-based, is a relevant comparator for patients with BRCAm TNBC who have been previously treated. Platinum chemotherapy is also a relevant comparator for patients who received immunotherapy in the first-line setting. In the EMBRACA trial, 44% of patients had TNBC and 71% of all patients in the trial had been previously treated with ≥1 prior antineoplastic therapy for aBC (CS, Table 14). If the EMBRACA trial population is representative of patients treated in NHS clinical practice, then these data suggest that 15% is an underestimate. Company cost effectiveness results demonstrate that including platinum chemotherapy in the model increases the size of the ICER per QALY gained; a more robust estimate of the proportion of NHS patients with TNBC who would receive platinum

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		cisplatin, - Administration costs including EDTA testing for carboplatin are included The base case ICER excluding platinum chemotherapy is £27,316, and the revised ICER including platinum chemotherapy is £30,586. Therefore, the impact on the ICER of including platinum chemotherapy is +£3,270, although we reiterate that we do not feel this is the most appropriate ICER on which to base decision making, and in practice we expect significantly fewer than 15% of patients to be platinum chemotherapy eligible.	chemotherapy is important for decision making.
Is it appropriate to assume that the effectiveness of the individual EMBRACA trial physician's choice of treatment (PCT) arm drugs have similar efficacy?	No	We acknowledge that there is a gap in the evidence base of trials comparing the efficacy of individual treatments in the PCT arm of EMBRACA, in patients with gBRCAm and advanced/metastatic breast cancer. Clinical advice received by the company is that it is reasonable to assume equivalent efficacy for all treatments in the PCT arm of EMBRACA in the economic model, in the absence of	The EAG agrees with the company. No additional comment

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		head-to-head data. However, clinical input to further validate this assumption in the committee meeting will be valuable.	
Prior treatments received by EMBRACA trial patients may not reflect prior treatments received by NHS patients	No	EMBRACA was a global trial which was initiated in 2013 and completed in 2021. Given the evolving treatment landscape for advanced/metastatic breast cancer patients, some prior treatments received by patients enrolled in EMBRACA are not reflective of treatments received in NHS clinical practice.	The EAG agrees with the company. No additional comment
Interpretation of EMBRACA trial overall survival (OS) results is problematic	No	The EAG highlights that, for the TNBC subgroup, the OS results require explanation, as median overall survival favours PCT, whilst the HR favours talazoparib (not statistically significant). The same trend is seen in the ITT population. Crossover in the OS K-M curves for TNBC patients occurs after month 9, and again at month 21, as shown in Figure 3. The hazard ratio and the median difference provide different contrasts of 2 time-to-event distributions, and a difference via the hazard ratio does not imply a difference in medians or vice versa. This difference is not	The EAG welcomes this new evidence. The presentation, description and a possible interpretation of OS K-M data were not previously provided by the company for this or any other subgroup. As the TNBC OS K-M curves show, and as the company/EAG describes, this new evidence illustrates that differences in the effectiveness of talazoparib versus PCT are challenging to interpret. The EAG highlights that the crossing of the TNBC OS K-M curves means that the hazard ratio may not be an appropriate measure of effect for OS for this subgroup. The EAG considers that the requested

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		explainable with the current evidence base, due to the smaller patient numbers and lack of statistical power to detect differences in OS in the TNBC subgroup, however the observed difference in median OS may be driven by subsequent treatments received by patients treated with PCT. Whilst we do understand that these results are challenging to interpret, we are reassured by the statistically significant PFS and Quality of Life results favouring talazoparib over PCT. Indeed, feedback from patients and clinicians is that PFS is a clinically meaningful outcome for advanced/metastatic breast cancer patients, and statistically significant improvement in PFS for talazoparib was observed in EMBRACA. As emphasised by Breast Cancer Now: *"As patients' time is limited, people tell us that quality of life is just as important to take into account as length of life, as this enables them to spend quality time with their loved ones."*	subgroup K-M curves requested at clarification (i.e., by hormone receptor status **and** line of treatment) may provide evidence to better understand the complexity.
Appropriateness of using EMBRACA trial	No	The scope of this submission is aligned with the population enrolled in EMBRACA, and	The EAG agrees that it is important to avoid inequity in access. However, if analyses

