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

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Declared competing interests of the authors

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

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Rider on responsibility for report

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

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Contributions of authors

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

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Abbreviations

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

1. EXECUTIVE SUMMARY

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

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

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

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

2. BACKGROUND

2.1. Why the cost-comparison approach has been considered

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

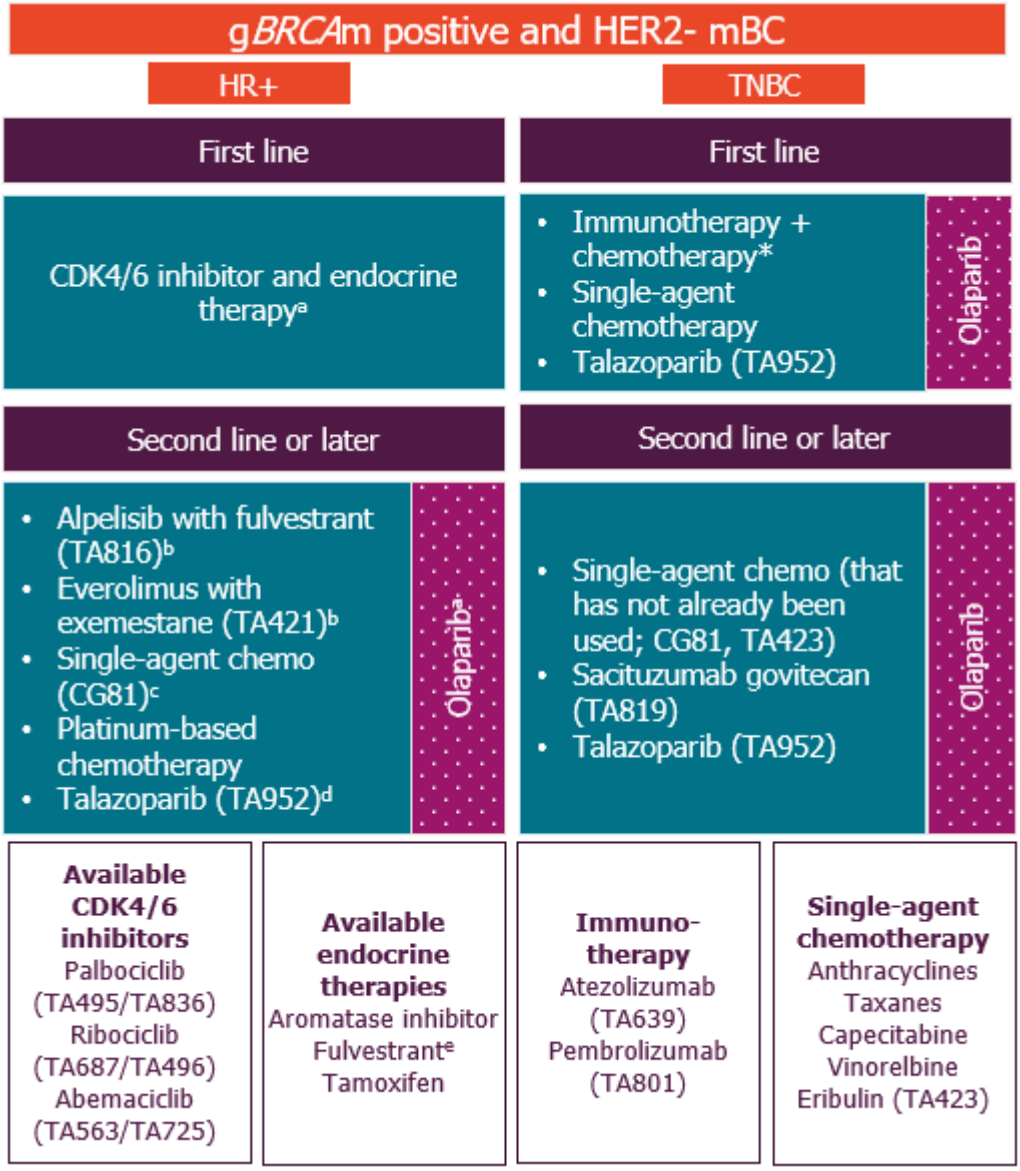
2.2. Company description of disease area and treatment pathway

