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

For public observers– fully redacted

Process: STA 2022

Technology appraisal committee A - 11 October 2022

Chair: Jane Adam

Lead team: Craig Buckley, Alan Thomas

External assessment group: Bristol TAG (The University of Bristol)

Technical team: Tom Jarratt, Zoe Charles, Janet Robertson

Company: AstraZeneca

NICE

Background on early-stage breast cancer (eBC)

This appraisal covers patients with high risk BRCA positive HER2 negative early disease

Epidemiology

- Around 55,000 new breast cancer cases annually, around 80-90% at an early stage

Genetic predisposition to breast cancer

- Up to 5% of BC patients carry a germline mutation for BRCA1 or BRCA2 gene. These may run in families and confer an increased risk of developing breast cancer and more aggressive disease

Diagnosis and classification

- In eBC the cancer is confined to the breast tissue or nearby lymph nodes
- eBC is classified by hormone receptor (HR; oestrogen or progesterone receptors) and human epidermal growth factor receptor 2 (HER2) biomarker status, which affect treatment and prognosis
- Testing negative for either/both of these is indicative of more aggressive disease

Prognostic factors

- Triple negative breast cancer (TNBC), when a person is negative on all three tests, has a worse prognosis than hormone receptor-positive breast cancers

Patient perspectives

Aggressive nature and heritability of this form of cancer can be particularly distressing for people

Submission from Breast Cancer Now

- People with BRCA mutations have fears surrounding the aggressive nature of their cancer and whether their children or other family members also carry the mutation
- It is important that there is a discussion about who is defined as 'high-risk' so it is clear who may be eligible for this treatment option
- There is a need for more effective adjuvant treatments. There has been little progress made on the treatments available on the NHS for TNBC
- A new treatment which could help reduce the risk of recurrence and increase the 'rate of cure' could have a significant impact on quality of life

"It (olaparib) definitely has a big positive mental impact – I feel better knowing I'm having a treatment which shows positive survival"

"my family may [...] be at significantly increased risk of developing these types of cancer and felt guilty for bringing this possibility into their lives"

Clinical perspectives

Limited treatment options available for a particularly high-risk type of breast cancer with relatively poorer prognosis

Submission from NCRI-ACP-RCP-RCR

- Outcomes for this high-risk patient group remain poor, with a 3-year invasive disease-free survival of 77.1% in the control group of the OlympiA study
- There are currently no targeted therapies for TNBC
- Improvement in invasive disease-free survival of 8.8% at 3 years in olaparib arm in OlympiA represents a statistically and clinically significant treatment response, in an area with poor prognosis and limited options
- Adjuvant olaparib in these high-risk patients has been shown to significantly improve outcomes without significantly impacting quality of life, with a manageable toxicity profile

Key issues

Key issues focus on maturity of data and measures of health-related quality of life (HRQoL)

Table 2 Key issues

No.	Issue	ICER impact
1	Immature trial data and need to extrapolate	Unknown
2	Risk of bias for HRQoL data	Unknown
3	HRQoL measures used in the economic model	Increases ICER in EAG base-case
4	Access to BCRA testing in HR+/HER2- population	Increases ICER in EAG base-case

Olaparib

Question: are people who have had both neoadjuvant and adjuvant therapy excluded?

