# 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:



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

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

**Draft guidance comments form**

**Consultation on the draft guidance document – deadline for comments** by the end of 18 August 2023. Please submit via NICE Docs.

| | |
|---|---|
| | Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly.<br><br>The Appraisal Committee is interested in receiving comments on the following:<br>• has all of the relevant evidence been taken into account?<br>• are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?<br>• are the provisional recommendations sound and a suitable basis for guidance to the NHS?<br><br>NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations:<br>• could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology;<br>• could have any adverse impact on people with a particular disability or disabilities.<br><br>Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.** |
| **Organisation name – Stakeholder or respondent** (if you are responding as an individual rather than a registered stakeholder please leave blank): | Pfizer UK |

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| **Disclosure**<br>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.]<br>Please state:<br>• the name of the company<br>• the amount<br>• the purpose of funding including whether it related to a | N/a |

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| • product mentioned in the stakeholder list<br>• whether it is ongoing or has ceased. | |
| Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry. | N/a |
| **Name of commentator person completing form:** | |

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| Comment number | Comments<br><br>Insert each comment in a new row.<br>Do not paste other tables into this table, because your comments could get lost – type directly into this table. |
|---|---|
| Summary | **Summary**<br><br>Pfizer is disappointed that NICE have chosen not to recommend talazoparib for the treatment of HER2-negative locally advanced or metastatic breast cancer with germline BRCA1/2-mutations following the Appraisal Committee Meeting (ACM) on 4th July 2023.<br><br>Talazoparib is the first targeted treatment indicated for gBRCAm HER2- aBC in England. In the EMBRACA trial, patients treated with talazoparib had significantly longer progression free survival than standard of care. As well as being efficacious, talazoparib provides a novel treatment mechanism and increases treatment choice, fulfilling a significant unmet need in this patient population.<br><br>Pfizer remains committed to securing access for patients and welcomes the opportunity to respond to the draft guidance document. Pfizer has provided a response to the following points:<br><br>• ***Increased the PAS*** – Pfizer has significantly increased the discount it is offering the NHS. All analysis incorporates this additional discount.<br><br>• ***Accepted the majority of committee preferences*** – Pfizer has accepted the following committee preferences:<br>  ○ Excluding relative dose intensity (RDI)<br>  ○ Cost of neutropenia<br>  ○ Utility value in the progressed disease (PD) health state<br>  ○ Assumption of no difference in resource use by complete/partial response (CR/PR) |

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| | ○ Red cell blood (RBC) transfusions rates<br>○ Kaplan-Meier (KM) data from EMBRACA to model time to treatment discontinuation (TTD)<br>• ***Exploration*** – Pfizer has responded to or explored the following:<br>○ Assumption of an overall survival benefit<br>○ Utility values for PCT in the progression-free health state<br>• ***Innovation and equity -*** Pfizer has provided a further explanation of the innovative nature of the treatment and the equity challenges<br>• ***Update base case –*** Pfizer has provided an updated base case of the cost effectiveness.<br><br>Pfizer believe that this response demonstrates that talazoparib would be a valued treatment for patients with HER2-negative locally advanced or metastatic breast cancer with germline BRCA1/2-mutations and is a cost-effective use of NHS resources. |
| Increase in PAS | Pfizer has increased the simple discount for talazoparib [redacted]. The updated base case and all scenario analyses include the updated price for talazoparib. |
| Committee assumptions | Pfizer has accepted the following committee assumptions:<br>○ Excluding relative dose intensity<br>○ Committee's preferred cost of neutropenia<br>○ Utility value in the progressed disease health state<br>○ Assumption of no difference in resource use by complete/partial response |

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|---|---|
| | ○ Mid-point for red cell blood transfusions rates<br>○ Kaplan-Meier (KM) data from EMBRACA to model time to treatment discontinuation (TTD) |
| Overall survival | The committee noted that they could not conclude that there was an overall survival benefit for those treated with talazoparib and requested analysis that considered no survival benefit (DG, paragraph 3.19). Pfizer acknowledge that the results demonstrate that a clear survival benefit is uncertain and have provided the analysis requested by the committee. However, given the large numerical benefit observed and skew of the data it is important to note a number of points and suggested an alternative:<br><br>**<u>Rationale for suggesting alternative approach:</u>**<br>• In the final OS analysis, the estimated HR was 0.848 (95% CI: 0.670, 1.073) and the p-value by stratified 2-sided log-rank test was 0.1693. This represents a 15% reduction in the risk of death. A higher percentage of patients in the PCT arm (47 patients [32.6%]) than in the talazoparib arm (13 patients [4.5%]) took a post-study PARP inhibitor, which may have influenced the OS outcome.<br>• There was an improvement in 2-, 3- and 4-year survival favouring talazoparib compared to PCT. The survival probabilities at 2 and 3 years for talazoparib compared to PCT were 0.42 (95% CI: 0.36, 0.47) versus 0.38 (95% CI: 0.30, 0.47) and 0.27 (95% CI: 0.22, 0.33) versus 0.21 (95% CI: 0.14, 0.29), respectively. The 4-year survival probabilities for talazoparib compared to PCT were 0.19 (95% CI: 0.14, 0,25) versus 0.07 (95% CI: 0.02, 0.15).<br>• Subgroup analyses were generally consistent with the primary OS outcome.<br>• Additional analyses assessing the impact of postbaseline treatment with PARP inhibitors only using a RPSFTM resulted in an HR of 0.82 (95% bootstrap CI: 0.62, 1.05). A lack of statistical significance does not prove the null hypothesis that there is no difference in overall survival between talazoparib and PCT.<br>• A retrospective analysis of patients in the intent-to-treat (ITT) population of EMBRACA was conducted in which patients were mapped into two groups based on response: |

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- LONG (patients in TALA arm with overall survival [OS] ≥30 months and duration of treatment ≥24 months (n=37); patients in PCT arm with OS ≥30 months (n=34));
- SHORT (pts in either arm with a PFS event [progressive disease by Independent Radiological Facility or death] ≤12 weeks).[1]

Of note, over half (52.9%) of PCT LONG responders received postbaseline olaparib (Figure 1), which is not part of the treatment pathway in UK clinical practice, and therefore potentially providing some rationale for the non-statistically significant improvement in survival versus PCT.

**Figure 1. Characterisation of long-term responders following treatment with talazoparib (TALA) or physician's choice of chemotherapy (PCT) in the phase 3 EMBRACA trial**

| | TALA – LONG (n = 37) | PCT – LONG (n = 34) | TALA – SHORT (n = 40) | PCT – SHORT (n = 32) |
|---|---|---|---|---|
| Median age, y | 50.0 | 50.5 | 42.5 | 45.5 |
| | No. (%) | | | |
| TNBC | 17 (45.9) | 10 (29.4) | 25 (62.5) | 20 (62.5) |
| HR+ BC | 20 (54.1) | 24 (70.6) | 15 (37.5) | 12 (37.5) |
| *BRCA1* status | 16 (43.2) | 7 (20.6) | 25 (62.5) | 18 (56.3) |
| *BRCA2* status | 20 (54.1) | 25 (73.5) | 12 (30.0) | 14 (43.8) |
| No prior CT for ABC | 21 (56.8) | 20 (58.8) | 8 (20.0) | 6 (18.8) |
| 1 prior CT for ABC | 12 (32.4) | 8 (23.5) | 14 (35.0) | 13 (40.6) |
| ≥2 prior CT for ABC | 4 (10.8) | 6 (17.6) | 18 (45.0) | 13 (40.6) |
| Prior platinum | 5 (13.5) | 4 (11.8) | 11 (27.5) | 10 (31.3) |
| Postbaseline olaparib | 1 (2.7) | 18 (52.9) | 0 | 5 (15.6) |

Given the above, we believe that this demonstrate that there are a proportion of patients for whom there is a survival benefit.

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| | • In a previous appraisals of PARP inhibitor, NICE committees have accepted a non-statistically significant but numerical difference in overall survival<br>  ○ TA784 (Niraparib, ovarian cancer) - The committee recalled that median overall survival had not been reached in the original appraisal of niraparib and that survival benefit with niraparib was the main clinical uncertainty. Updated data from NOVA showed: The difference in median overall survival between niraparib and placebo was 5.4 months (HR 1.1; 95% CI 0.83 to 1.46).<br>  ○ The committee noted that NOVA was not powered to test for statistical significance for overall survival, and the company and ERG explained that the results for the placebo arm are confounded by a high rate of subsequent PARP inhibitor use and missing data. In response to the committee's request for a conservative scenario assuming no overall survival benefit for people without a BRCA mutation, the company highlighted that the assumption of a gain in progression-free survival resulting in zero overall survival gain is not clinically plausible.<br>  ○ It noted that this was supported by trial evidence for maintenance therapies in advanced relapsed ovarian cancer and that a 1:1 progression-free survival to overall survival ratio should be the minimum survival benefit with niraparib compared with routine surveillance. The committee concluded that estimating overall survival for people without a BRCA mutation using data from Study 19 for routine surveillance which results in a survival benefit for people without a BRCA mutation is reasonable.<br><br>**<u>Alternative approach</u>**<br><br>Pfizer believe that it is not appropriate to disregard the overall survival data based on the uncertainty. The NICE manual states that ***"…in general, uncertainty around individual parameters is not a reason to exclude them from probabilistic analyses; rather, that uncertainty should be captured in the analysis" (4.7.12).***[2] While uncertain, Pfizer believe that the overall survival data should remain and be sampled probabilistically as part of the probabilistic estimate in the economic model. This is reflected in the updated company base case presented in the results. |
| Subgroups | The committee noted that '*subgroup analyses should be interpreted with caution*' (DG, paragraph 3.11), specifically relating to the overall survival analysis. '*But, given the entirety of the evidence and the uncertainties, it concluded that additional evidence or analysis* |

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| | *from the trial exploring talazoparib's effect on overall survival in the overall population and subgroups would provide further insight to inform decision making'* (DG, paragraph 3.11).<br><br>Pfizer has previously provided the KM curve of overall survival for the TNBC subgroup in the technical engagement response.<br><br>The draft guidance does not recognise the strong clinical opinions repeatedly voiced during the committee meeting that stated the EMBRACA trial was not powered to detect these differences in these results and should not be considered by the committee. The company agrees with the clinical experts' opinions and maintains that it is inappropriate to draw conclusions about the clinical and cost-effectiveness results by subgroup. The company has previously provided the overall survival results from EMBRACA and doesn't consider it appropriate to interrogate these further. However, Pfizer has provided cost-effectiveness results by subgroup, although it should be noted that Pfizer does not consider it appropriate to consider the subgroups, for the following reasons:<br><br>• The EMBRACA trial enrolled a molecularly selected population, as inherited mutations in BRCA1 and BRCA2 genes account for about 4-6% of all breast cancer cases in women and around 11-12% of cases in men.[3] As a result, less than [redacted] patients are expected to be eligible to receive treatment with talazoparib per year across England and Wales.<br><br>• Paragraph 3.11 of the DG: "*The clinical experts explained that there was no biological mechanism that would predict that hormone receptor status would affect the treatment effect of talazoparib in people with advanced breast cancer."*<br><br>However, if the committee consider it to be appropriate to explore subgroup analyses, it is important to consider the following unmet need and equity considerations for TNBC:<br><br>• There is a higher unmet need within the TNBC population raising concern of equity. TNBC can be more aggressive and harder to treat than other types of breast cancer, resulting in potentially poorer outcomes and short prognoses, with a lack of targeted treatment options.<br><br>• TNBC are more likely to be younger and from black or Hispanic ethnic backgrounds[4] and TNBC disproportionately affects women under 40 years.[5] The median age of TNBC patients in EMBRACA was 43 years.[6] Using the MVH value set + HSE 2014 ALDVMM model, and 1.02 QALYs with PCT, the proportional shortfall for TNBC patients is 0.9432. QALY shortfall calculation results are included in the appendix to this document. |

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| | • To capture the severity of disease in the TNBC subgroup, it is arguable that the severity modifier of 1.7 should be applied. As outlined in the 2022 NICE methods guidance **6.2.18** ***"If either the proportional or absolute QALY shortfall calculated falls on the cut-off between severity levels, the higher severity level will apply."*** [2]<br><br>The company strongly believes that the committee should consider the ITT population. We also request that if this topic is to be discussed further, the clinical experts are present so the committee can be fully informed for their decision making. |
| Transfusion rates | Pfizer accepts the committee conclusion that "the rate of red cell blood transfusions for talazoparib in the NHS is likely to be a value between the trial and the Mahtani study" (DG, paragraph 3.16). Therefore, Pfizer has applied a mid-value of 23.1% has been used in the revised company base case, which is the midpoint between 8.3% and 38.1%.<br>The committee also requested further information on "*triggers of blood transfusion from EMBRACA, and analyses exploring the relationship between dosing, dose reduction, red blood transfusion rate and treatment effect of talazoparib*" (DG, paragraph 3.16). Pfizer has explored this, however, there is insufficient evidence to ascertain whether the dose reduction impacted PFS. 53.1% of patients had at least 1 dose reduction in EMBRACA[7] and therefore the efficacy observed in the trial accounts for this. The clinical experts present in the committee meeting were confident that the difference in their approach to transfusions would not affect the clinical effectiveness of talazoparib (DG, paragraph 3.16). Furthermore, there is evidence from clinical trials shows that restrictive transfusion strategies (transfusing one unit at a time and using a lower haemoglobin threshold) do not increase morbidity or mortality among diverse populations of hospitalised patients.[8] |
| Utility values | The company agrees with the committee that there may be 'other factors that may affect utility when receiving talazoparib or the comparator treatment' (DG, paragraph 3.17), for example, needing red blood transfusions and hospital visits associated with the chemotherapies. We consider that it is reasonable to assume a difference in utility values between talazoparib and PCT, and as a result have explored alternative PCT utility values.<br><br>Real-world PROs showed a 0.08 difference in utility values between PARPi and chemotherapy,[9] which is higher than the 0.063 difference observed in EMBRACA. However, we do acknowledge the limitations of this study which included no UK patients, and unlike EMBRACA the chemotherapy cohort in the study included 50% of patients who received platinum-based chemotherapy. |