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intention-to-treat (ITT) data in the company model		includes HR+/HER2-negative and TNBC patients. Drawing conclusions about the efficacy and cost-effectiveness of talazoparib within subgroups would be inappropriate due to smaller and lack of statistical power in the trial. As discussed above, patient groups have highlighted the unmet need in both HR+/HER2-negative, and TNBC patient populations, and we wish to avoid inequity in access by subgrouping the EMBRACA population.	suggest that a new treatment is cost effective for a specific subgroup (or not) then it should be recommended (or not) for that subgroup.
EMBRACA trial talazoparib red blood cell (RBC) transfusion rates were not used in the model and the relationship between transfusion rates, dose modifications/reductions and efficacy is unknown	No	We received strong clinical advice that transfusion rates are far lower in the UK than seen in the trial (38.1%) and much closer to the US RWD rates of 8.3%. This is partly because of the difference in RBC transfusion thresholds between the EMBRACA threshold for transfusion (10 g/dL pre protocol amendment; 9 g/dL post protocol amendment) and UK/US guidelines for transfusion (7 g/dL), but also the decision to transfuse Is a clinical decision factoring in not just guidelines but also patient symptoms. However, we do understand the concerns	The EAG considers that as EMBRACA trial efficacy and HRQoL data for patients treated with talazoparib (and PCT) are dependent on trial RBC transfusion rates, the company model should be populated with RBC data from the EMBRACA trial. The EAG agrees with the company that there are concerns about using RW transfusion rates instead of trial rates and whether the lower transfusion rates seen in the RW (in the USA) would lead to (more dose interruptions and/or) different outcomes. A simple comparison of

Key issue	Does this response contain new evidence, data or analyses?	Response	EAG response
		about using RW transfusion rates instead of trial rates and the question as to whether lower transfusion rates seen in the RW (in the USA) would lead to (more dose interruptions and/or) different outcomes. The correlation between transfusion rates, dose modifications/reductions and efficacy observed in EMBRACA is unknown but we do welcome a Committee discussion and further clinical input on this assumption. The median PFS of talazoparib observed in the US real-world study was 8.7 months (95% CI 8.0-9.9)[1], which is consistent with EMBRACA in which median PFS for talazoparib was 8.6 months (95% CI 7.2-9.3), despite the higher transfusion rates noted above. Nonetheless, it is plausible that lower transfusion rates impact upon quality of life. Unfortunately, we do not have any data on the link between transfusion and utility and so we have explored the impact of modifying the utility of talazoparib to be equal to that of PCT (0.687), where the transfusion rate in EMBRACA was 6% (i.e. comparable to the	median PFS between the EMBRACA trial and a US RW study is insufficient to conclude that if the EMBRACA trial had lower RBC transfusion rates, the EMBRACA trial OS and PFS K-M data and utility values used to inform the company economic model would be unaffected. Decreasing RBC transfusion rates associated with treatment with talazoparib would likely lead to different patient utility values.

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		US RWD transfusion rate for talazoparib). Using the RW transfusion rate (8.3%) and reduced utility rate (0.687) for talazoparib results in a revised ICER is £35,366. We believe this is a pessimistic approach because quality of life is impacted by more than just the transfusion rate – however we hope this gives an upper bound to explore the uncertainty around more realistic transfusion rates. As above, we welcome the Committee and clinical input to explore the best way of accurately representing the true cost to the NHS of introducing talazoparib.	
The derivation of the relative dose intensity multipliers used in the model are not clearly described	Yes	Detailed dosing from EMBRACA have been provided to provide an accurate representation of actual doses received by patients. However, it is acknowledged that this may not accurately reflect the whole duration of the trial. Therefore, an updated model is provided with this response, in which it is assumed that 100% of patients receive the 1 mg dose of talazoparib, with a relative	Detailed dosing data have not been provided by the company. It remains unclear how the talazoparib RDI multiplier has been calculated. As the price of a 1mg dose of talazoparib is the same price as a 0.75mg dose, then if even part of the company RDI multiplier estimate represents a change in dose from 1mg to 0.75mg, then application of the company RDI multiplier will underestimate the cost of