Table 3 Technology details

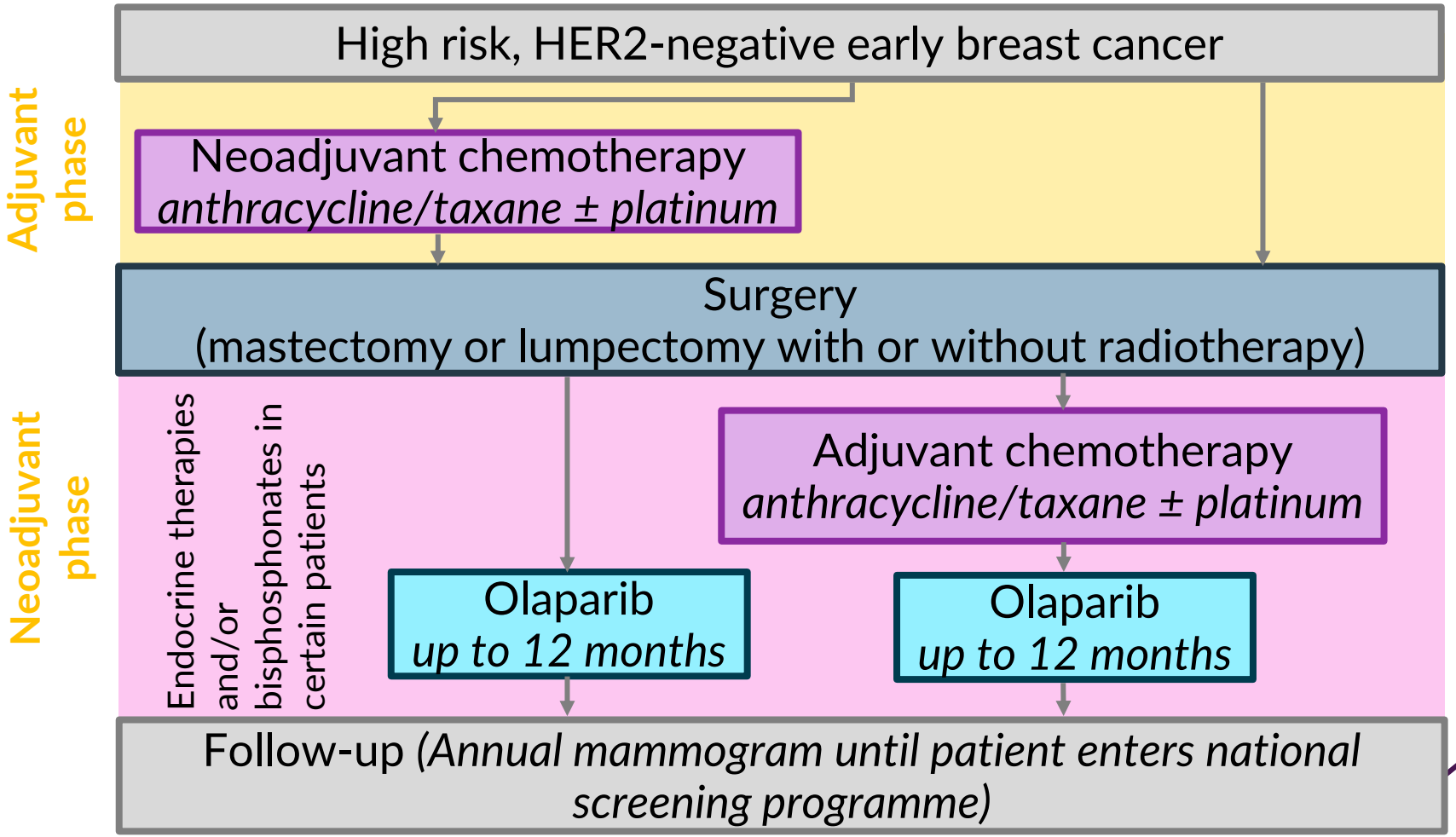
Marketing authorisation – Granted September 2022	• Monotherapy or in combination with endocrine therapy for adjuvant treatment of adult patients with germline BRCA1/2-mutations who have HER2-negative, high risk eBC previously treated with neoadjuvant or adjuvant chemotherapy
Mechanism of action	• Poly-ADP-ribose polymerase (PARP) inhibitor which inhibits PARP proteins involved in DNA repair
Administration	• Orally: 2 x 150mg tablets daily for a maximum of 12 months, or until radiological disease recurrence or unacceptable toxicity
Price	• List price: £2,317.50 (56 x 150mg tablets) • Confidential discount applicable