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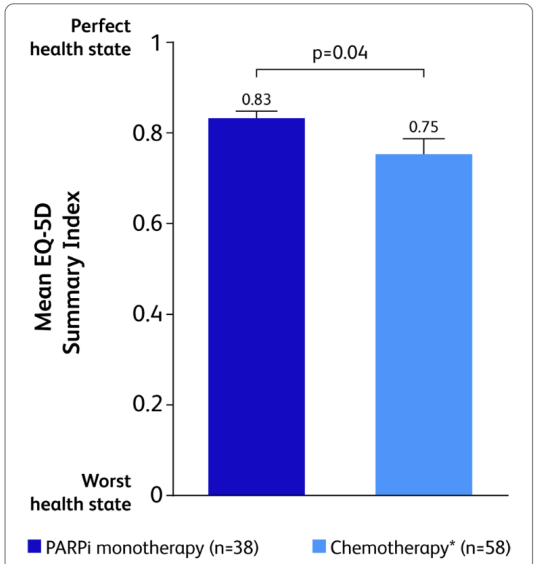
|---|---|
| | **Figure 2. PROs for PARPi monotherapy and chemotherapy (*from Mahtani et al. (2022)*[9]**   Pfizer has explored PCT utility values accepted in previous breast cancer appraisals:<br>• In TA423, the appraisal of eribulin for treating locally advanced or metastatic breast cancer after 2 or more chemotherapy regimens (TA423), the reported utility values for eribulin and TPC were 0.705 and 0.701 respectively.<br>• In TA704 (trastuzumab deruxtecan for treating HER2-positive mBC), the company used utility values from TA423. Treatment dependent utility values for the 'progression-free on treatment' health state were calculated as a function of the overall response rate for each treatment. The clinical expert confirmed that in metastatic breast cancer, there was a clear link between health-related quality of life and objective response rate, progression-free survival, and treatment-emergent adverse events. The accepted utility values for eribulin/ capecitabine/ vinorelbine were 0.715/0.718/0.728. |

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| | • In TA786 (tucatinib – for HER2-positive advanced breast cancer), utilities for the comparator therapies were from TA423. The ERG explained the company approach was inappropriate because the differences in utilities between tucatinib and comparators were not based on comparative evidence. The clinical experts in this appraisal explained that the company's approach was not methodologically robust because it used utility values from 2 different sources in a 'naive comparison', that is, without adjusting for any differences between populations in these sources that might have affected the utility values. The committee noted that in future they would prefer 'evidence-based utilities'.<br>• EMBRACA is an evidence-based source of utility data for talazoparib and PCT, which is supported by RWD. Therefore, the company have maintained the EMRACA utility values for talazoparib (0.75) and PCT (0.687) in its base case.<br><br>Pfizer acknowledge that there may be some limitations to the utility evidence generated in EMBRACA but agree that there are important factors between treatment arms that should be taken into consideration. We recognise previous decisions that have accepted such differences in advanced breast cancer in addition to committee's preference for evidenced based utilities. Weighing this up Pfizer has kept the utilities observed in the trial as we feel they represent important difference experienced by patients. However, we have also provided 2 more conservative scenarios exploring the utility values<br>• Where 0.701 from TA423 reported for treatment of physician's choice, representing an incremental utility gain of 0.049 for talazoparib in the revised economic model, a reduction from the 0.063 difference observed in EMBRACA.<br>• Where the baseline utility value for PCT 0f 0.701 (obtained from TA423) is weighted by the incremental utility of response accepted in TA704 (0.076). In EMBRACA, the objective response rate was higher in the talazoparib group than in the PCT group (62.6% vs. 27.2%; odds ratio, 5.0; 95% CI, 2.9 to 8.8; P<0.001.[10] This results in utility values of 0.72 for PCT and 0.75 for talazoparib. |
| Innovation and uncaptured benefits | A letter from the Association of Cancer Physicians letter to the Department of Health in May 2023 highlighted serious concerns about a critical lack of capacity within oncology departments, a lack of equivalent investment or support for the oncology workforce means departments are failing to keep pace and the resulting compromise on patient safety and quality of care.[11] The availability of an oral treatment with a demonstrated improvement in progression-free survival can minimise inpatient attendance and resource use. We |

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<table>
<tr><td></td><td>agree with the statement from Breast Cancer Now, that fewer hospital visits would “free up valuable time for both patients and overstretched clinics.”[12]<br><br>There is currently no BRCA targeted therapy available in the NHS in the metastatic breast cancer space, even though patients who may benefit from talazoparib are being identified through NHS BRCA testing. The availability of talazoparib for this patient population is aligned with the NHS genomics strategy, which states the ambition of accelerating the use of genomic medicine across the NHS, providing a world leading, equitable service to populations and individuals.<br><br>In the company submission in January 2023, [redacted] patients were predicted to be eligible for talazoparib. This number is now expected to be lower since the approval of olaparib for BRCA mutated HER2-negative high-risk early breast cancer in May 2023 (TA886). Therefore, the budget impact, and associated absolute decision risk for this appraisal are low.</td></tr>
<tr><td>Updated base case results</td><td>Pfizer’s updated base case includes committee’s preferred assumption with the following exceptions:<ul><li>Overall survival – taken from the EMBRACA with uncertainty factored into probabilistic analysis.</li><li>Utility values for PCT from EMBRACA (0.75 for talazoparib and 0.687 for PCT)</li></ul>Pfizer’s base case is in the ITT population, however, subgroup analysis has been provided. Scenario analysis in the ITT population has been provided exploring:<ul><li>Overall survival – excluding any survival benefit</li><li>Transfusion rates</li><li>PCT utility value from TA423</li></ul>The updated base case results are presented below:
<table>
<tr><th></th><th colspan="3">Talazoparib</th><th colspan="3">PCT</th><th colspan="3">Incremental</th><th>Probabilistic</th></tr>
<tr><th>Population</th><th>Cost</th><th>QALYs</th><th>LYs</th><th>Cost</th><th>QALYs</th><th>LYs</th><th>Cost</th><th>QALYs</th><th>LYs</th><th>ICER at [redacted] PAS</th></tr>
<tr><td>ITT</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>£19,810</td></tr>
</table>
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| | The cost-effectiveness acceptability curve (Figure 4) and probabilistic scatter plot (Figure 5) for the ITT population are also presented below, demonstrating that talazoparib has a 65% probability of being cost-effective at the £30,000 WTP threshold.<br><br>**Figure 4. Cost-effectiveness acceptability curve**<br><br>  |

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**Figure 5. Scatter plot of probabilistic sensitivity analysis**

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Scenario analysis results

**1. Overall survival**

Scenario analyses are presented below, by subgroup, assuming that there is no survival benefit associated with talazoparib over PCT:

| | Talazoparib | | | PCT | | | Incremental | | | Probabilistic |
|---|---|---|---|---|---|---|---|---|---|---|
| **Population** | **Cost** | **QALYs** | **LYs** | **Cost** | **QALYs** | **LYs** | **Cost** | **QALYs** | **LYs** | **ICER at [redacted] PAS** |
| **ITT** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | Dominant |
| **HR+/HER2-** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | Dominant |
| **TNBC** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | Dominant |

**2. Subgroup analyses**

Subgroup analyses for the HR+/HER2- and TNBC populations are presented below based on new company base case. Results are presented using both the 1.2 and 1.7 severity modifier for TNBC.

| | Talazoparib | | | PCT | | | Incremental | | | Probabilistic |
|---|---|---|---|---|---|---|---|---|---|---|
| **Population** | **Cost** | **QALYs** | **LYs** | **Cost** | **QALYs** | **LYs** | **Cost** | **QALYs** | **LYs** | **ICER at [redacted] PAS** |
| **ITT (SM 1.2)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £19,810 |
| **HR+/HER2- (SM 1.2)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £15,981 |
| **TNBC (SM 1.7)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £21,427 |
| **TNBC (SM 1.2)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £30,356 |
| SM = severity modifier | | | | | | | | | | |

In addition, the KM curves for subgroups are presented in an appendix to this document.
In conclusion, whilst analysis of select patients in the ITT population may result in higher ICER values, the average population is cost-effective with the revised PAS offer.

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

**Draft guidance comments form**

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**3. Transfusion rate**

A scenario analysis is also presented, in which the post-amendment transfusion rate of 32.4% is applied in the model. This scenario increases the ICER by £2,079. The results are presented below:

| | Talazoparib | | | PCT | | | Incremental | | | Probabilistic |
|---|---|---|---|---|---|---|---|---|---|---|
| **Population** | **Cost** | **QALYs** | **LYs** | **Cost** | **QALYs** | **LYs** | **Cost** | **QALYs** | **LYs** | **ICER at [redacted] PAS** |
| **ITT** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £21,889 |

**4. Utilities**

a. An alternative scenario for utilities (using the PCT utility value of 0.701 from TA423) is presented below. This scenario increases the ICER by £1,638.

| | Talazoparib | | | PCT | | | Incremental | | | Probabilistic |
|---|---|---|---|---|---|---|---|---|---|---|
| **Population** | **Cost** | **QALYs** | **LYs** | **Cost** | **QALYs** | **LYs** | **Cost** | **QALYs** | **LYs** | **ICER at [redacted] PAS** |
| **ITT** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £21,448 |

b. An additional alternative scenario for utilities is presented, where the baseline utility value for PCT 0f 0.701 (obtained from TA423) is weighted by the incremental utility of response accepted in TA704 (0.076). This results in utility values of 0.72 for PCT and 0.75 for talazoparib. This scenario increases the ICER by £2,115.

| | Talazoparib | | | PCT | | | Incremental | | | Probabilistic |
|---|---|---|---|---|---|---|---|---|---|---|
| **Population** | **Cost** | **QALYs** | **LYs** | **Cost** | **QALYs** | **LYs** | **Cost** | **QALYs** | **LYs** | **ICER at [redacted] PAS** |
| **ITT** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £21,925 |

Insert extra rows as needed

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

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- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is [redacted] and information that is [redacted]. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

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**Appendix:**

**QALY shortfall calculation results**

| **Outcome** | **Total QALYs** | **Shortfall** | |
|---|---|---|---|
| | | **Absolute** | **Proportional** |
| General Population | 17.95 | | |
| Disease Specific | 1.02 | 16.93 | 0.9432 |

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**Deterministic results:**

**Company base case**

| | Talazoparib | | | PCT | | | Incremental | | | Deterministic |
|---|---|---|---|---|---|---|---|---|---|---|
| **Population** | **Cost** | **QALYs** | **LYs** | **Cost** | **QALYs** | **LYs** | **Cost** | **QALYs** | **LYs** | **ICER at [redacted] PAS** |
| **ITT** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £20,647 |

**Scenario analyses**

1. Removing talazoparib survival benefit (by subgroup)

| | Talazoparib | | | PCT | | | Incremental | | | Deterministic |
|---|---|---|---|---|---|---|---|---|---|---|
| **Population** | **Cost** | **QALYs** | **LYs** | **Cost** | **QALYs** | **LYs** | **Cost** | **QALYs** | **LYs** | **ICER at [redacted] PAS** |
| **ITT** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | Dominant |
| **HR+/HER2-** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | Dominant |
| **TNBC** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | Dominant |

2. Subgroup analyses

| | Talazoparib | | | PCT | | | Incremental | | | Deterministic |
|---|---|---|---|---|---|---|---|---|---|---|
| **Population** | **Cost** | **QALYs** | **LYs** | **Cost** | **QALYs** | **LYs** | **Cost** | **QALYs** | **LYs** | **ICER at [redacted] PAS** |
| **ITT (SM 1.2)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £ 20,647 |
| **HR+/HER2- (SM 1.2)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £18,355 |
| **TNBC (SM 1.7)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £22,750 |
| **TNBC (SM 1.2)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £32,229 |
| SM = severity modifier | | | | | | | | | | |