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

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

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

Figure 1: Current treatment pathway



[a] Endocrine monotherapy may be considered in first line in a small group of patients with comorbidities or a performance status that prevents the use of CDK4/6 inhibitor combinations. For patients whose disease is imminently life-threatening or requires early relief of symptoms because of significant visceral organ involvement, chemotherapy may be considered as first-line treatment; [b]Therapies typically used at second-line in patients who progress following first-line therapy but remain sensitive to endocrine therapy; [c]Single-agent chemotherapy is an option for patients who are not (or are no longer) responsive to endocrine therapy at second or later line; [d]For patients with HR+ disease, talazoparib is recommended only in patients with mBC who have had prior endocrine therapy (i.e. second line or later), unless this is not suitable. Olaparib is positioned in the same population for which talazoparib received a recommendation. [e]Fulvestrant monotherapy is not recommended by NICE. *The EAG notes that no footnote is provided for "*" in the CS.
Abbreviations: CDK: cyclin-dependent kinase; g*BRCA*m: germline breast cancer susceptibility gene mutation; HR: hormone receptor; mBC: metastatic breast cancer; TNBC: triple negative breast cancer.
Source: Reproduced from CS Figure 4. **Source in CS:** TA816; TA421; TA423; TA81; TA819; TA495; TA836; TA687; TA496; TA563; TA725; TA639; ´TA801.

2.3. Testing for breast cancer subtypes and mutation status

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

2.4. Mechanism of action of olaparib and talazoparib

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

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

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

3.1. Marketing authorisations and NICE recommendations for olaparib and talazoparib

The olaparib marketing authorisation is as follows: "*Lynparza (olaparib) is indicated as monotherapy for the treatment of adult patients with germline BRCA1/2 mutations, who have human epidermal growth factor receptor 2 negative (HER2−) locally advanced or metastatic breast cancer. Patients should have previously been treated with an anthracycline and a taxane in the (neo)adjuvant or metastatic setting unless patients were not suitable for these treatments. Patients with hormone receptor positive (HR+) breast cancer should also have progressed on or after prior endocrine therapy, or be considered unsuitable for endocrine therapy*."[3]

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

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

3.2. Licensed indication for olaparib vs. talazoparib

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

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

3.3. Company decision problem: similarity to NICE final scope

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

3.4. Clinical evidence and relevance to patient population in England

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

3.5. Relevance of comparator

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

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

4.1. Critique of company systematic review methods

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

4.2. Overview of trials of olaparib and talazoparib

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

4.3. Key differences in trial design and baseline characteristics

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

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

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

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

4.4. Quality assessment of trials

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

4.5. Results of individual trials

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

Table 1: Summary of PFS, OS and ORR

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

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

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

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

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

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

4.7. Comparative effectiveness results from ITCs

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

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

Table 2: Summary of ITCs for effectiveness

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

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

4.8. Subgroup analyses

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

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

Table 3: Summary of ITCs for subgroup analyses of PFS

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

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

4.9. Comparative safety results from ITCs

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

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

Table 4: Summary of ITCs for safety

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

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

4.10. Clinical expert views on comparative effectiveness and safety

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

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

4.11. Summary of comparative clinical effectiveness

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

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

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

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

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

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

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

6. COMPANY AND EAG COST COMPARISON RESULTS

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

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

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

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

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

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

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

7. EQUALITIES AND INNOVATION

No equality or innovation considerations were noted in the CS.