Abbreviations: eBC, early breast cancer

Treatment pathway

Proposed positioning of olaparib: after neoadjuvant/adjuvant chemotherapy where established practice is “watch and wait” (routine monitoring for disease recurrence)

Figure 1 Treatment pathway



No NICE guidance for adjuvant treatments in HER2- BRCA+ eBC
Due Nov 22: Pembrolizumab with chemo for neoadjuvant & adjuvant treatment: early & locally advanced non-met TNBC (unspecified BRCA)

Model also includes treatments which patients may receive following local or metastatic recurrence

Abbreviations: eBC, early breast cancer

Decision problem

Population includes early-stage, BRCA+ HER2- disease at high risk of recurrence in line with marketing authorisation

Table 4 Population, intervention, comparators and outcomes from scope

	Final scope	Company	EAG comments
Population	BRCA1- or BRCA2-positive, HER2-negative, high risk eBC that has been treated with surgery and neoadjuvant or adjuvant chemotherapy	As per NICE scope but specifies 'germline BCRAm' *Reflects marketing authorisation*	In line with scope. There is variation in how "high risk" can be defined: approach taken by company is appropriate
Comparator	Established clinical management without olaparib	Established practice is "watch and wait"	Agree
Outcomes	• Invasive disease-free survival (iDFS) • Distant disease-free survival (dDFS) • Overall survival (OS) • Adverse events • HRQoL	As in scope	Agree

Clinical effectiveness

NICE National Institute for Health and Care Excellence

Key clinical trial: OlympiA

EAG: Appropriate trial design and broadly reflective of clinical practice in England

Table 5 Clinical trial design and outcomes

	OlympiA
Design	Phase 3 randomised double blinded placebo-controlled trial
Population	High-risk HER2-, germline BRCAm eBC who have completed definitive local treatment and adjuvant **or** neoadjuvant **chemotherapy**
Intervention	Olaparib 300 mg (2 x 150 mg tablets) twice daily
Comparator(s)	Placebo tablets twice daily
Duration	Median 3.5 years follow-up
Primary outcome	Invasive disease-free survival
Key secondary outcomes	Overall survival; distant disease-free survival; HRQoL; safety and tolerability
Locations	Worldwide including 22 UK sites
Used in model?	Yes

Abbreviations: eBC, early-stage breast cancer, BRCAm, BCRA mutated; HRQoL, health-related quality of life.

Definition of high-risk in OlympiA

EAG: High-risk disease is defined appropriately

Table 6 Definition of high risk by chemotherapy type and HR/HER2 biomarker status

Chemotherapy	Subgroup	Criteria
Adjuvant	TNBC	axillary node-positive (any tumour size) or axillary node-negative with invasive primary tumour pathological size >2 cm
Adjuvant	HR+/HER2-	≥4 pathologically confirmed positive lymph nodes
Neoadjuvant	TNBC	residual invasive cancer in the breast and/or resected lymph nodes (non pCR)
Neoadjuvant	HR+/HER2-	residual invasive cancer in the breast and/or the resected lymph nodes (non pCR) and a CPS&EG score ≥3

EAG comments	Expert comments
• OlympiA results are generalisable to UK population • More had TNBC (n=1,511) than HR+/HER2- (n=325)	• HR+/HER2- patients in OlympiA were selected as high risk of relapse (**comparable risk to TNBC**)

OlympiA results

Olaparib improves iDFS, dDFS and OS in the ITT population but a large % in both arms were still alive and disease free at 4 years

Table 7 OlympiA efficacy results at DCO2 (12 July 2021)