3. EMBRACA post-amendment transfusion rate

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| | Talazoparib | | | PCT | | | Incremental | | | Deterministic |
|---|---|---|---|---|---|---|---|---|---|---|
| **Population** | **Cost** | **QALYs** | **LYs** | **Cost** | **QALYs** | **LYs** | **Cost** | **QALYs** | **LYs** | **ICER at [redacted] PAS** |
| **ITT** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £23,061 |

4a. TA423 utility for PCT in progression-free health state

| | Talazoparib | | | PCT | | | Incremental | | | Deterministic |
|---|---|---|---|---|---|---|---|---|---|---|
| **Population** | **Cost** | **QALYs** | **LYs** | **Cost** | **QALYs** | **LYs** | **Cost** | **QALYs** | **LYs** | **ICER at [redacted] PAS** |
| **ITT** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £21,206 |

4b. Baseline utility from TA423 weighted by EMBRACA response rates

| | Talazoparib | | | PCT | | | Incremental | | | Deterministic |
|---|---|---|---|---|---|---|---|---|---|---|
| **Population** | **Cost** | **QALYs** | **LYs** | **Cost** | **QALYs** | **LYs** | **Cost** | **QALYs** | **LYs** | **ICER at [redacted] PAS** |
| **ITT** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £22,014 |

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**Overall survival in HR+/HER2- population:**

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**Progression-free survival in HR+/HER2- population:**

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**Overall survival in TNBC population:**

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**Progression-free survival in TNBC population**:

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**References**


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| | Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly.<br><br>The Appraisal Committee is interested in receiving comments on the following:<br>• has all of the relevant evidence been taken into account?<br>• are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?<br>• are the provisional recommendations sound and a suitable basis for guidance to the NHS?<br><br>NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations:<br>• could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology;<br>• could have any adverse impact on people with a particular disability or disabilities.<br><br>Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.** |
| **Organisation name – Stakeholder or respondent** (if you are responding as an individual rather than a registered stakeholder please leave blank): | Breast Cancer Now |

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|---|---|
| **Disclosure**<br>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.]<br>Please state:<br>• the name of the company<br>• the amount<br>• the purpose of funding including whether it related to a product mentioned in the stakeholder list<br>• whether it is ongoing or has ceased. | In the last 12 months (7/8/22-7/8/23), Breast Cancer Now has received the following funding from Pfizer:<br><br>- £30,000 one-off payment towards our Living with Secondary Breast Cancer face-to-face service (March 2023).<br><br>Breast Cancer Now does not accept any funding towards our policy and influencing work, which includes our work on access to medicines.<br><br>Breast Cancer Now-funded researchers contributed to the discovery of a targeted use for PARP inhibitors. The charity receives a share of royalties from the Institute of Cancer Research for sales of PARP inhibitor drugs being used in a targeted way to treat cancers with changes in BRCA genes, or other similar defects which mean that cancer cells are unable to properly repair their DNA. Income raised through the royalties/payments for PARP inhibitor drugs is invested back into the charity, so that Breast Cancer Now can continue to fund world-class research and life-changing support for everyone affected by breast cancer. |
| Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry. | N/A |
| **Name of commentator person completing form:** | [redacted] |

| **Comment number** | **Comments**<br><br>Insert each comment in a new row.<br>Do not paste other tables into this table, because your comments could get lost – type directly into this table. |
|---|---|
| 1 | It is very disappointing that NICE has provisionally been unable to recommend talazoparib as a treatment option for people with HER2-negative, locally advanced or secondary (metastatic) breast cancer with germline BRCA1 or BRCA 2 mutations.<br><br>As the ACD recognises, there is a high disease burden for people with this type of breast cancer. For many people, the uncertainty of living with secondary breast cancer can be the hardest part. In |

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| | |
|---|---|
| | addition to uncertainty and the emotional toll, people face different symptoms depending where their cancer has spread to as well as potential side effects of treatment, which can all significantly impact their day to day lives. One patient with this type of breast cancer explains *"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."*<br><br>Although around 5-10% of women with breast cancer carry an inherited altered gene, of which the BRCA1 and 2 genes are the most common, this provisional rejection means there remain no BRCA-targeted treatments available on the NHS for people living with incurable secondary breast cancer.<br><br>Talazoparib could help fill this gap and as noted in the ACD the committee has concluded that there is an unmet need for effective treatments for HER2-negative advanced breast cancer with germline BRCA mutations.<br><br>Evidence has shown that it could bring patients precious extra time before their disease progresses, compared with chemotherapy. This could enable people to continue doing what matters most to them. An improvement in progression free survival would be highly valued by patients.<br><br>It is important to recognise how the treatment may help maintain quality of life which is important for patients living with incurable secondary breast cancer. The trial did show improvements in quality of life compared to standard chemotherapy treatment, resulting in a delay in onset of clinically meaningful deterioration.<br><br>The ACD recognises transfusions which impacts cost-effectiveness and highlights the potential impact for patients. As with all breast cancer treatments they can have 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 and this would be a conversation for the patient to have with their treatment team. It does seem that the 38.1% rate is high especially given the reasons outlined by clinical experts during the committee regarding what they would expect to see in NHS practice and that using a figure below this would be more appropriate.<br><br>As talazoparib is taken as a daily tablet, it can potentially mean fewer hospital visits are required compared to intravenous chemotherapy which would also be valued by patients. As research (MacEwan JP, Doctor J, et al The Value of Progression-Free Survival in Metastatic Breast Cancer) has shown a wide range of factors are important from a patient perspective– including the administration method, the potential treatment side effects, and progression free survival.<br><br>As set out in our original submission, a patient with experience of this treatment explains:<br><br>*"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.*<br><br>*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."* |

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| | |
|---|---|
| | Talazoparib continues to be recognised in international guidelines as a possible treatment option including ESMO Clinical Practice Guideline and NCCN Clinical Guidelines and it is important that practice in England is not out of step.<br><br>During this consultation stage, we urge Pfizer and NICE to work together to help ensure that talazoparib can reach the patients who could potentially benefit from it on the NHS in England.<br><br>Talazoparib would provide an important alternative treatment option to chemotherapy on the NHS for this group of patients. |

Insert extra rows as needed

**Checklist for submitting comments**

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

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| | Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly.<br><br>The Appraisal Committee is interested in receiving comments on the following:<br>• has all of the relevant evidence been taken into account?<br>• are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?<br>• are the provisional recommendations sound and a suitable basis for guidance to the NHS?<br><br>NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations:<br>• could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology;<br>• could have any adverse impact on people with a particular disability or disabilities.<br><br>Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.** |
| **Organisation name – Stakeholder or respondent** (if you are responding as an individual rather than a registered stakeholder please leave blank): | METUPUK |

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|---|---|
| **Disclosure**<br>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.]<br>Please state:<br>• the name of the company<br>• the amount<br>• the purpose of funding including whether it related to a product mentioned in the stakeholder list<br>• whether it is ongoing or has ceased. | None |
| Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry. | None |
| **Name of commentator person completing form:** | [redacted] |

| **Comment number** | **Comments**<br><br>Insert each comment in a new row.<br>Do not paste other tables into this table, because your comments could get lost – type directly into this table. |
|---|---|
| Example 1 | We are concerned that this recommendation may imply that …….. |
| 1 | No, all the relevant evidence has not been taken into account. |

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| | |
|---|---|
| | The fact that NICE has not approved any parp inhibitor for germline BRCA mutated metastatic breast cancer has not been given proper consideration.<br><br>Parp inhibitors are targeted therapies and seen as the way forward in cancer care to treat specific mutations. A number of parp inhibitors are licenced in the UK and have been approved by NICE, for example olaparib for germline BRCA mutations in the early stage breast cancer setting and olaparib for the metastatic prostrate setting. The provisional rejection by NICE of talazoparib in the metastatic breast cancer setting has left life limited patients with the inherited harmful BRCA1 and BRCA2 variant devastated. They cannot comprehend why the licenced targeted treatment for their mutation has not been approved. They believe they are being left behind other cancer patients, they feel forgotten about and left to die on harsh chemotherapy drugs.<br>Patients with germline BRCA1/2 mutations value the option of a parp inhibitor, because targeted drugs help maintain a good quality of life for longer, compared to conventional chemotherapy. Patients on parp inhibitors can and do lead full and productive lives, with many still working and caring for their families.<br>Patients explain the devastation that the germline BRCA gene has on families. Because the harmful BRCA variant is inherited it has implications for all the generations within families. The mental health anguish of metastatic breast cancer is increased significantly when there are consequences across generations. It is seen as a family death sentence. NICE's provisional rejection of talazoparib has implications for current metastatic patients but also for family members in the next generation. Patients are devastated for the loss of quality time promised by talazoparib and the loss that their children will also face if and when they are diagnosed with metastatic disease.<br>A patient with a BRCA1 mutation who has been accessing olaparib for triple negative metastatic breast cancer shared her experience. She writes, "Being diagnosed with stage 4 breast cancer aged 26, with twins who were just days old was nothing short of heartbreaking. Thankfully, I'm still here and we're almost approaching their 3rd birthday. Now that may not have been the case if it wasn't for access to a parp inhibitor. This treatment line has lasted me 17 months so far, 17 months of watching my 3 children grow, learn and enjoy life with their mummy and the hope of more time to come." |
| 2 | The summaries of clinical and cost effectiveness are not reasonable interpretations of the evidence.<br><br>Blood transfusions – The EAG proposed using the rate of red cell blood transfusions in the EMBRACA trial to model cost effectiveness. The clinical experts were clear that the EMBRACA protocol does not reflect UK clinical practice for red cell transfusions. In the UK blood transfusions are used with caution, and so the clinical experts guidance of using dose reductions to manage moderate anaemia should have been given more weight. The lower rate of blood transfusions in the trial by Mahtani was deemed to be uncertain, despite it being on real life data from patients receiving talazoparib. Even by taking the Committee's preferred estimate of a rate of red cell transfusions between the EMBRACA trial and the Mahtani study, this gives much more weight to the EMBRACA protocol than is justified or reasonable.<br><br>The time benefit of progression free survival of talazoparib is significant 8.6 months versus 5.6 months, over a 50% increase in quality time with less anxiety and toxicity around progression. Metastatic breast cancer patients value quality time on kinder treatments. |
| 3 | No the recommendations are not sound and suitable guidance for the NHS.<br><br>There is a clear unmet need for a PARP inhibitor option for patients with metastatic breast cancer. Presently, the parp inhibitor olaparib is offered to patients with primary breast cancer, but if metastatic disease is confirmed, this option is removed with no parp inhibitor offered. Talazoparib is a targeted treatment, and patients value targeted treatments. Talazoparib offers patients a |

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

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| | better quality of life compared with intravenous chemotherapy which is the alternative treatment. Depending on the intravenous chemotherapy regimen, patients can spend two days in every week or every three weeks at the hospital having bloods checked or receiving treatment. For patients, hospital visits, with the associated routine long waits are debilitating, draining time, energies and take your soul which is extremely difficult for patients who know their lives are already shortened by their cancer. When length of life is short, time spent away from hospitals is particularly valued. As talazoparib is a tablet taken at home, capacity is freed up in stretched chemotherapy day units. |
| 4 | Breast cancer is a common disease, and approximately one in eight women will get it in their lifetime, with 80% of cases being in women over 50. The incidence and prevalence of germline mutated BRCA breast cancer is quite different to most breast cancer and disproportionately affects certain protected groups. Therefore these protected groups will be disproportionately disadvantaged if talazoparib is not approved, since there is no alternative parp inhibitor available to NHS patients with metastatic breast cancer.<br>• Age – BRCA mutated breast cancer usually occurs at a younger age than non-BRCA mutated breast cancer, is more aggressive and has a higher risk of death. Patients in this younger group are economically active, often with caring responsibilities for young children or elderly relatives.<br>• Sex – Breast cancer is rare males, but occurs more often in males who carry a mutated BRCA gene than other males.<br>• Race/religion – BRCA mutations occur at a higher frequency among Ashkenazi Jewish people and patients who carry a BRCA mutation have a higher risk of death compared Ashkenazi Jewish people who do not carry a BRCA mutation. |
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| 6 | |

Insert extra rows as needed

**Checklist for submitting comments**

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- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.

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**Note:** We reserve the right to summarise and edit comments received during consultations, 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 our consultations 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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| **Organisation name – Stakeholder or respondent** (if you are responding as an individual rather than a registered stakeholder please leave blank): | NHS England Genomics Unit |

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| Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry. | [Insert disclosure here] |
| **Name of commentator person completing form:** | [redacted] |

| **Comment number** | **Comments**<br>Insert each comment in a new row.<br>Do not paste other tables into this table, because your comments could get lost – type directly into this table. |
|---|---|
| Example 1 | We are concerned that this recommendation may imply that …….. |
| 1 | Section 3.20 of the draft guidance states that germline BRCA testing was not included in the economic analysis and that the committee's preferred assumption was not to include BRCA testing in the economic model, stated on page 21 of the draft guidance. |

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| | |
|---|---|
| | We believe that a substantial proportion of patients with BRCA positive metastatic breast cancer are currently not covered by NHSE funding for germline BRCA mutations. [redacted] |
| 2 | |
| 3 | |
| 4 | |
| 5 | |
| 6 | |

Insert extra rows as needed

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

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# ID1342 Talazoparib for BRCA-mutated metastatic breast cancer (MBC): the issue of how much BRCA testing is currently commissioned.