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

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

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10. APPENDICES

Appendix 1: Study characteristics

Table 6: Study characteristics for OlympiAD and EMBRACA

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

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

Appendix 2: Baseline patient characteristics

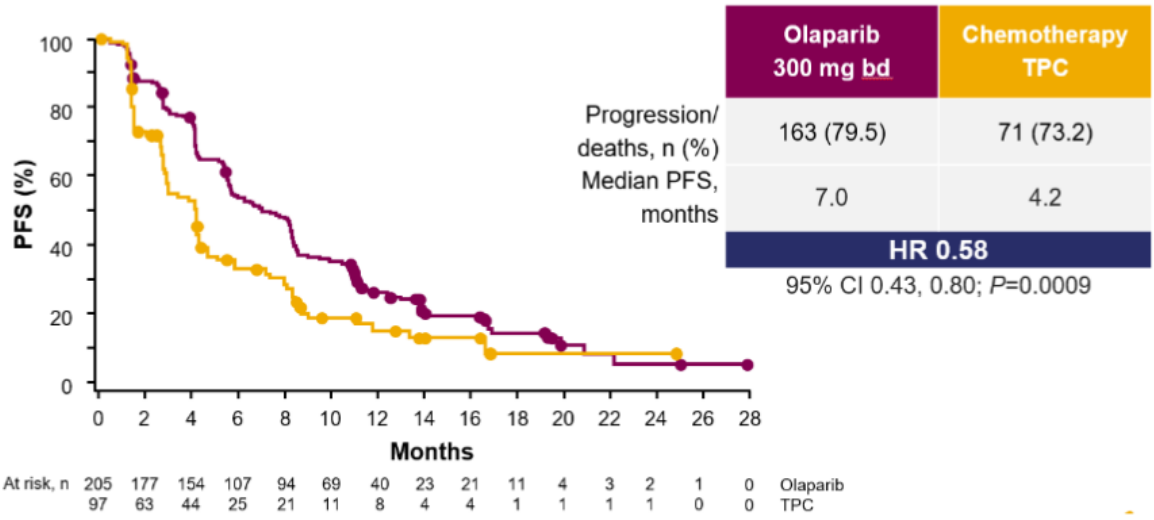
Table 7: Baseline patient characteristics in OlympiAD and EMBRACA

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

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

Appendix 3: PFS and OS in OlympiAD and EMBRACA

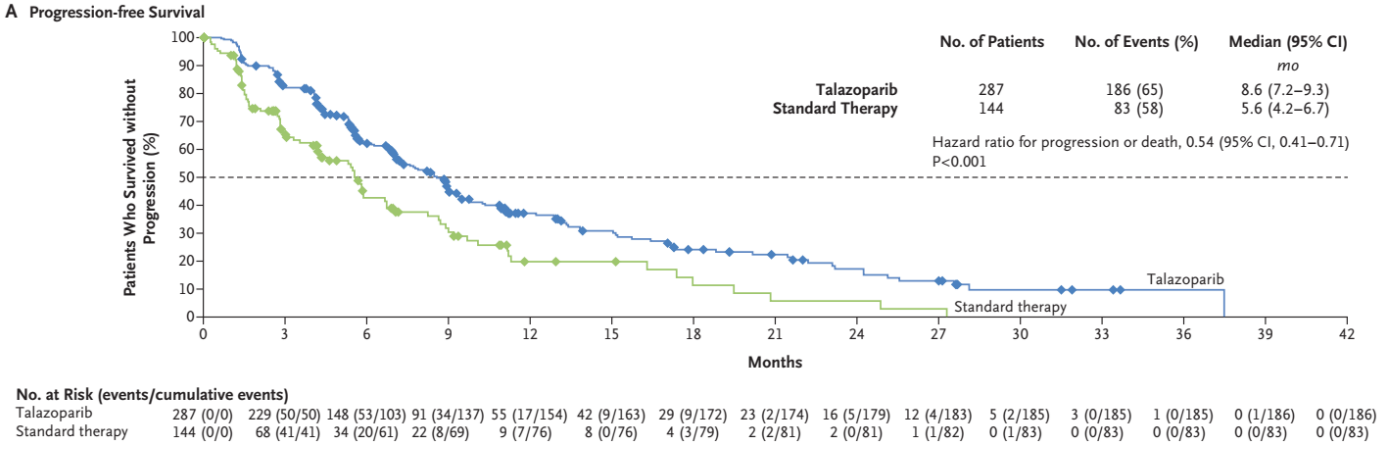
Figure 2: PFS by BICR in OlympiAD trial of olaparib vs. TPC