Outcome		Olaparib (n=921)	Placebo (n=915)	Hazard ratio (95% CI)
iDFS	Events	[redacted]	[redacted]	0.63 (0.50 to 0.78)
	Disease-free	1 Year: [redacted] 4 years: 82.7%	1 Year: [redacted] 4 years: 75.4%	
dDFS	Events	[redacted]	[redacted]	0.61 (0.48 to 0.77)
	Disease-free	1 Year: [redacted] 4 years: 86.5%	1 Year: [redacted] 4 years: 79.1%	
OS	Events	8.1%	11.9%	0.68 [redacted]
	Alive	1 Year: [redacted] 4 years: 89.8%	1 Year: [redacted] 4 years: 86.4%	

- Median duration follow-up in olaparib arm: [redacted]
- Median time-to-event not met for any effectiveness outcome

EAG: interpret hazard ratios with caution as proportional hazards assumption not held

Abbreviations: ITT, intention to treat; CI, confidence interval; DC02, data cut-off 2; iDFS, invasive disease free survival; dDFS, distant disease free survival; OS, overall survival

OlympiA subgroup results

Data for HR+/HER2- subgroup are too immature to provide reliable estimates

Background: Most patients had TNBC (olaparib: 81.8%; placebo: 82.8%). Patients with HR+ eBC not enrolled until a late protocol amendment

Table 8 OlympiA subgroup results for iDFS

	Subgroup	Hazard ratio (95% CI)
HR status	HR+/HER2- ([redacted])	[redacted]
	TNBC ([redacted])	[redacted]
Prior chemotherapy	Adjuvant [redacted])	[redacted]
	Neoadjuvant ([redacted])	[redacted]
Prior use of platinum-based therapy	Yes ([redacted])	[redacted]
	No ([redacted])	[redacted]

Company: iDFS benefit consistent across subgroups as shown by lack of statistical evidence of heterogeneity between subgroups and ITT iDFS treatment effect

Adverse events (AEs)

Similar rate of serious AEs but more grade ≥3 AEs and AEs leading to dose interruption/reduction with olaparib

Table 9 Summary of safety analyses for DCO2

Adverse events*	Olaparib (n= 911)	Placebo (n= 904)
Any AE	[redacted]	[redacted]
Any grade ≥3 AE	[redacted]	[redacted]
Serious AE	[redacted]	[redacted]
Dose interruptions due to AE	[redacted]	[redacted]
Dose reductions due to AE	[redacted]	[redacted]
Discontinuations due to AE	[redacted]	[redacted]

*Patients with multiple events counted only once

EAG comments

- Limited inclusion in model (only grade ≥3 in ≥2% of patients: anaemia & neutropenia)
- Potentially serious but rare AEs may not have been identified