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		dose intensity of 90.8% as observed in EMBRACA. The revised ICER is £33,854 (an increase of £6,538 compared to the deterministic base case ICER).	talazoparib. Until accurate dosing data are incorporated into the model, the EAG considers that all RDI multipliers should be excluded from drug cost estimates. The implementation of this adjustment in the company model was incorrectly applied.
Other issues identified by NICE technical team (not included in the EAR): **QALY multiplier – Please apply the multiplier to QALYs, not ICERs**	Yes	An updated model is provided with this response, with the 1.2 multiplier applied to incremental QALYs, rather than the ICER threshold. In the company base case, the incremental QALYs increase from [redacted] with the 1.2 severity modifier applied. Updated cost-effectiveness analysis results are presented in Table 5.	The EAG can confirm that the new company base case has been correctly calculated in terms of the application of the severity modifier. However, the EAG identified some errors/unexplained revisions to the company TE model. The EAG has made two corrections to the company TE model; it is possible that further errors/unexplained revisions may be present as costs do not match CS model costs. The ICERs per QALY gained generated following EAG revisions are provided in Table 5.

1. Zimmerman Savill, K. M., Ivanova, J., Asgarisabet, P., Falkenstein, A., Balanean, A., Niyazov, A., ... & Mahtani, R. L. (2023). Characteristics, Treatment, and Outcomes of Real-World Talazoparib-Treated Patients With Germline BRCA-Mutated Advanced HER2-Negative Breast Cancer. The Oncologist, oyad021.

Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

Table 3 Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response	EAG response
Additional issue 1: KM treatment duration	Section 6.4 of EAG report	Yes	As the EMBRACA trial time to treatment discontinuation (TTD) K-M data are not complete at the end of 5 years (PCT: no patients still on treatment; talazoparib: 4.4% of patients may still be receiving treatment), parametric survival curves have been fitted to the trial TTD KM data to align with PFS approach and to estimate the costs of talazoparib more accurately. AIC and BIC for the talazoparib and PCT extrapolations are presented in Figure 1 and Figure 2 respectively. The AIC and BIC values are presented in Table 4. Based on AIC/BIC values, the generalised gamma distribution is a good fit to the talazoparib and PCT data. However, based on visual inspection, it may be more appropriate to use the lognormal distribution for the PCT arm.	As TTD K-M data from the EMBRACA trial are complete for the SoC arm, there is no need to fit a parametric survival curve. All the talazoparib TTD curves fitted by the company appear to be very poor visual fits to EMBRACA trial talazoparib TTD K-M data; the EAG considers it is, therefore, more appropriate to use talazoparib TTD K-M data directly in the model.

Table 4. AIC/BIC and ICERs for parametric survival curves fitted to KM data for treatment duration

	Talazoparib		PCT	
Distribution	AIC	BIC	AIC	BIC
Exponential	1482.1	1485.759	595.8143	598.7842
GenGamma	**1418.825**	**1429.803**	**547.0365**	**555.9459**
Gompertz	1484.099	1491.418	591.1438	597.0834
Log-normal	1422.72	1430.039	551.9063	557.8459
Weibull	1469.265	1476.584	574.7606	580.7003

Figure 1. Parametric distributions fitted to Kaplan-Meier treatment duration for talazoparib