## 1 Population

1.1 There are approx. 47500 new patients presenting with breast cancer each year in England, a few without recording of the staging at diagnosis. 68% are HR pos Her2 neg, 15% are triple negative and 17% are Her2 pos.

| Known staging | Proportion | England patient numbers |
|---|---|---|
| Stage 1 | 44% | 20900 |
| Stage 2 | 41% | 19400 |
| Stage 3 | 9% | 4300 |
| Stage 4 | 5% | 2400 |
| Total | | 47000 |

1.2 We recognise that some of these assumptions can be challenged but the calculations below give two estimations and thus a range of the increased BRCA testing costs required for modelling of the implementation of any NICE recommendation for talazoparib in this indication.

## 2 Assumption of the proportion of patients with metastatic BC (all figures are approximate):

2.1 Assume 5% of stage 1 develop metastatic disease in the long run: about 1000 patients. 700 patients with HR pos Her2 neg, 150 with TNBC and 150 with Her 2 pos disease.

2.2 Assume 20% of stage 2 develop metastatic disease in the long run: 3900 patients. 2650 with HR pos Her2 neg, 600 with TNBC and 650 with Her2 pos disease.

2.3 40% of stage 3 develop metastatic disease in the long run: 1700 patients. 1150 have HR pos Her2 neg, 250 with TNBC and 300 with Her2 pos disease.

2.4 2400 patients present with de novo MBC. 1650 have HR pos Her2 neg, 350 with TNBC and 400 have Her2 pos disease.

2.5 Total/year is therefore about 9000 patients with MBC and 83% being her2 neg (7500 patients, 5500 recurrent to stage 4 and 2000 de novo stage 4).

## 3 BRCA testing for metastatic BC

3.1 Of the 2400 patients who present with MBC, 1650 have HR pos her2 neg and so need testing. 350 have TNBC and BRCA testing is already done. 400 patients have Her2 pos disease and thus are ineligible for talazoparib. Total of 1650 BRCA tests required. This figure needs to be reduced as some patients will already have had familial BRCA testing (estimated at 15%) and therefore assume that the number of BRCA tests required for de novo MBC reduces to 1400.

## 4 BRCA testing for recurrent BC

4.1 Of 6600 stage 1-3 patients who recur with MBC, 4500 have HR pos her2 neg and so need testing. 1000 have TNBC and BRCA testing is already commissioned. 1100 have Her2 pos disease and thus are ineligible for talazoparib.

4.2 The next issue is what proportion of these 4500 HR pos Her2 neg patients have already had BRCA testing for the adjuvant olaparib indication in high risk early BC. All the 1000 TNBC patients have had testing and the 1100 Her2 pos patients do not require testing.

4.3 Scenario A: this assumes that BRCA testing is performed when HR and Her2 testing results are done for early BC in which case all patients who relapse have already had BRCA testing. Zero additional BRCA tests are required for those patients who present with stage 1-3 disease.

4.4 Scenario B is that BRCA testing is done only in the high-risk HR pos Her2 neg early disease group if eligibility for adjuvant olaparib is being actively assessed according to the high risk definition used for this adjuvant olaparib indication (TA886). Since the chance of recurrence is obviously highest in those with high risk early BC, this scenario assumes that 60% of stage 3, 30% of stage 2 and 0% of stage 1 have already had BRCA testing.

4.5 This therefore means that 40% of 1150 patients developing MBC after stage 3 disease (about 450 patients) require tests and 70% of 2650 patients developing MBC after stage 2 disease (1850 patients) also require testing. All the 700 patients who develop MBC after stage 1 disease need to be tested. This means a total of 3000 (450+1850+700) extra tests are required but some will already have been done for familial BRCA testing in place for early breast cancer patients and so this figure falls to about 2500 tests (15% reduction, see section 2).

4.6 This means that 2000 (4500 – 2500) of the required 4500 tests (see 4.2) for HR pos Her 2 neg group are already being done in Scenario B and 2500 new tests will be required.

Scenario A means that new testing costs will be required for 1400 patients. (3.1)

Scenario B means that new testing costs will be required for 3900 (1400 + 2500) patients. (3.1 & 4.6)

**5 Testing Costs**

5.1 What is the cost to NHSE for a new diagnosis of BRCA pos MBC to go into a NICE TA? £525 per test and 10% incidence in MBC so superficially testing cost is £5250 per BRCA pos patient.

5.2 The overall Her 2 neg MBC patient number is 7500 patients.

5.3 Scenario A means that testing is only required for 1400 patients. The test cost of £525 is multiplied by 1400 and then divided by 7500 to give an average additional testing cost per Her2 neg patient of about £100. A 10% incidence of BRCA pos in Her 2 neg MBC patients therefore means that the incremental cost of BRCA testing to Her2 neg patients is about £1000 per BRCA pos patient.

5.4 Scenario B means that testing is required for 3900 patients. The test cost of £525 is multiplied by 3900 and then divided by 7500 to give an average additional testing cost per Her2 neg patient of about £275. A 10% incidence of BRCA pos in Her 2 neg MBC patients therefore means that the incremental cost of BRCA testing to Her2 neg patients is about £2750 per BRCA pos patient.

5.5 BRCA testing in NHS England is evolving due to the inclusion of TNBC in the Genomic Test Directory and more recently the consequence of adjuvant olaparib being approved in TA886. NHSE believes that the testing in place is currently more likely to closer to that of scenario B than scenario A.

Prof Peter Clark
NHS England Clinical Lead for the Cancer Drugs Fund
August 2023

# Comments on the Draft Guidance received from the public through the NICE Website

| | |
|---|---|
| **Name** | [redacted] |
| **Role** | Not specified |
| **Other role** | Not specified |
| **Organisation** | Not specified |
| **Location** | Not specified |
| **Conflict** | No |
| **Notes** | |

**Comments on the Draft Guidance:**

- Has all of the relevant evidence been taken into account?

Yes

- Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?

Yes

- Are the recommendations sound and a suitable basis for guidance to the NHS?

Yes

- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Yes

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

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| **Organisation name – Stakeholder or respondent** (if you are responding as an individual rather than a registered stakeholder please leave blank): | Pfizer UK |

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| • product mentioned in the stakeholder list<br>• whether it is ongoing or has ceased. | |
| Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry. | N/a |
| **Name of commentator person completing form:** | |

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| Comment number | Comments<br><br>Insert each comment in a new row.<br>Do not paste other tables into this table, because your comments could get lost – type directly into this table. |
|---|---|
| Summary | **Summary**<br><br>Pfizer is disappointed that NICE have chosen not to recommend talazoparib for the treatment of HER2-negative locally advanced or metastatic breast cancer with germline BRCA1/2-mutations following the Appraisal Committee Meeting (ACM) on 4th July 2023.<br><br>Talazoparib is the first targeted treatment indicated for gBRCAm HER2- aBC in England. In the EMBRACA trial, patients treated with talazoparib had significantly longer progression free survival than standard of care. As well as being efficacious, talazoparib provides a novel treatment mechanism and increases treatment choice, fulfilling a significant unmet need in this patient population.<br><br>Pfizer remains committed to securing access for patients and welcomes the opportunity to respond to the draft guidance document. Pfizer has provided a response to the following points:<br><br>• ***Increased the PAS*** – Pfizer has significantly increased the discount it is offering the NHS. All analysis incorporates this additional discount.<br><br>• ***Accepted the majority of committee preferences*** – Pfizer has accepted the following committee preferences:<br>  ○ Excluding relative dose intensity (RDI)<br>  ○ Cost of neutropenia<br>  ○ Utility value in the progressed disease (PD) health state<br>  ○ Assumption of no difference in resource use by complete/partial response (CR/PR) |

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| | ○ Red cell blood (RBC) transfusions rates<br>○ Kaplan-Meier (KM) data from EMBRACA to model time to treatment discontinuation (TTD)<br>• ***Exploration*** – Pfizer has responded to or explored the following:<br>○ Assumption of an overall survival benefit<br>○ Utility values for PCT in the progression-free health state<br>• ***Innovation and equity -*** Pfizer has provided a further explanation of the innovative nature of the treatment and the equity challenges<br>• ***Update base case –*** Pfizer has provided an updated base case of the cost effectiveness.<br><br>Pfizer believe that this response demonstrates that talazoparib would be a valued treatment for patients with HER2-negative locally advanced or metastatic breast cancer with germline BRCA1/2-mutations and is a cost-effective use of NHS resources. |
| Increase in PAS | Pfizer has increased the simple discount for talazoparib [redacted]. The updated base case and all scenario analyses include the updated price for talazoparib. |
| Committee assumptions | Pfizer has accepted the following committee assumptions:<br>○ Excluding relative dose intensity<br>○ Committee's preferred cost of neutropenia<br>○ Utility value in the progressed disease health state<br>○ Assumption of no difference in resource use by complete/partial response |

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| | ○ Mid-point for red cell blood transfusions rates<br>○ Kaplan-Meier (KM) data from EMBRACA to model time to treatment discontinuation (TTD) |
| Overall survival | The committee noted that they could not conclude that there was an overall survival benefit for those treated with talazoparib and requested analysis that considered no survival benefit (DG, paragraph 3.19). Pfizer acknowledge that the results demonstrate that a clear survival benefit is uncertain and have provided the analysis requested by the committee. However, given the large numerical benefit observed and skew of the data it is important to note a number of points and suggested an alternative:<br><br>**<u>Rationale for suggesting alternative approach:</u>**<br>• In the final OS analysis, the estimated HR was 0.848 (95% CI: 0.670, 1.073) and the p-value by stratified 2-sided log-rank test was 0.1693. This represents a 15% reduction in the risk of death. A higher percentage of patients in the PCT arm (47 patients [32.6%]) than in the talazoparib arm (13 patients [4.5%]) took a post-study PARP inhibitor, which may have influenced the OS outcome.<br>• There was an improvement in 2-, 3- and 4-year survival favouring talazoparib compared to PCT. The survival probabilities at 2 and 3 years for talazoparib compared to PCT were 0.42 (95% CI: 0.36, 0.47) versus 0.38 (95% CI: 0.30, 0.47) and 0.27 (95% CI: 0.22, 0.33) versus 0.21 (95% CI: 0.14, 0.29), respectively. The 4-year survival probabilities for talazoparib compared to PCT were 0.19 (95% CI: 0.14, 0,25) versus 0.07 (95% CI: 0.02, 0.15).<br>• Subgroup analyses were generally consistent with the primary OS outcome.<br>• Additional analyses assessing the impact of postbaseline treatment with PARP inhibitors only using a RPSFTM resulted in an HR of 0.82 (95% bootstrap CI: 0.62, 1.05). A lack of statistical significance does not prove the null hypothesis that there is no difference in overall survival between talazoparib and PCT.<br>• A retrospective analysis of patients in the intent-to-treat (ITT) population of EMBRACA was conducted in which patients were mapped into two groups based on response: |

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- LONG (patients in TALA arm with overall survival [OS] ≥30 months and duration of treatment ≥24 months (n=37); patients in PCT arm with OS ≥30 months (n=34));
- SHORT (pts in either arm with a PFS event [progressive disease by Independent Radiological Facility or death] ≤12 weeks).[1]

Of note, over half (52.9%) of PCT LONG responders received postbaseline olaparib (Figure 1), which is not part of the treatment pathway in UK clinical practice, and therefore potentially providing some rationale for the non-statistically significant improvement in survival versus PCT.

**Figure 1. Characterisation of long-term responders following treatment with talazoparib (TALA) or physician's choice of chemotherapy (PCT) in the phase 3 EMBRACA trial**

| | TALA – LONG (n = 37) | PCT – LONG (n = 34) | TALA – SHORT (n = 40) | PCT – SHORT (n = 32) |
|---|---|---|---|---|
| Median age, y | 50.0 | 50.5 | 42.5 | 45.5 |
| | No. (%) | | | |
| TNBC | 17 (45.9) | 10 (29.4) | 25 (62.5) | 20 (62.5) |
| HR+ BC | 20 (54.1) | 24 (70.6) | 15 (37.5) | 12 (37.5) |
| *BRCA1* status | 16 (43.2) | 7 (20.6) | 25 (62.5) | 18 (56.3) |
| *BRCA2* status | 20 (54.1) | 25 (73.5) | 12 (30.0) | 14 (43.8) |
| No prior CT for ABC | 21 (56.8) | 20 (58.8) | 8 (20.0) | 6 (18.8) |
| 1 prior CT for ABC | 12 (32.4) | 8 (23.5) | 14 (35.0) | 13 (40.6) |
| ≥2 prior CT for ABC | 4 (10.8) | 6 (17.6) | 18 (45.0) | 13 (40.6) |
| Prior platinum | 5 (13.5) | 4 (11.8) | 11 (27.5) | 10 (31.3) |
| Postbaseline olaparib | 1 (2.7) | 18 (52.9) | 0 | 5 (15.6) |

Given the above, we believe that this demonstrate that there are a proportion of patients for whom there is a survival benefit.