Abbreviations: DC02, data cut-off 2

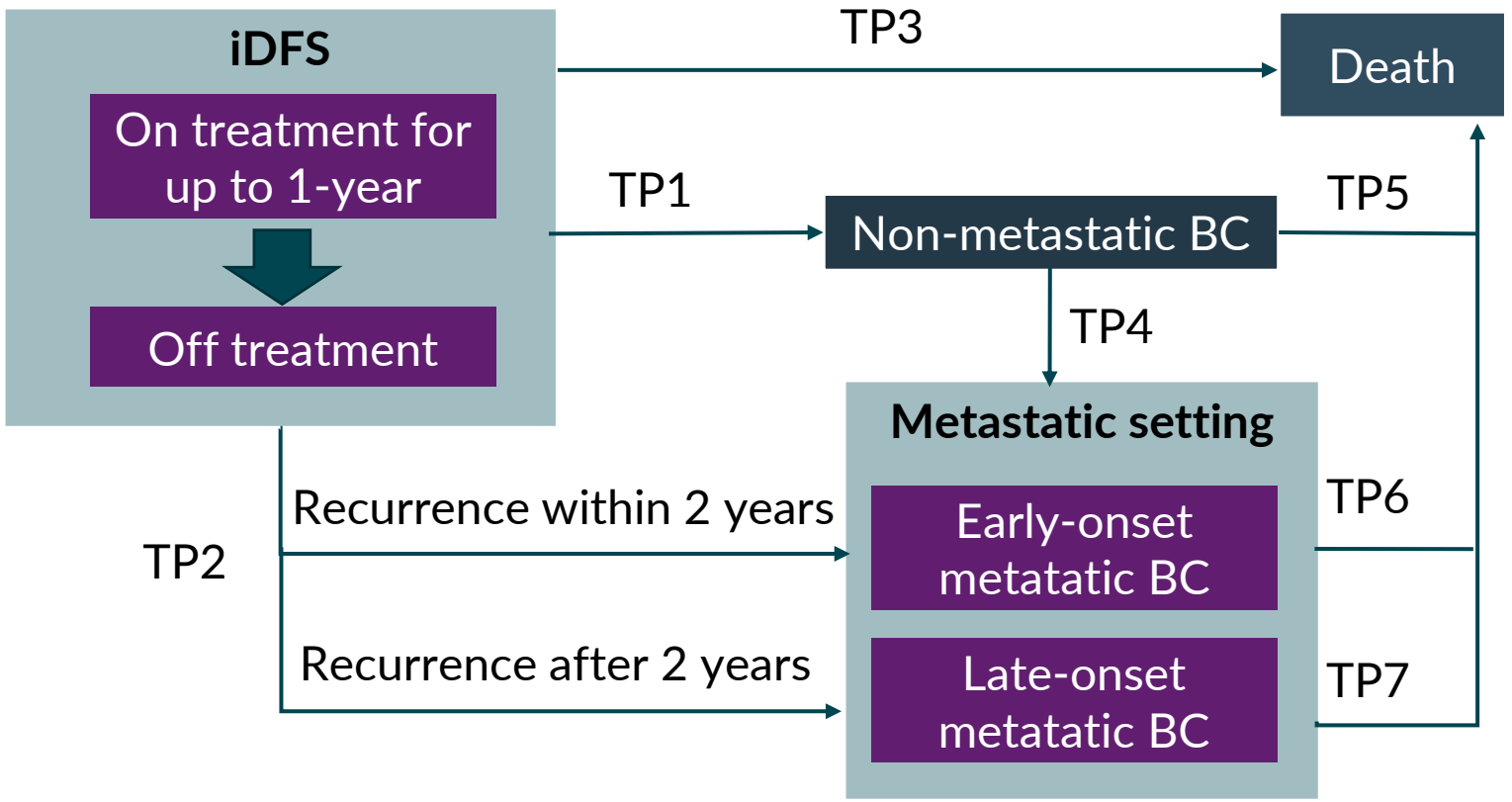
Cost effectiveness

NICE National Institute for Health and Care Excellence

Company's model structure

EAG: High-quality model largely aligned with NICE methods for economic evaluation

Figure 2 5-state semi-Markov model structure (same for TNBC and HR+/HER2-)



Technology affects **costs** by:

- Drug and administration costs
- Reducing need for subsequent treatments and end-of-life costs
- Costs of treating AEs

Technology affects **QALYs** by:

- Reducing recurrences and mortality
- Causing adverse events

Assumptions with greatest ICER effect:

- BRCA testing costs in HR+/HER2-
- Varying utility values
- Recurrence distribution (TP1/2)
- Time point when no longer at risk of recurrence

Abbreviations: BC, breast cancer; TP, transition probability; iDFS, invasive disease-free survival

Key issue 1: Immaturity of trial data and need to extrapolate

Background

- Median follow-up in OlympiA 3.5 years, Only [redacted] experienced an iDFS event
- HR+/HER2- group is smaller so there is higher uncertainty: company used full ITT results from OlympiA as a proxy to account for this (TNBC subgroup data used to model TNBC group)
- Company & EAG make different assumptions based on expert advice & published literature

Company

- Assumes zero risk of recurrence after 5 years in TNBC population
- Risk of recurrence: lognormal for both TNBC and HR+/HER2- groups
- Risk of death following early metastatic recurrence: exponential in both groups