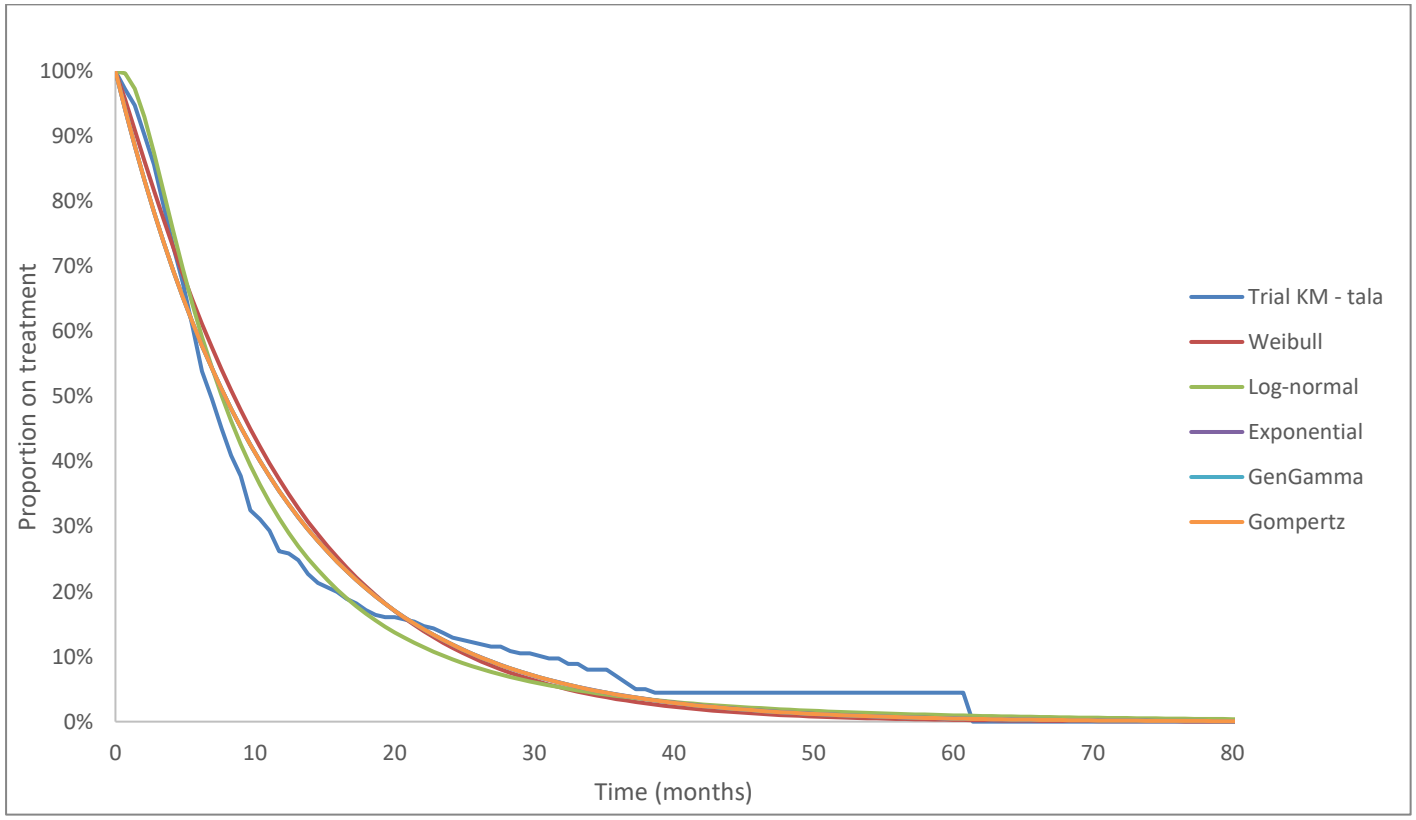


Figure 2. Parametric distributions fitted to Kaplan-Meier treatment duration for PCT