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

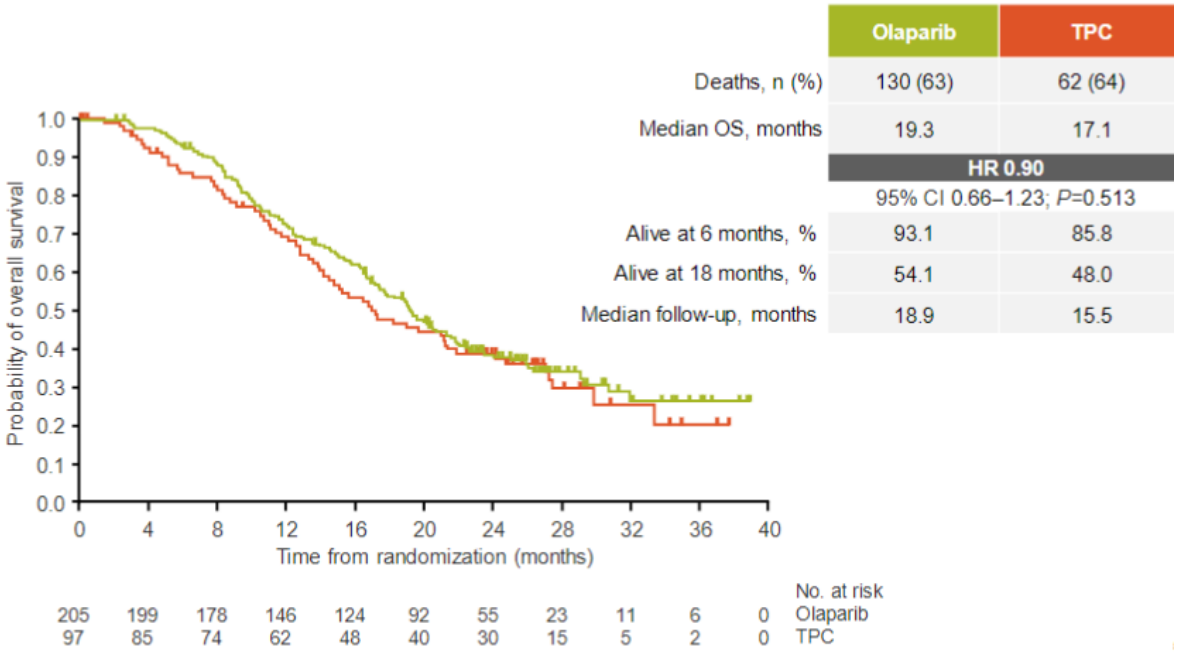
Source: Robson *et al.*[9], data cut-off Dec 2016