EAG comments

- Assumes 5% risk of recurrence 5 - 15 years in TNBC population
- Risk of recurrence: generalised gamma for HR+/HER2- group instead of lognormal
- Risk of death following early metastatic recurrence: Gompertz, both groups instead of exponential

Clinical and patient experts

- Limited number of events expected due to relatively good prognosis (60-70% 5-year survival)
- No meaningful difference between company and EAG approaches for extrapolation

Survival models (1)

Different assumptions for **recurrence** have a moderate impact on ICER

Figure 3 iDFS extrapolation curves for **TNBC (left)** and **HR+/HER2- (right)**

Company: lognormal: risk of death equal at 14.5 yrs

EAG: gen. gamma more conservative for HR+/HER2- & gives smallest difference in long-term iDFS: risk of death equal at 5.4 yrs

Company assumes 0% recurrence risk after 5 years in TNBC **EAG** assumes 5% over subsequent 10 years

Clinical experts: risk in TNBC very low after 5 years, estimates 2-3% in years 5-8, 0% after

Which distribution is most plausible? Is recurrence in TNBC likely after 5 years?

Survival models (2)

Different distributions for early onset met. disease to death, smaller impact on ICER

Figure 4 early metastatic recurrence to death extrapolation curve (TNBC and HR+/HER2-)

[redacted]

Company uses **exponential**

EAG: exponential not appropriate when proportional hazards assumption violated: **Gompertz** is suitable, gives plausible survival difference between arms and is more conservative given long-term uncertainty

Which survival distribution after early metastatic recurrence is most appropriate?

Key issues 2 and 3: Utility values (1)

Background

- OlympiA used EORTC QLQ-C30 HRQoL questionnaires. Response rates [redacted] after baseline [redacted] to [redacted] at 6 and 12 months, [redacted] at 18 months, and [redacted] at 24 months
- Company **maps** these responses onto EQ-5D-3L to provide utility values
- Utility values needed for 3 health states: disease-free (DF), non-metastatic BC (non-mBC) and metastatic BC (mBC)

Company base-case

- Crott & Briggs (2010) algorithm used to map utility values for DF state; non-mBC assumed the same as DF mapped value (actual value was lower than DF but non-significant)
- Response rates are in line with clinical trials in this setting
- Different mapping algorithms do not substantially impact ICER (e.g. Gray 2021 algorithm increases base case ICER by approx £3,000 (DF utility value 0.815)

Abbreviations: HRQoL, Health-related quality of life

Key issues 2 and 3: Utility values (2)

EAG base-case

- Although missing data from HRQoL is common in clinical trials, it poses a risk of bias
- Mapping algorithms were developed mostly in HER2+ populations, older algorithms have been shown to be biased and newer ones insufficiently tested
- Uses EQ-5D utility values from external UK study (Verrill 2020) instead of mapping: **increases ICER by >£7,000 and >£10,000 per QALY in TNBC & HR+/HER2- respectively**
- Uses the midpoint between DF and mBC as utility value for non-mBC – small ICER impact

Clinical and patient expert comments

- Verrill relates to very different patient group so may not be appropriate for comparison
- Key QoL decrement is with mBC, reasonable to treat non-mBC the same as DF
- EORTC QLQ-C30 is a reliable and valid measure: results showed no difference in QoL between arms

Abbreviations: HRQoL, Health-related quality of life

Key issues 3: Utility values (3)

Source of HRQoL evidence has substantial impact on ICER

Table 10 Company and EAG utility values

Health state	Company base case	Source	EAG base case	Source	EAG age-adjusted
DF	0.869	OlympiA mapped	0.732	Verrill et al 2020	0.7695
Non-mBC	0.869	Same as DF	0.667	DF-mBC midpoint	0.7017
mBC	0.685	Lidgren 2007	0.603	Verrill et al 2020	0.6339