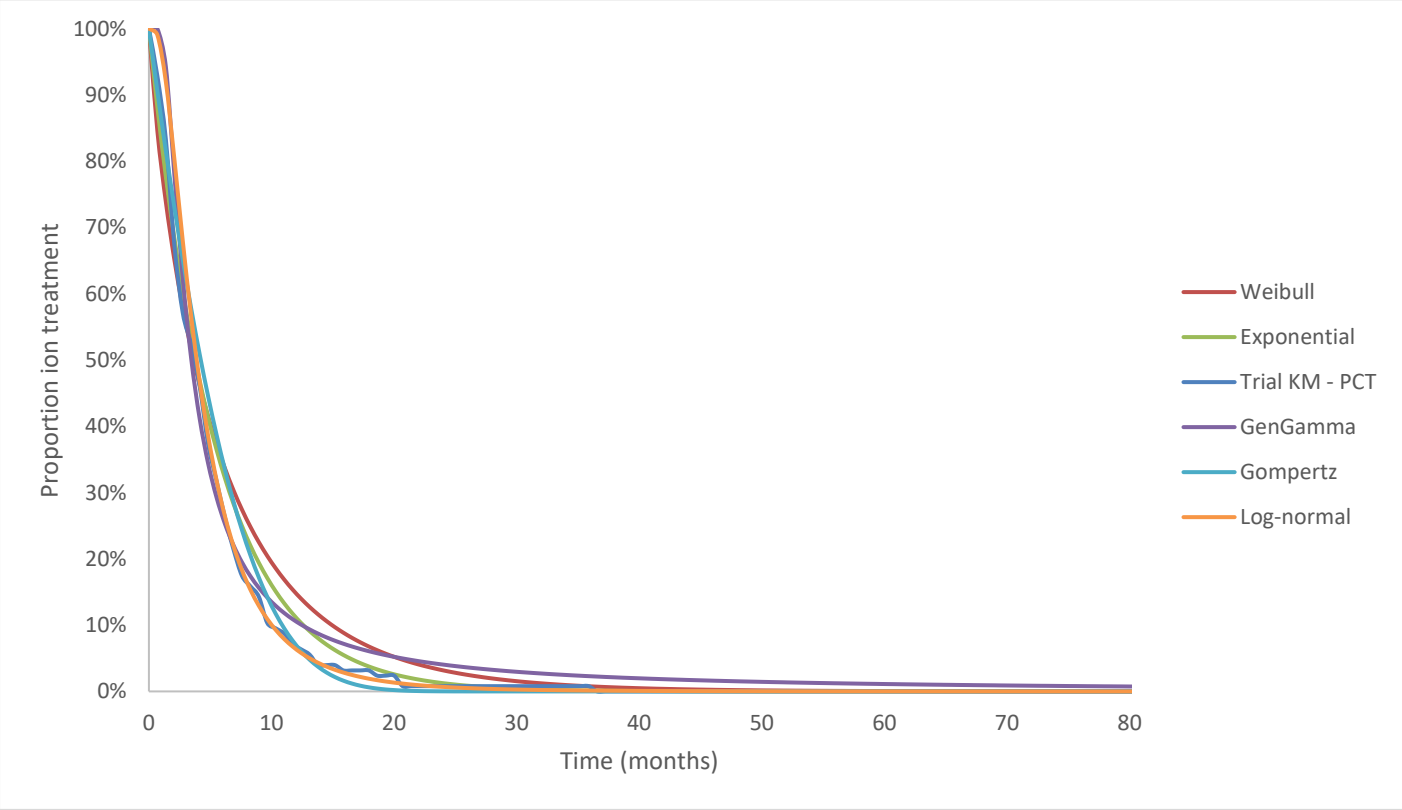
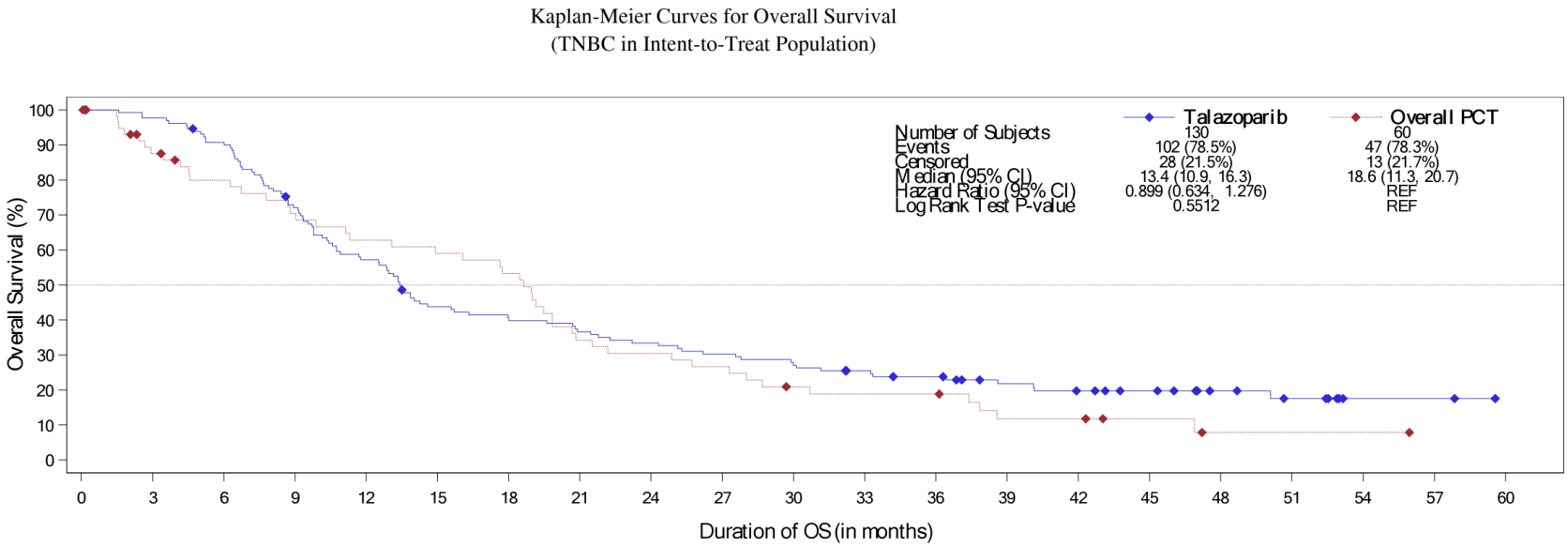