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| | • In a previous appraisals of PARP inhibitor, NICE committees have accepted a non-statistically significant but numerical difference in overall survival<br>  ○ TA784 (Niraparib, ovarian cancer) - The committee recalled that median overall survival had not been reached in the original appraisal of niraparib and that survival benefit with niraparib was the main clinical uncertainty. Updated data from NOVA showed: The difference in median overall survival between niraparib and placebo was 5.4 months (HR 1.1; 95% CI 0.83 to 1.46).<br>  ○ The committee noted that NOVA was not powered to test for statistical significance for overall survival, and the company and ERG explained that the results for the placebo arm are confounded by a high rate of subsequent PARP inhibitor use and missing data. In response to the committee's request for a conservative scenario assuming no overall survival benefit for people without a BRCA mutation, the company highlighted that the assumption of a gain in progression-free survival resulting in zero overall survival gain is not clinically plausible.<br>  ○ It noted that this was supported by trial evidence for maintenance therapies in advanced relapsed ovarian cancer and that a 1:1 progression-free survival to overall survival ratio should be the minimum survival benefit with niraparib compared with routine surveillance. The committee concluded that estimating overall survival for people without a BRCA mutation using data from Study 19 for routine surveillance which results in a survival benefit for people without a BRCA mutation is reasonable.<br><br>**<u>Alternative approach</u>**<br><br>Pfizer believe that it is not appropriate to disregard the overall survival data based on the uncertainty. The NICE manual states that ***"…in general, uncertainty around individual parameters is not a reason to exclude them from probabilistic analyses; rather, that uncertainty should be captured in the analysis" (4.7.12).***[2] While uncertain, Pfizer believe that the overall survival data should remain and be sampled probabilistically as part of the probabilistic estimate in the economic model. This is reflected in the updated company base case presented in the results. |
| EAG response | OS improvements for patients treated with talazoparib versus PCT are not statistically significant even after adjustment for subsequent PARP inhibitor use. The EAG considers that the company has presented no new evidence specifically for talazoparib to support a claim |

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

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| | for an OS gain. The information from previous appraisals provided by the company is informative, each NICE STA submission is unique; prior committee decisions can be informative for future submissions but they are not binding.<br><br>The EAG is unable to identify exactly how ITT OS has now been implemented in the company's PSA. ITT OS does not appear to vary significantly between PSA runs and remains close to the deterministic value. The uncertainty around OS does not therefore appear to have been captured by the PSA.<br><br>The company has run a scenario in which OS for patients treated with PCT is the same as OS for patients treated with talazoparib (as requested by the NICE AC). The EAG highlights that this scenario removes most of the QALY gain from treatment with talazoparib and therefore leads to a large increase in the ICER per QALY gained for the comparison of talazoparib versus PCT. |
| Subgroups | The committee noted that '*subgroup analyses should be interpreted with caution*' (DG, paragraph 3.11), specifically relating to the overall survival analysis. '*But, given the entirety of the evidence and the uncertainties, it concluded that additional evidence or analysis from the trial exploring talazoparib's effect on overall survival in the overall population and subgroups would provide further insight to inform decision making'* (DG, paragraph 3.11).<br><br>Pfizer has previously provided the KM curve of overall survival for the TNBC subgroup in the technical engagement response.<br><br>The draft guidance does not recognise the strong clinical opinions repeatedly voiced during the committee meeting that stated the EMBRACA trial was not powered to detect these differences in these results and should not be considered by the committee. The company agrees with the clinical experts' opinions and maintains that it is inappropriate to draw conclusions about the clinical and cost-effectiveness results by subgroup. The company has previously provided the overall survival results from EMBRACA and doesn't consider it appropriate to interrogate these further. However, Pfizer has provided cost-effectiveness results by subgroup, although it should be noted that Pfizer does not consider it appropriate to consider the subgroups, for the following reasons:<br><br>• The EMBRACA trial enrolled a molecularly selected population, as inherited mutations in BRCA1 and BRCA2 genes account for about 4-6% of all breast cancer cases in women and around 11-12% of cases in men.[3] As a result, less than [redacted] patients are expected to be eligible to receive treatment with talazoparib per year across England and Wales. |

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| | • Paragraph 3.11 of the DG: "*The clinical experts explained that there was no biological mechanism that would predict that hormone receptor status would affect the treatment effect of talazoparib in people with advanced breast cancer."*<br><br>However, if the committee consider it to be appropriate to explore subgroup analyses, it is important to consider the following unmet need and equity considerations for TNBC:<br>• There is a higher unmet need within the TNBC population raising concern of equity. TNBC can be more aggressive and harder to treat than other types of breast cancer, resulting in potentially poorer outcomes and short prognoses, with a lack of targeted treatment options.<br>• TNBC are more likely to be younger and from black or Hispanic ethnic backgrounds[4] and TNBC disproportionately affects women under 40 years.[5] The median age of TNBC patients in EMBRACA was 43 years.[6] Using the MVH value set + HSE 2014 ALDVMM model, and 1.02 QALYs with PCT, the proportional shortfall for TNBC patients is 0.9432. QALY shortfall calculation results are included in the appendix to this document.<br>• To capture the severity of disease in the TNBC subgroup, it is arguable that the severity modifier of 1.7 should be applied. As outlined in the 2022 NICE methods guidance **6.2.18** ***"If either the proportional or absolute QALY shortfall calculated falls on the cut-off between severity levels, the higher severity level will apply."*** [2]<br><br>The company strongly believes that the committee should consider the ITT population. We also request that if this topic is to be discussed further, the clinical experts are present so the committee can be fully informed for their decision making. |
| EAG response | The company suggests that EMBRACA trial subgroup results should be ignored due to the trial not being sufficiently powered to detect a statistical difference for OS subgroups. The EAG notes that the EMBRACA trial was powered to detect a clinically meaningful difference in OS for the ITT population but no statistically significant difference in OS was found. If trial power is important for interpreting trial results, then the EAG considers that the non-significant OS gain for the ITT population should not be modelled. If an OS gain for the ITT population is modelled, the EAG considers that subgroup OS results should also be modelled.<br><br>The EAG highlights that the subgroup analyses that were presented by the company could not be critiqued as no information was provided to show how subgroup OS, PFS and TTD curves were chosen. |

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| Transfusion rates | Pfizer accepts the committee conclusion that "the rate of red cell blood transfusions for talazoparib in the NHS is likely to be a value between the trial and the Mahtani study" (DG, paragraph 3.16). Therefore, Pfizer has applied a mid-value of 23.1% has been used in the revised company base case, which is the midpoint between 8.3% and 38.1%.<br>The committee also requested further information on "*triggers of blood transfusion from EMBRACA, and analyses exploring the relationship between dosing, dose reduction, red blood transfusion rate and treatment effect of talazoparib*" (DG, paragraph 3.16). Pfizer has explored this, however, there is insufficient evidence to ascertain whether the dose reduction impacted PFS. 53.1% of patients had at least 1 dose reduction in EMBRACA[7] and therefore the efficacy observed in the trial accounts for this. The clinical experts present in the committee meeting were confident that the difference in their approach to transfusions would not affect the clinical effectiveness of talazoparib (DG, paragraph 3.16). Furthermore, there is evidence from clinical trials shows that restrictive transfusion strategies (transfusing one unit at a time and using a lower haemoglobin threshold) do not increase morbidity or mortality among diverse populations of hospitalised patients.[8] |
| EAG response | The EAG accepts that transfusion rates for patients treated with talazoparib will be lower in NHS clinical practice than transfusion rates for patients in the EMBRACA trial. However, the EAG considers that transfusion rates could directly impact outcomes, including patient reported outcomes, e.g., EQ-5D and efficacy (PFS and OS) due to the explicit link between Hb levels and dose reduction or time on treatment for patients treated with talazoparib.<br><br>The EAG notes that evidence from clinical trials about changing transfusion strategies in a diverse population is of limited relevance to this appraisal as, in this appraisal, patients treated with talazoparib are given transfusions to allow them to remain on treatment. |
| Utility values | The company agrees with the committee that there may be 'other factors that may affect utility when receiving talazoparib or the comparator treatment' (DG, paragraph 3.17), for example, needing red blood transfusions and hospital visits associated with the chemotherapies. We consider that it is reasonable to assume a difference in utility values between talazoparib and PCT, and as a result have explored alternative PCT utility values.<br><br>Real-world PROs showed a 0.08 difference in utility values between PARPi and chemotherapy,[9] which is higher than the 0.063 difference observed in EMBRACA. However, we do acknowledge the limitations of this study which included no UK patients, and unlike EMBRACA the chemotherapy cohort in the study included 50% of patients who received platinum-based chemotherapy. |

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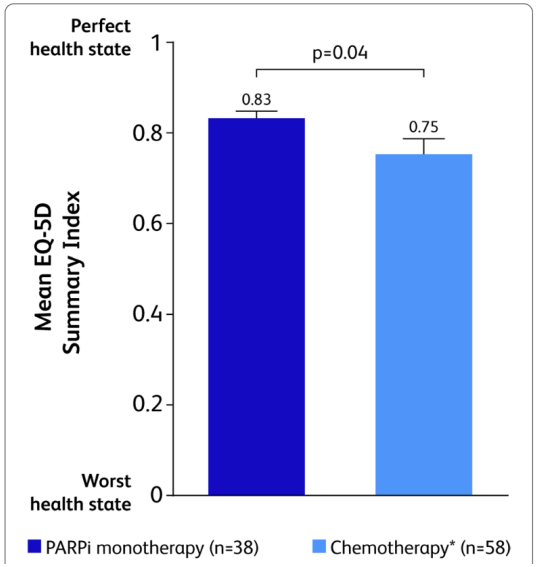
| | **Figure 2. PROs for PARPi monotherapy and chemotherapy (*from Mahtani et al. (2022)[9]*)**<br>  <br><br>Pfizer has explored PCT utility values accepted in previous breast cancer appraisals:<br>• In TA423, the appraisal of eribulin for treating locally advanced or metastatic breast cancer after 2 or more chemotherapy regimens (TA423), the reported utility values for eribulin and TPC were 0.705 and 0.701 respectively.<br>• In TA704 (trastuzumab deruxtecan for treating HER2-positive mBC), the company used utility values from TA423. Treatment dependent utility values for the 'progression-free on treatment' health state were calculated as a function of the overall response rate for each treatment. The clinical expert confirmed that in metastatic breast cancer, there was a clear link between health-related quality of life and objective response rate, progression-free survival, and treatment-emergent adverse events. The accepted utility values for eribulin/ capecitabine/ vinorelbine were 0.715/0.718/0.728. |

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| | • In TA786 (tucatinib – for HER2-positive advanced breast cancer), utilities for the comparator therapies were from TA423. The ERG explained the company approach was inappropriate because the differences in utilities between tucatinib and comparators were not based on comparative evidence. The clinical experts in this appraisal explained that the company's approach was not methodologically robust because it used utility values from 2 different sources in a 'naive comparison', that is, without adjusting for any differences between populations in these sources that might have affected the utility values. The committee noted that in future they would prefer 'evidence-based utilities'.<br><br>• EMBRACA is an evidence-based source of utility data for talazoparib and PCT, which is supported by RWD. Therefore, the company have maintained the EMRACA utility values for talazoparib ([redacted]) and PCT ([redacted]) in its base case.<br><br>Pfizer acknowledge that there may be some limitations to the utility evidence generated in EMBRACA but agree that there are important factors between treatment arms that should be taken into consideration. We recognise previous decisions that have accepted such differences in advanced breast cancer in addition to committee's preference for evidenced based utilities. Weighing this up Pfizer has kept the utilities observed in the trial as we feel they represent important difference experienced by patients. However, we have also provided 2 more conservative scenarios exploring the utility values<br>• Where 0.701 from TA423 reported for treatment of physician's choice, representing an incremental utility gain of 0.049 for talazoparib in the revised economic model, a reduction from the 0.063 difference observed in EMBRACA.<br><br>• Where the baseline utility value for PCT 0f 0.701 (obtained from TA423) is weighted by the incremental utility of response accepted in TA704 (0.076). In EMBRACA, the objective response rate was higher in the talazoparib group than in the PCT group (62.6% vs. 27.2%; odds ratio, 5.0; 95% CI, 2.9 to 8.8; P<0.001.[10] This results in utility values of 0.72 for PCT and 0.75 for talazoparib. |
| EAG response | The EAG's primary concern about using EMBRACA trial treatment-specific utility values is that the EMBRACA trial was unblinded and therefore self-reported outcomes (such as EQ-5D) are prone to bias. The company has not addressed this concern. The EAG considers that using treatment specific utility values from a different trial (and potentially different treatments) provides results that may be biased. |