Verrill 2020:
- UK study
- EQ-5D
- HER2+
- 108 early BC
- 102 mBC

Company TE response
- DF value of 0.732 lacks face validity: should not be much lower than age-matched UK general population value for women (0.877), and not consistent with values accepted in previous high-risk eBC and mBC appraisals
- Verrill population older (55 vs. 43 in OlympiA) with HER2+ disease & unknown BRCA and risk status

EAG TE response
- Sensitivity analysis increasing EAG's values proportionally for age reduces ICER by £2,000-£3,000 (represents best-case scenario as HER2+ population will be healthier)

Which utility values are most appropriate?

Abbreviations: DF, disease-free; mBC, metastatic breast cancer; ICER, incremental cost-effectiveness ratio

Key issues 4: Access to BRCA testing (1)

Background
- Company assumes all patients receive routine BRCA testing
- BRCA testing costs therefore not included in company base-case

EAG comments
- Testing likely to become widely available for TNBC soon
- Unclear if this will happen for HR+/HER2- group: **including BRCA costs increases ICER by £7,000**

Expert comments
- Testing is routinely available for TNBC patients (National Genomic Test Directory)
- NICE recommends testing HR+/HER2- if combined BRCA1+2 mutation probability is ≥10% (CG164)
- Ongoing research into rapid testing for all BC patients is likely to increase future testing
- Other benefits to testing include tailoring surgery and risk reduction strategies for affected relatives

NHSE Genomics unit
- Testing is not yet routinely available for all patients potentially eligible for olaparib
- Testing for patients who do not fulfil NGTD criteria would be additional costs for NHS
- TNBC: pilot underway will allow for testing at any age and any point in pathway
- Suggests testing costs should be included for HR+/HER2- patients, and for TNBC patients aged over 60 while testing is at pilot stage

Abbreviations: BC, breast cancer, HRQoL, Health-related quality of life; NGTD, National Genomic Test Directory

Key issues 4: Access to BRCA testing (2)

Company TE response

Most high-risk HR+/HER2- patients in OlympiA meet eligibility criteria for testing:

Table 11 NGTD testing criteria

NGTD testing criteria	HR+/HER2- OlympiA characteristics
Breast cancer (<40 years, excluding grade 1 breast cancers)	Median age [redacted] years, [redacted] < 40
Bilateral breast cancer (age <50 years)	[redacted] had bilateral disease
Male breast cancer (any age)	[redacted] of patients were male
Breast cancer (<45 years) + first degree relative with breast cancer (<45 years)	[redacted] had first degree relative <50 years of age with breast cancer
Pathology-adjusted Manchester score ≥15 or CanRisk score ≥10%	Not recorded
Ashkenazi Jewish ancestry and breast cancer at any age	[redacted]

EAG response

- Unclear how many people in HR+/HER2- group would be eligible without knowing overlap in categories

How routine is BRCA testing? Should testing costs be included in model?

Abbreviations: HRQoL, Health-related quality of life; NGTD, National Genomic Test Directory

Other considerations (1)

Discount rates

- **Company** makes case for 1.5% discount rate for TNBC population, instead of 3.5%
- **EAG**: trial data are too immature to ensure criteria 2 and 3 are met, particularly the latter

Criteria required by NICE	Company comments
1. technology is for people who would otherwise die or have a very severely impaired life	Those with metastatic recurrence have low 5-year survival rates
2. It is likely to restore them to full/near-full health	Those who do not recur have good quality of life
3. Benefits are likely to be sustained over a very long period	Long-term risk of recurrence is low: particularly pronounced in TNBC population

Which discount rates for the TNBC population are appropriate?