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



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

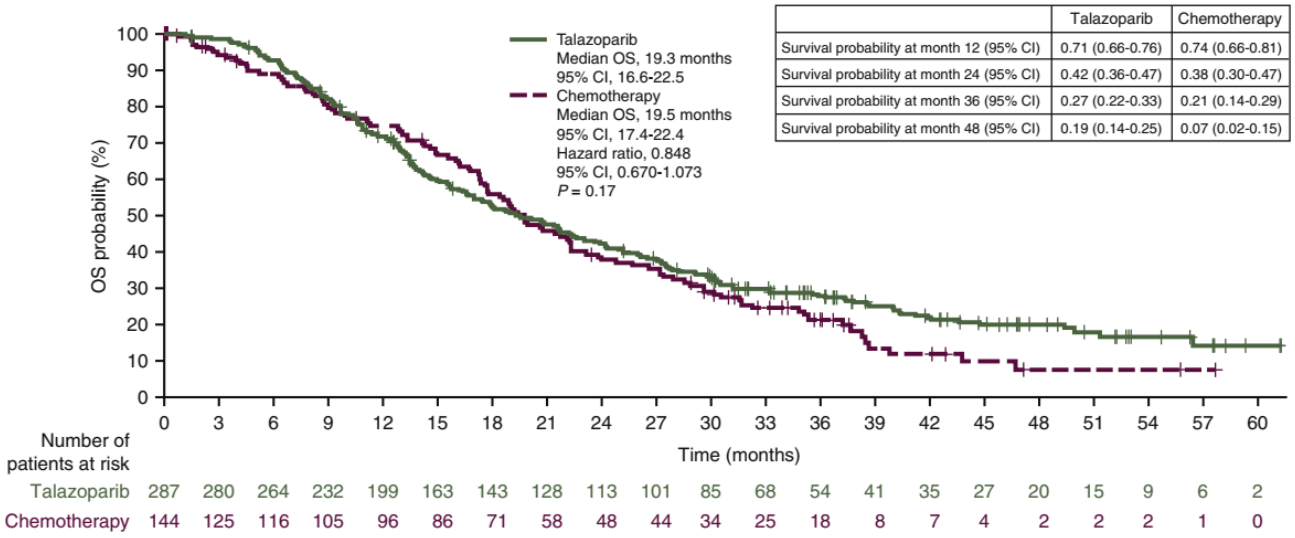
Figure 4: OS in OlympiAD trial of olaparib vs. TPC



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

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

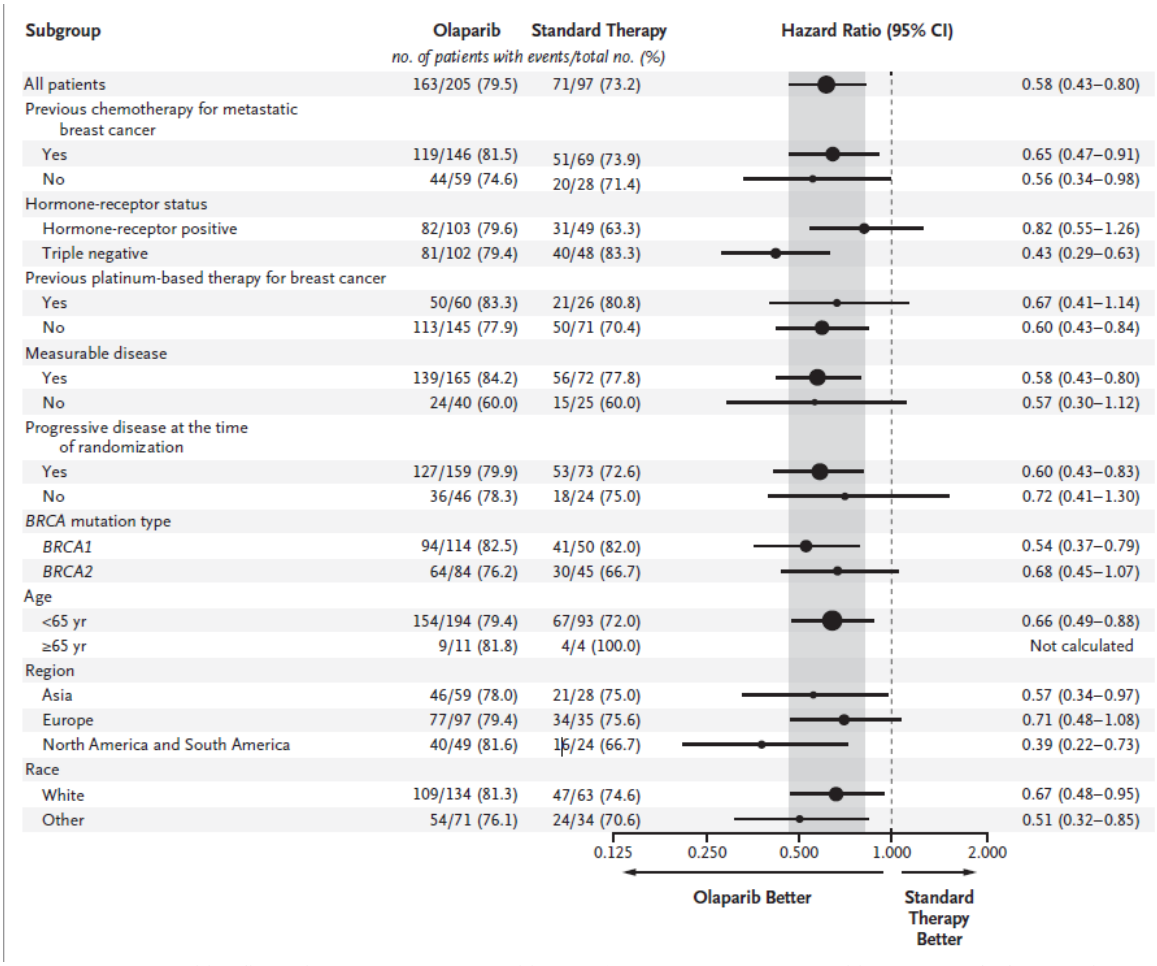
Figure 5: OS in EMBRACA trial of talazoparib vs. TPC