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| | The EAG considers that use of treatment-specific utility values derived from the EMBRACA trial data should not be used to inform decision making. |
| Innovation and uncaptured benefits | A letter from the Association of Cancer Physicians letter to the Department of Health in May 2023 highlighted serious concerns about a critical lack of capacity within oncology departments, a lack of equivalent investment or support for the oncology workforce means departments are failing to keep pace and the resulting compromise on patient safety and quality of care.[11] The availability of an oral treatment with a demonstrated improvement in progression-free survival can minimise inpatient attendance and resource use. We agree with the statement from Breast Cancer Now, that fewer hospital visits would *"free up valuable time for both patients and overstretched clinics."*[12]<br><br>There is currently no BRCA targeted therapy available in the NHS in the metastatic breast cancer space, even though patients who may benefit from talazoparib are being identified through NHS BRCA testing. The availability of talazoparib for this patient population is aligned with the NHS genomics strategy, which states the ambition of accelerating the use of genomic medicine across the NHS, providing a world leading, equitable service to populations and individuals.<br><br>In the company submission in January 2023, [redacted] patients were predicted to be eligible for talazoparib. This number is now expected to be lower since the approval of olaparib for BRCA mutated HER2-negative high-risk early breast cancer in May 2023 (TA886). Therefore, the budget impact, and associated absolute decision risk for this appraisal are low. |
| EAG response | No comment. |
| Updated base case results | Pfizer's updated base case includes committee's preferred assumption with the following exceptions:<br>• Overall survival – taken from the EMBRACA with uncertainty factored into probabilistic analysis.<br>• Utility values for PCT from EMBRACA ([redacted] for talazoparib and 0.687 for [redacted])<br><br>Pfizer's base case is in the ITT population, however, subgroup analysis has been provided. Scenario analysis in the ITT population has been provided exploring:<br>• Overall survival – excluding any survival benefit |

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- Transfusion rates
- PCT utility value from TA423

The updated base case results are presented below:

| | Talazoparib | | | PCT | | | Incremental | | | Probabilistic |
|---|---|---|---|---|---|---|---|---|---|---|
| **Population** | **Cost** | **QALYs** | **LYs** | **Cost** | **QALYs** | **LYs** | **Cost** | **QALYs** | **LYs** | **ICER at [redacted] PAS** |
| **ITT** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £19,810 |

The cost-effectiveness acceptability curve (Figure 4) and probabilistic scatter plot (Figure 5) for the ITT population are also presented below, demonstrating that talazoparib has a 65% probability of being cost-effective at the £30,000 WTP threshold.

**Figure 4. Cost-effectiveness acceptability curve**

[redacted]

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| | |
|---|---|
| | **Figure 5. Scatter plot of probabilistic sensitivity analysis**<br>  |
| EAG comment | The EAG was unable to replicate the company revised base case results due to errors in the model submitted in response to the draft guidance, namely:<br>• the EAG micro-costing and subsequent treatment reweighting revision was missing<br>• the EAG neutropenia revision was not active in the model<br>• some EAG model drug prices were not used.<br>Company revised base case and NICE ACM1 preferred cost effectiveness results (and relevant assumptions) can in found in the post-ACM1 appendix (PAS price for talazoparib, publicly available prices for all other drugs) and the post-ACM1 confidential appendix (confidential prices). These results have been generated using the EAG model submitted to NICE pre-ACM1 (25 May 2023).<br><br>NHS England has advised NICE that costs for BRCA testing should be included in the cost effectiveness analyses and NHS England has provided the costs of a BRCA test (£525). Only 10% of those tested will be BRCA+ and therefore eligible for treatment with |

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talazoparib. The cost of BRCA testing to identify one patient who is BRCA+ is therefore £5,250. The EAG has estimated that, based on information provided by NHS England, if talazoparib is routinely commissioned, 52% of the ITT population, 64% of the HR+/HER2- population and 0% of the TNBC population will require a BRCA test. These proportions correspond to NHS England Scenario B which assumed that patients who present with both de novo and recurrent MBC require BRCA testing. NHS England also presented a scenario which assumed that only patients who present with de novo MBC require BRCA testing as all patients with recurrent MBC will have previously been tested (Scenario A). In Scenario A, if talazoparib is routinely commissioned, 19% of the ITT population and 23% of the HR+/HER2- population will require a BRCA test. NHS England considered Scenario B was likely to be more representative than Scenario A of anticipated NHS BRCA testing practice.

Scenario analysis results

1. **Overall survival**

Scenario analyses are presented below, by subgroup, assuming that there is no survival benefit associated with talazoparib over PCT:

| | Talazoparib | | | PCT | | | Incremental | | | Probabilistic |
|---|---|---|---|---|---|---|---|---|---|---|
| **Population** | **Cost** | **QALYs** | **LYs** | **Cost** | **QALYs** | **LYs** | **Cost** | **QALYs** | **LYs** | **ICER at [redacted] PAS** |
| **ITT** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | Dominant |
| **HR+/HER2-** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | Dominant |
| **TNBC** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | Dominant |

2. **Subgroup analyses**

Subgroup analyses for the HR+/HER2- and TNBC populations are presented below based on new company base case. Results are presented using both the 1.2 and 1.7 severity modifier for TNBC.

| | Talazoparib | | | PCT | | | Incremental | | | Probabilistic |
|---|---|---|---|---|---|---|---|---|---|---|
| **Population** | **Cost** | **QALYs** | **LYs** | **Cost** | **QALYs** | **LYs** | **Cost** | **QALYs** | **LYs** | **ICER at [redacted] PAS** |
| **ITT (SM 1.2)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £19,810 |
| **HR+/HER2- (SM 1.2)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £15,981 |
| **TNBC (SM 1.7)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £21,427 |
| **TNBC (SM 1.2)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £30,356 |

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SM = severity modifier

In addition, the KM curves for subgroups are presented in an appendix to this document.
In conclusion, whilst analysis of select patients in the ITT population may result in higher ICER values, the average population is cost-effective with the revised PAS offer.

### 3. Transfusion rate

A scenario analysis is also presented, in which the post-amendment transfusion rate of 32.4% is applied in the model. This scenario increases the ICER by £2,079. The results are presented below:

| | Talazoparib | | | PCT | | | Incremental | | | Probabilistic |
|---|---|---|---|---|---|---|---|---|---|---|
| **Population** | **Cost** | **QALYs** | **LYs** | **Cost** | **QALYs** | **LYs** | **Cost** | **QALYs** | **LYs** | **ICER at [redacted] PAS** |
| **ITT** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £21,889 |

### 4. Utilities

a. An alternative scenario for utilities (using the PCT utility value of 0.701 from TA423) is presented below. This scenario increases the ICER by £1,638.

| | Talazoparib | | | PCT | | | Incremental | | | Probabilistic |
|---|---|---|---|---|---|---|---|---|---|---|
| **Population** | **Cost** | **QALYs** | **LYs** | **Cost** | **QALYs** | **LYs** | **Cost** | **QALYs** | **LYs** | **ICER at [redacted] PAS** |
| **ITT** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £21,448 |

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b. An additional alternative scenario for utilities is presented, where the baseline utility value for PCT 0f 0.701 (obtained from TA423) is weighted by the incremental utility of response accepted in TA704 (0.076). This results in utility values of 0.72 for PCT and 0.75 for talazoparib. This scenario increases the ICER by £2,115.

| | Talazoparib | | | PCT | | | Incremental | | | Probabilistic |
|---|---|---|---|---|---|---|---|---|---|---|
| **Population** | **Cost** | **QALYs** | **LYs** | **Cost** | **QALYs** | **LYs** | **Cost** | **QALYs** | **LYs** | **ICER at [redacted] PAS** |
| **ITT** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £21,925 |

Insert extra rows as needed

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- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
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**Appendix:**

**QALY shortfall calculation results**

| **Outcome** | **Total QALYs** | **Shortfall** | |
|---|---|---|---|
| | | **Absolute** | **Proportional** |
| General Population | 17.95 | | |
| Disease Specific | 1.02 | 16.93 | 0.9432 |

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**Deterministic results:**

**Company base case**

| | Talazoparib | | | PCT | | | Incremental | | | Deterministic |
|---|---|---|---|---|---|---|---|---|---|---|
| **Population** | **Cost** | **QALYs** | **LYs** | **Cost** | **QALYs** | **LYs** | **Cost** | **QALYs** | **LYs** | **ICER at [redacted] PAS** |
| **ITT** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £20,647 |

**Scenario analyses**

1. Removing talazoparib survival benefit (by subgroup)

| | Talazoparib | | | PCT | | | Incremental | | | Deterministic |
|---|---|---|---|---|---|---|---|---|---|---|
| **Population** | **Cost** | **QALYs** | **LYs** | **Cost** | **QALYs** | **LYs** | **Cost** | **QALYs** | **LYs** | **ICER at [redacted] PAS** |
| **ITT** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | Dominant |
| **HR+/HER2-** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | Dominant |
| **TNBC** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | Dominant |

2. Subgroup analyses

| | Talazoparib | | | PCT | | | Incremental | | | Deterministic |
|---|---|---|---|---|---|---|---|---|---|---|
| **Population** | **Cost** | **QALYs** | **LYs** | **Cost** | **QALYs** | **LYs** | **Cost** | **QALYs** | **LYs** | **ICER at [redacted] PAS** |
| **ITT (SM 1.2)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £ 20,647 |
| **HR+/HER2- (SM 1.2)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £18,355 |
| **TNBC (SM 1.7)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £22,750 |
| **TNBC (SM 1.2)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £32,229 |
| SM = severity modifier | | | | | | | | | | |

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

**Draft guidance comments form**

**Consultation on the draft guidance document – deadline for comments** by the end of 18 August 2023. Please submit via NICE Docs.

3. EMBRACA post-amendment transfusion rate

| | Talazoparib | | | PCT | | | Incremental | | | Deterministic |
|---|---|---|---|---|---|---|---|---|---|---|
| **Population** | **Cost** | **QALYs** | **LYs** | **Cost** | **QALYs** | **LYs** | **Cost** | **QALYs** | **LYs** | **ICER at [redacted] PAS** |
| **ITT** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £23,061 |

4a. TA423 utility for PCT in progression-free health state

| | Talazoparib | | | PCT | | | Incremental | | | Deterministic |
|---|---|---|---|---|---|---|---|---|---|---|
| **Population** | **Cost** | **QALYs** | **LYs** | **Cost** | **QALYs** | **LYs** | **Cost** | **QALYs** | **LYs** | **ICER at [redacted] PAS** |
| **ITT** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £21,206 |

4b. Baseline utility from TA423 weighted by EMBRACA response rates

| | Talazoparib | | | PCT | | | Incremental | | | Deterministic |
|---|---|---|---|---|---|---|---|---|---|---|
| **Population** | **Cost** | **QALYs** | **LYs** | **Cost** | **QALYs** | **LYs** | **Cost** | **QALYs** | **LYs** | **ICER at [redacted] PAS** |
| **ITT** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £22,014 |

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**Overall survival in HR+/HER2- population:**

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**Draft guidance comments form**

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**Progression-free survival in HR+/HER2- population:**

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

**Draft guidance comments form**

**Consultation on the draft guidance document – deadline for comments** by the end of 18 August 2023. Please submit via NICE Docs.

**Overall survival in TNBC population:**

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

**Draft guidance comments form**

**Consultation on the draft guidance document – deadline for comments** by the end of 18 August 2023. Please submit via NICE Docs.

**Progression-free survival in TNBC population**:

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

**Draft guidance comments form**

**Consultation on the draft guidance document – deadline for comments** by the end of 18 August 2023. Please submit via NICE Docs.

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EAG POST-ACM1 APPENDIX

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

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

## EAG response to the company response to post-ACM1 draft guidance. Cost effectiveness results generated using discounted prices for talazoparib

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

Completed 30th August 2023

CONTAINS COMMERCIAL IN CONFIDENCE DATA



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This appendix contains company revised base case (post ACM1) cost effectiveness results; these cost effectiveness results were generated by applying company revisions to the EAG model (25 May 2023).

The following cost effectiveness results, also generated using the EAG model (25 May 2023), are presented:

- NICE ACM1 preference (Table 1, Table 2a, Table 2b and Table 3a and Table 3b); the only difference between the NICE ACM1 analysis and company base case analysis is that the NICE ACM1 preference was to use the same PFS utility value irrespective of treatment (PCT value of 0.750)
- company scenarios presented in the company response to NICE ACM1 draft guidance (Table 4 and Table 5)
- PMB2 discussions (Table 6 and Table 7).

The revised company base case analysis includes the following assumptions:

- OS benefit for talazoparib versus PCT (modelled using best fit parametric distributions)
- PFS utility values differ by treatment arm
- RDI excluded
- cost of filgrastim as a 14-day course for treating an episode of neutropenia
- utility value of 0.650 from Lambert-Obry 2018 used for the PD health state
- assumption of no difference in resource use by CR/PR
- RBC transfusions rate of 23.1% (midpoint between the EMBRACA trial and the Mahtani study)
- EMBRACA trial K-M data were used to model TTD.