Other considerations (2)

Equalities issues

- Black women and younger women are more likely to develop TNBC

Innovation

- Company: olaparib is first personalised treatment for HR+/HER2- eBC patients with a BRCAm and may drive more routine genetic testing

Future data

- 3rd data cut for OlympiA is expected [redacted]

Summary of company and EAG base case assumptions

Table 12 Assumptions in company and EAG base case

Assumption	Company base case	EAG base case
Risk of recurrence after 5 years in TNBC	0%	5% over next 10 years
Extrapolation of recurrence in TNBC	Log-normal	Log-normal
Extrapolation of recurrence in HR+/HER2-	Log normal	Generalised gamma
Extrapolation of survival following early metastatic recurrence (both populations)	Exponential	Gompertz
Source of utility data	EORTC QLQ-C30 mapped to EQ-5D (Crott & Briggs)	Literature derived: Verrill 2020
Disease-free health state utility value	0.869	0.732
Non-metastatic disease health state utility value	0.869	0.667
Metastatic disease health state utility value	0.685	0.603
Costing for BRCA testing in TNBC	Not included	Not included
Costing for BRCA testing in HR+/HER2-	Not included	Included
Discount rates	3.5% (argues 1.5% forTNBC)	3.5%

Cost-effectiveness results

As confidential discounts are available for subsequent treatments in the pathway, ICERs are not reported in Part 1

ICERs including confidential discounts will be presented in Part 2

Summary

- Company and EAG ICERs are **higher** than what would usually be considered a cost-effective use of NHS resources
- ICERs are higher for people with HR+/HER2- disease than for people with TNBC
- EAG's ICERs are higher than the company's:
  - For TNBC group, this is due to the different source of utility values, followed by assumptions about risk of recurrence after 5 years and estimated survival after metastatic disease
  - For HR+/HER2- group, this is due to the different source of utility values, followed by the addition of BRCA testing costs, estimated recurrence and estimated survival after metastatic disease

Cost-effectiveness results

The following scenario analyses will be presented in part 2

No.	Scenario (applied to company base case)
1	EAG base case
2	Increasing utility values to account for older age in Verrill
3	Using Gray for DF, mid-point for non-mBC, Verrill for mBC
4	Applying company's base case utility values
5	Lidgren literature utility value for DF (non-mBC same as DF)
6	1.5% discount rate
7	No BRCA testing costs
8	Lognormal for recurrence (risk of death equal at 14.5 years)
9	Lognormal for recurrence (risk of death equal at 10 years)
10	Lognormal for recurrence (risk of death equal at 7.5 years)
11	Risk of recurrence after 5 years is 0% instead of 5% (TNBC)

Managed access

Criteria for a managed access recommendation

The committee can make a recommendation with managed access if:

- the technology cannot be recommended for use because the evidence is too uncertain

- the technology has the **plausible potential** to be cost effective at the **currently agreed price**

- new evidence that could **sufficiently support the case for recommendation** is expected from ongoing or planned clinical trials, or could be collected from people having the technology in clinical practice

- data could feasibly be collected within a reasonable timeframe (up to a **maximum of 5 years**) without **undue burden**

Managed access: Feasibility assessment

Is Managed Access appropriate- Overall rating	Comments / Rationale
Yes	Immaturity of data is a key uncertainty. There is a large (n=1836), phase III trial ongoing until 2029 that would provide more mature data. The company have submitted a managed access proposal, which lists immaturity of data and effectiveness in HR+/HER- subgroup as uncertainties. The EAG identified potential bias in how the company have measured HRQoL and used it in the economic model. Further data collection would not resolve this uncertainty.

Abbreviations

Table 1 Abbreviations

TNBC	Triple-negative breast cancer	QALY	Quality-adjusted life year
OS	Overall survival	ICER	Incremental cost-effectiveness ratio
HR	Hormone receptor	HER2	Human epidermal growth factor receptor 2
eBC	Early-stage breast cancer	mBC	Metastatic breast cancer
iDFS	Invasive disease-free survival	dDFS	Distant disease-free survival (dDFS)
TP	Transition probability	PARP	Poly-ADP-ribose polymerase

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Thank you.