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

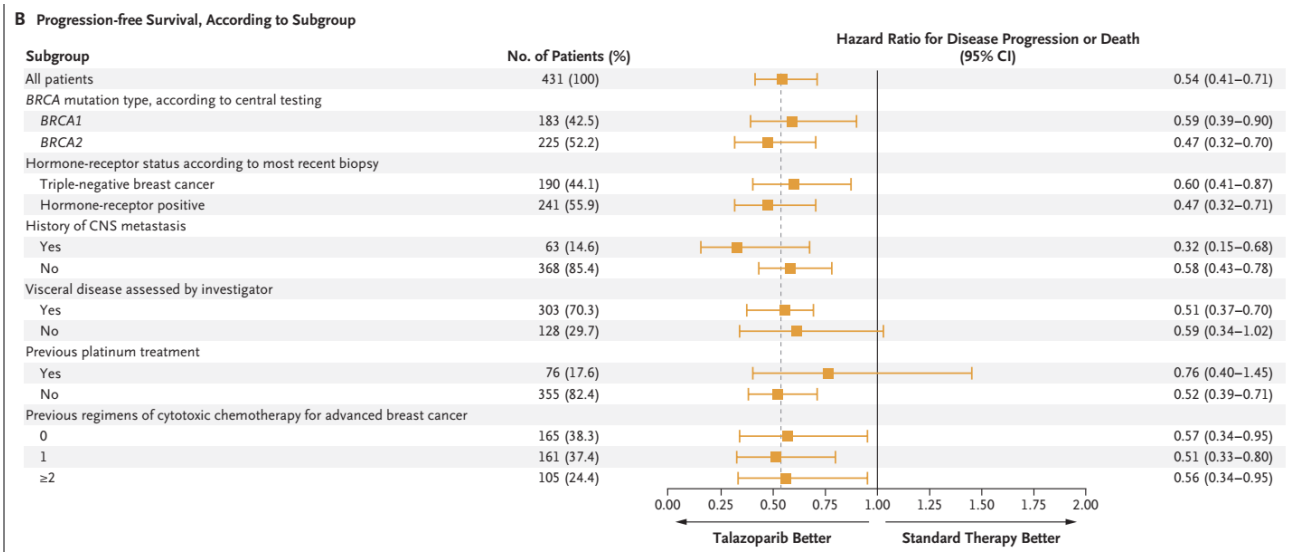
Appendix 4: Subgroup analyses of PFS and OS in OlympiAD and EMBRACA

Figure 6: Subgroup analyses of PFS in OlympiAD



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

Figure 7: Subgroup analyses of PFS in EMBRACA



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