Table 1 Company revised base case (ITT population, updated PAS price for talazoparib)*

| Analysis | Talazoparib | | | PCT | | | Incremental | | | Probabilistic ICER† |
|---|---|---|---|---|---|---|---|---|---|---|
| | Cost | QALYs | LYs | Cost | QALYs | LYs | Cost | QALYs | LYs | |
| Company | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| NICE ACM1 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

*Company revisions applied to EAG model (25 May 2023)
†Generated using a 1.2 QALY multiplier
ACM1=Appraisal Committee Meeting 1; ICER=incremental cost effectiveness ratio; ITT=intention to treat; LY=life years; PAS=Patient Access Scheme; PCT=physician choice of treatment; QALY=quality adjusted life year

Table 2a Company scenario 1 - no overall survival benefit (updated PAS price for talazoparib)*

| Analysis | Talazoparib | | | PCT | | | Incremental | | | Probabilistic ICER† |
|---|---|---|---|---|---|---|---|---|---|---|
| | Cost | QALYs | LYs | Cost | QALYs | LYs | Cost | QALYs | LYs | |
| ITT | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| HR+/HER2- | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| TNBC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

*Company revisions applied to EAG model (25 May 2023)
†Generated using a 1.2 QALY multiplier
HR+=hormone receptor positive; HER2=human epidermal growth factor 2; ICER=incremental cost effectiveness ratio; LY=life years; PAS=Patient Access Scheme; PCT=physician choice of treatment; QALY=quality adjusted life year; TNBC=triple negative breast cancer

Table 2b Company scenario 1 – no overall survival benefit, NICE AC preferred assumptions (updated PAS price for talazoparib)*

| Analysis | Talazoparib | | | PCT | | | Incremental | | | Probabilistic ICER† |
|---|---|---|---|---|---|---|---|---|---|---|
| | Cost | QALYs | LYs | Cost | QALYs | LYs | Cost | QALYs | LYs | |
| ITT | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| HR+/HER2- | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| TNBC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

*Company revisions applied to EAG model (25 May 2023)
†Generated using a 1.2 QALY multiplier
HR+=hormone receptor positive; HER2=human epidermal growth factor 2; ICER=incremental cost effectiveness ratio; LY=life years; PAS=Patient Access Scheme; PCT=physician choice of treatment; QALY=quality adjusted life year; TNBC=triple negative breast cancer

Table 3a Company scenario 2 - subgroup analyses (updated PAS price for talazoparib)*

| Analysis | Talazoparib | | | PCT | | | Incremental | | | Probabilistic ICER† |
|---|---|---|---|---|---|---|---|---|---|---|
| | Cost | QALYs | LYs | Cost | QALYs | LYs | Cost | QALYs | LYs | |
| ITT | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| HR+/HER2- | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| TNBC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

*Company revisions applied to EAG model (25 May 2023)
†Generated using a 1.2 QALY multiplier
HR+=hormone receptor positive; HER2=human epidermal growth factor 2; ICER=incremental cost effectiveness ratio; LY=life years; PAS=Patient Access Scheme; PCT=physician choice of treatment; QALY=quality adjusted life year; TNBC=triple negative breast cancer

Table 3b Company scenario 2 - subgroup analyses, NICE AC preferred assumptions (updated PAS price for talazoparib)*

| Analysis | Talazoparib | | | PCT | | | Incremental | | | Probabilistic ICER† |
|---|---|---|---|---|---|---|---|---|---|---|
| | Cost | QALYs | LYs | Cost | QALYs | LYs | Cost | QALYs | LYs | |
| ITT | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| HR+/HER2- | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| TNBC | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

*Company revisions applied to EAG model (25 May 2023)
†Generated using a 1.2 QALY multiplier
HR+=hormone receptor positive; HER2=human epidermal growth factor 2; ICER=incremental cost effectiveness ratio; LY=life years; PCT=physician choice of treatment; QALY=quality adjusted life year; TNBC=triple negative breast cancer

Table 4 Company scenario 3 - alternative transfusion rate (32.4%) (ITT population, updated PAS price for talazoparib)*

| Analysis | Talazoparib | | | PCT | | | Incremental | | | Probabilistic ICER† |
|---|---|---|---|---|---|---|---|---|---|---|
| | Cost | QALYs | LYs | Cost | QALYs | LYs | Cost | QALYs | LYs | |
| Company | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| NICE ACM1 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

*Company revisions applied to EAG model (25 May 2023)
†Generated using a 1.2 QALY multiplier
ACM1=Appraisal Committee Meeting 1; ICER=incremental cost effectiveness ratio; LY=life years; PAS=Patient Access Scheme; PCT=physician choice of treatment; QALY=quality adjusted life year

Table 5 Company scenario 4 - alternative PCT PFS utility values (ITT population, updated PAS price for talazoparib)*

| Analysis | Talazoparib | | | PCT | | | Incremental | | | Probabilistic ICER† |
|---|---|---|---|---|---|---|---|---|---|---|
| | Cost | QALYs | LYs | Cost | QALYs | LYs | Cost | QALYs | LYs | |
| Utility value: 0.701 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Utility value: 0.720 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

*Company revisions applied to EAG model (25 May 2023)
†Generated using a 1.2 QALY multiplier
ICER=incremental cost effectiveness ratio; ITT=intention to treat; LY=life years; PAS=Patient Access Scheme; PCT=physician choice of treatment; QALY=quality adjusted life year; TNBC=triple negative breast cancer

Table 6 Base case results with BRCA testing cost included (NHS England Scenario B, ITT population, updated PAS price for talazoparib)*

| Analysis | Talazoparib | | | PCT | | | Incremental | | | Probabilistic ICER† |
|---|---|---|---|---|---|---|---|---|---|---|
| | Cost | QALYs | LYs | Cost | QALYs | LYs | Cost | QALYs | LYs | |
| Company | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| NICE ACM1 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

*Company revisions applied to EAG model (25 May 2023)
†Generated using a 1.2 QALY multiplier
ACM1=Appraisal Committee Meeting 1; ICER=incremental cost effectiveness ratio; LY=life years; PAS=Patient Access Scheme; PCT=physician choice of treatment; QALY=quality adjusted life year; TNBC=triple negative breast cancer

Table 6 Base case results with BRCA testing cost included (NHS England Scenario A, ITT population, updated PAS price for talazoparib)*

| Analysis | Talazoparib | | | PCT | | | Incremental | | | Probabilistic ICER† |
|---|---|---|---|---|---|---|---|---|---|---|
| | Cost | QALYs | LYs | Cost | QALYs | LYs | Cost | QALYs | LYs | |
| Company | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| NICE ACM1 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

*Company revisions applied to EAG model (25 May 2023)
†Generated using a 1.2 QALY multiplier
ACM1=Appraisal Committee Meeting 1; ICER=incremental cost effectiveness ratio; LY=life years; PAS=Patient Access Scheme; PCT=physician choice of treatment; QALY=quality adjusted life year; TNBC=triple negative breast cancer

EAG RESPONSE

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

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

## EAG response to additional evidence provided by the company in response to a request by NICE following the postponed ACM2

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

Completed 21st September 2023

CONTAINS COMMERCIAL IN CONFIDENCE DATA



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# 1 EAG RESPONSE

This appendix contains the EAG response to the company response to the additional information, requested by NICE, following the postponement of ACM2. The company provided the following additional information:

- company rationale for the choice of distributions used to model OS, PFS and TTD for the HR+/HER2- and TNBC subgroups
- methods used by the company to vary OS in PSA
- company view on the inclusion of *BRCA* testing in the cost effectiveness analysis.

## *1.1 EMBRACA trial HR+/HER2 and TNBC subgroup analyses*

The company has provided cost effectiveness results for the HR+/HER2- and TNBC patient subgroups using EMBRACA trial PFS, OS and TTD data.

For PFS and TTD, the company has used EMBRACA trial PFS and TTD K-M data directly in the company model. Given the maturity of the EMBRACA trial data for these two endpoints, the EAG considers this approach is reasonable.

For OS, the company has fitted standard parametric curves to the EMBRACA trial OS K-M data and then selected distributions based on AIC/BIC test statistics and consideration of whether long-term survival projections were reasonable. The company's definition of reasonable was not provided.

The EAG considers that the distributions chosen by the company to model survival for the HR+/HER2- and (especially) for the TNBC subgroups are overly reliant on the tails of the EMBRACA trial OS K-M data where numbers at risk are very small. In the ITT population, at 36 months, there were only 18 patients still at risk in the PCT arm, meaning that single events had large impacts on the EMBRACA trial OS K-M curves. This means that:

- any long-term OS gains (the key driver of cost effectiveness results) for a minority of patients treated with talazoparib, rather than PCT, are highly uncertain (as was the case for the ITT population)
- model OS predictions produce conclusions that seem optimistic compared to EMBRACA trial OS K-M data.

HR+/HER2- subgroup EMBRACA trial OS K-M data suggest that survival is essentially the same for patients treated with talazoparib or PCT for around the first 30 months of the trial, over which period OS K-M data are robust. However, the company model predicts that, compared with patients treated with PCT, at 30 months, [redacted]% more patients treated with talazoparib will still be alive; this proportion rises to [redacted]% at 5 years.

For patients with TNBC, the company model predicts a median OS gain of 0.7 months for patients treated with talazoparib compared with patients treated with PCT. However, EMBRACA trial median OS results show that patients treated with PCT gain 5.2 months compared to patients treated with talazoparib. Further, EMBRACA trial results show that the absolute difference in survival at 2 years is [redacted] and favours PCT; however, company model results suggest that [redacted] more patients will be alive at 2 years if treated with talazoparib rather than PCT.

The EAG considers that the fitted OS distributions presented by the company that have associated AIC/BIC statistics that are within 5 points of the distribution with the lowest AIC/ BIC statistics are statistically indistinguishable. None of the distributions selected by the company meaningfully improved the proximity of projected OS to EMBRACA trial OS K-M data over the first 2 years. The EAG considered using the EMBRACA trial OS K-M data directly in the model, but this would have resulted in no long-term survivors (beyond about 7 years) in either arm; the EAG did not consider this approach was reasonable given that long-term survival is the key driver of the cost effectiveness of talazoparib versus PCT.

As is the case with the ITT population, the existence or magnitude of any survival benefit for patients treated with talazoparib compared to PCT in the HR+/HER2- and TNBC subgroups is uncertain. The additional evidence provided by the company appears to show that survival benefits, and therefore the cost effectiveness of talazoparib versus PCT, for the HR+/HER2- and TNBC subgroups, are likely to be different. The OS projections chosen by the company are uncertain and appear to favour treatment with talazoparib, particularly for the TNBC subgroup; the EAG therefore considers that the company ICERs per QALY gained should be considered optimistic.

## *1.2 Company PSA: varying OS*

The EAG thanks the company for providing information on how OS was varied in the PSA. Varying survival curves directly in PSA in the way described by the company is problematic. When selecting base case OS distributions, the company methods included an exploration of the plausibility of long-term projections generated by the model. The distribution chosen to model OS for the ITT population treated with talazoparib (the log-normal) generated a prediction that, at 10 years, [redacted]% of patients treated with talazoparib would still be alive. However, in 1,000 runs of the PSA, 10-year survival varied between [redacted]% and [redacted]%. The EAG considers that, if a base case distribution was considered plausible based on 10-year survival estimates, then a variation of this same distribution which generates survival estimates that are two to three times higher or lower than the base case distribution cannot also be considered plausible. As, in some runs, the PSA is generating survival estimates that

are not plausible, this renders the PSA confounded and PSA results should not be used to inform decision making.

### *1.3 BRCA testing*

The EAG considers that the issues raised around the inclusion of BRCA testing are reasonable; the decision for inclusion rests with NHS England/NICE.

NICE National Institute for Health and Care Excellence

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

**Response from clinical experts to questions from the NICE technical team.**

**BRCA testing:**

NHS England's comments on the draft guidance suggested that the cost of BRCA testing should be included for some people with HR-positive/HER2-negative BC, and provided a brief summary calculating the number of people for whom BRCA testing will be needed in 2 scenarios. Attached please see the NHSE comments and would you be able to advise the following:

1) Are the assumptions regarding the proportion of patients at each stage developing metastatic BC, and number of patients with metastatic or recurrent BC needing BRCA testing largely in line with what you observe in practice?