Figure 3. Kaplan-Meier curve for Overall Survival in TNBC



Talazoparib: Evt/Cum.	0/0	3/3	9/12	24/36	19/55	17/72	4/76	5/81	4/85	4/89	4/93	2/95	2/97	2/99	2/101	0/101	0/101	1/102	0/102	0/102	0/102
Patients at Risk	130	127	117	92	73	55	51	46	42	38	34	30	27	21	18	15	10	7	2	2	0
Overall PCT: Evt/Cum.	0/0	7/7	4/11	5/16	4/20	2/22	3/25	10/35	2/37	2/39	3/42	1/43	0/43	3/46	0/46	0/46	1/47	0/47	0/47	0/47	0/47
Patients at Risk	60	48	42	37	33	31	28	18	16	14	10	9	9	5	5	3	1	1	1	0	0

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base

Technical engagement response form

Talazoparib for treating HER2-negative locally advanced or metastatic breast cancer with germline BRCA1/2 -mutations (ID1342)

case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

The revised base case ICER, when the severity modifier is applied to incremental QALYs, is £27,316. Scenario analyses based on the key issues identified by the EAG are presented in Table 5.Table 5 Changes to the company's cost-effectiveness estimate

Table 5 Changes to the company's cost-effectiveness estimate

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)	EAG corrected results
Additional issue identified by NICE	Severity modifier applied to WTP threshold	Severity modifier applied to incremental QALYs	The incremental QALYs increase from [redacted] with the severity modifier of 1.2 applied. The revised base case ICER is **£27,316.**	Corrected company base case ICER: **£29,383** • RDI set to original value in CS model • resource use in PFS health state in line with CS model • some eMIT prices updated
Key issue 2	Platinum chemotherapy is not included as a comparator	Platinum chemotherapy is included within the basket of comparators for TNBC patients (15% of all patients)	£30,586 (+£3,270)	£32,615 (+£3,233)

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)	EAG corrected results
Key issue 7	RBC transfusion rate from US RWD, which is expected to be more reflective of transfusion rates in UK clinical practice	Scenario analysis presented exploring the impact of lower transfusion rates on utility, in which the utility of talazoparib is assumed to be equal to PCT (0.687).	£35,366 (+£8,050)	£38,043 (+£8,660)
Key issue 8	The derivation of the relative dose intensity multipliers used in the model are not clearly described	Relative dose intensity of 90.8% as observed in EMBRACA	£33,854 (+£6,538)	£30,110 (+£727)

Probabilistic sensitivity analyses around the revised base case are presented in Figure 1Figure 4 below. The base case probabilistic ICER for talazoparib compared to PCT is £25,181.

Figure 4. Probabilistic sensitivity analyses