Response:

*I am afraid they are not.*

*I think the numbers are probably correct re numbers of metastatic disease patients per stage but I am sure NHSE have real figures on Stage IV BC numbers.*
*I think that the assumptions re testing that might be directly related to opportunity for Talazoparib therapy are not correct.*
*The vast majority of patients who we would find a +ve gBRCA1/2 test result in would already meet the testing criteria approved by NHSE it is just that we have been missing some of them due to medical education but that is changing fast.*
*The fact there are BRCA mutation specific therapy options simply means that breast cancer teams are aware of testing more and are referring now more based on approved test directories. The awareness of the fact that gBRCA1 and particularly gBRCA2 mut happens in ER+ve braest cancer and not just TNBC is a medical education need for breast cancer teams. The reasons to test are already approved and covered by the existing test directories in for genetic testing and therapy in early BC.*
*We have referred patients for genetic testing based on its effects on platinum chemotherapy choice for patients with gBRCA1/2 breast cancer and associated international guidance for years (TNBC or ER+) ( see TNT Trial Tutt et al Nat Medicine 2018). I don't think the testing in*

*the stage IV setting if missed before should be seen as cost that is exclusive to talazoparib. It should be stimulated at diagnosis of BC in the vast majority of those that need as covered by current NHSE funded approvals.*

2) Would you have any comments on the 2 costing scenarios concerning HR-positive/HER2-negative BC below:
   - scenario A: Extra testing needed for de novo metastatic BC only (as test would have been done during early BC): EAG calculated based on NHS England info that 19% of the intention-to-treat population and 23% of the HR+/HER2- population will require a BRCA test

   Response:

   *Scenario A is closer to reality than Scenario B but is still and overestimate of the number of tests that will need to be performed that would not have needed to be performed based on already approved NHSE funded Test directory indications as outlined above. Even in de novo met disease man patients would meet the criteria for genetic testing already funded by the original genetics test directory criteria based on age, family history, ethnicity. They were just missed. Testing would still need to be performed to inform family counselling etc even if there was no Talazoparib license.*

   - scenario B: test also needed for people not at high risk during early BC as per adjuvant Olaparib TA886 criteria (i.e., tests for both de novo and recurrent metastatic BC needed): EAG calculated that 52% of the intention-to-treat population, 64% of the HR+/HER2- population will require a BRCA test

   Response

   *I don't think this is correct*

**The difference in quality of life for people having talazoparib or chemo before disease progression:**

The committee recognised that having talazoparib or chemo may affect how a person feels and there may be factors affecting patient's quality of life such as red blood cell transfusion and hospital visits. Would you be able to comment on this or any other differences if there is any in this health state?

Response

*As I commented at the committee meeting - Yes Talazoparib does cause some anaemia but this is managed rapidly by does reduction and very rarely leads to blood transfusion in real clinical practice. The alternative chemotherapy regimens usually require many more hospital visits for blood tests prior to often weekly or 2/3 weekly IV chemo sessions. Patient time*

*away from home and family and travel expense is a major issue and is in my experience much more impacted by the chemotherapy alternatives than oral PARPi therapy.*

**BRCA testing:**

NHS England's comments on the draft guidance suggested that the cost of BRCA testing should be included for some people with HR-positive/HER2-negative BC, and provided a brief summary calculating the number of people for whom BRCA testing will be needed in 2 scenarios. Attached please see the NHSE comments and would you be able to advise the following:

1) Are the assumptions regarding the proportion of patients at each stage developing metastatic BC, and number of patients with metastatic or recurrent BC needing BRCA testing largely in line with what you observe in practice?

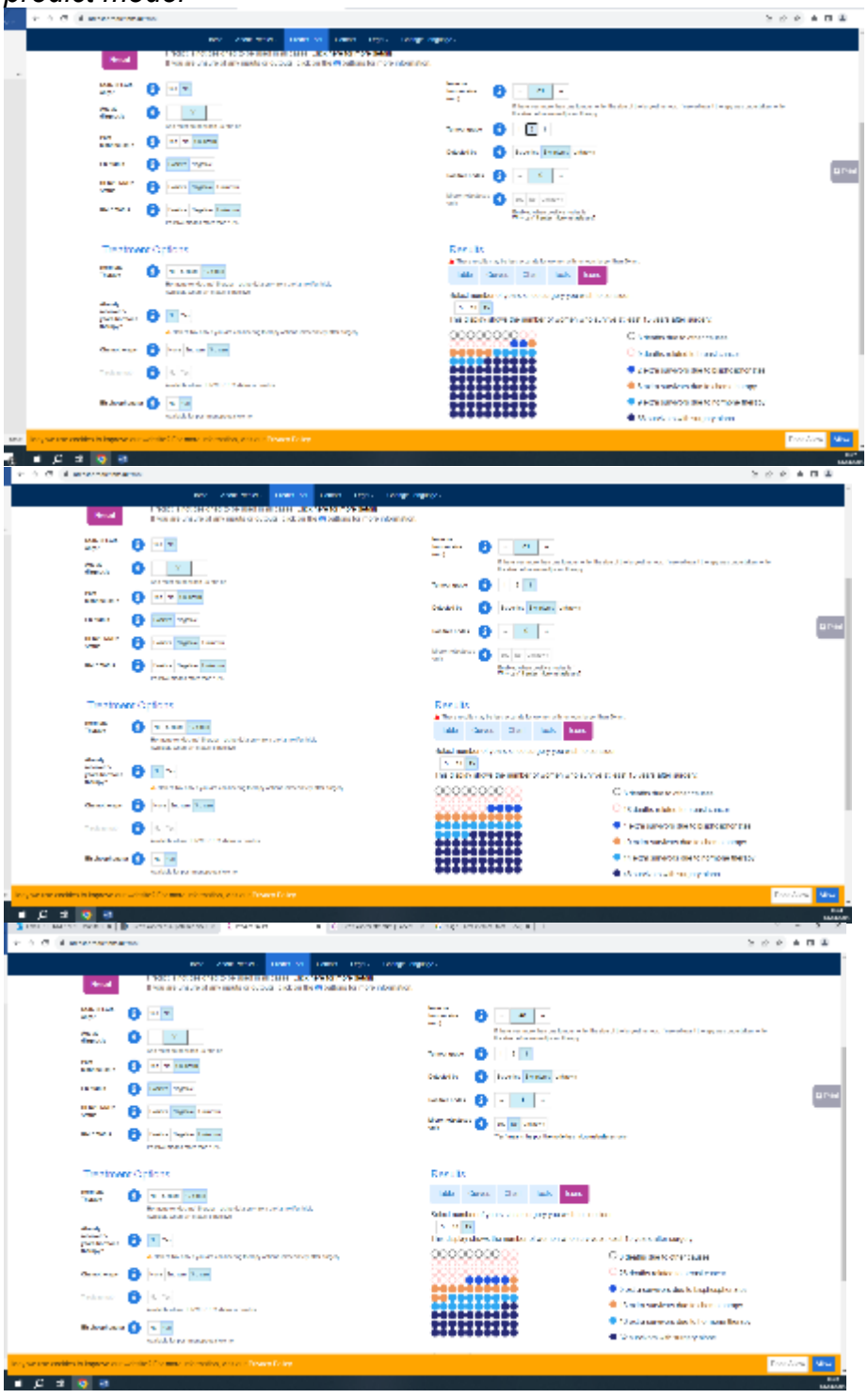
2) Would you have any comments on the 2 costing scenarios concerning HR-positive/HER2-negative BC below:
   - scenario A: Extra testing needed for de novo metastatic BC only (as test would have been done during early BC): EAG calculated based on NHS England info that 19% of the intention-to-treat population and 23% of the HR+/HER2- population will require a BRCA test
   - scenario B: test also needed for people not at high risk during early BC as per adjuvant Olaparib TA886 criteria (i.e., tests for both de novo and recurrent metastatic BC needed): EAG calculated that 52% of the intention-to-treat population, 64% of the HR+/HER2- population will require a BRCA test

Response

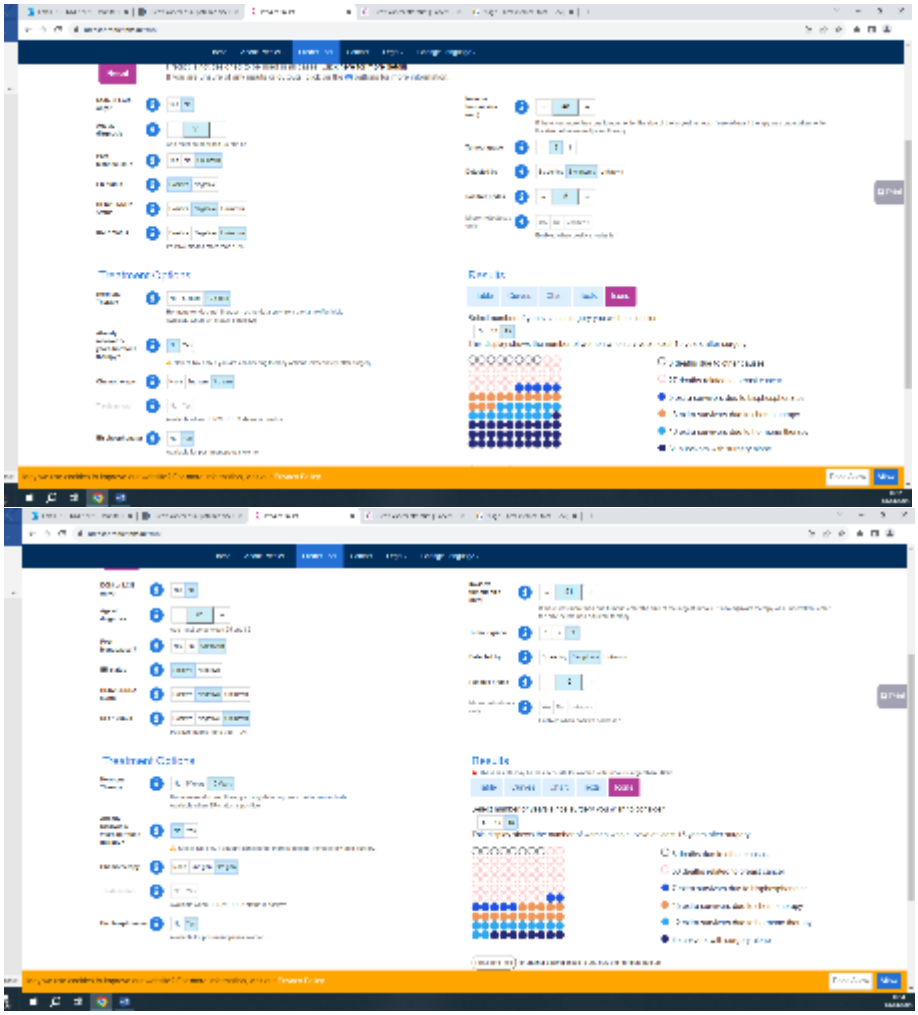
- *TNBC- completely agree currently the overwhelming majority would be tested in EBC setting, but also if present with de novo metastatic*
- *HR positive- I am worried that you have only considered the potentially olaparib eligile population for testing in currently. Please also consider the other criteria for testing*
  - *EBC or de novo- currently eligible for testing if manchester score >15*
  - *Age at EBC or MBC is relevant. New this year is the revisions to age of cancer enabling testing irrespective of manchester score ALL under 40 with EBC or ABC ER+ Her2 neg are now eligible for testing- even if ER +ve DCIS (pre cancer). So the proportions who would have had no prior test at ABC after EBC diagnosis will be reducing*
- *proportions that develop mets in the long run. These feel a bit high esp stage 2 and 3?*

*eg stage 2 that relapse you have stated 20%. This feels high to me. Playing around with the NHS predict tool considering the over 40's (as all under relapsing would now be tested prior to relapse) supports that this is high- a few examples below. You have to really push to the upper end of stage 2 to get find a situation where the relapse rate exceeds 20%. In the third (G3, higher end T2 and N1 it does) but falls back as you take the age of diagnosis higher AND you also have to remember that the impact of abemaciclib,*

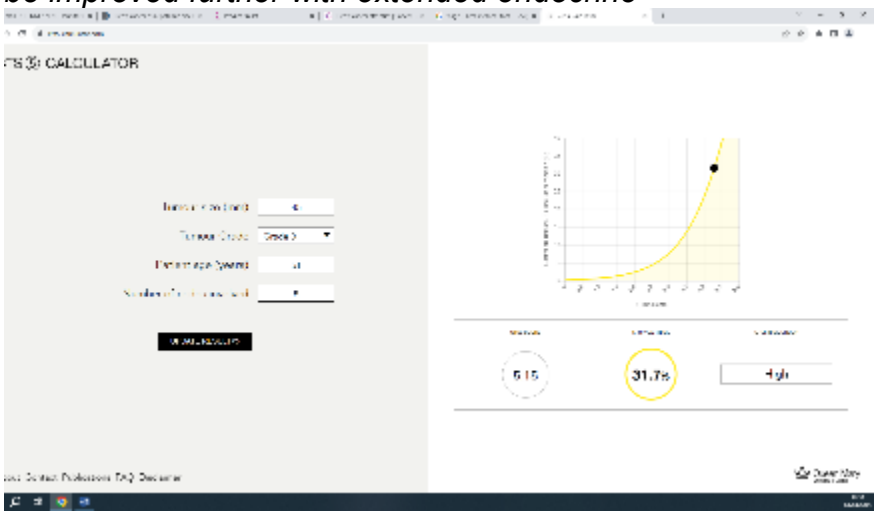
*extended endocrine to 10yrs and OFS for the pre menopausal women which isnt in the predict model but carry further survival benefit beyond the NHS predict model*



*eg stage 3, 40% relapse also feels too high with modern use of bisphosphonates, abemaciclib and escalated endocrine*



*eg considering extended endocrine therapy. NHS predict doesn't show the extra lives saved with extending endocrine beyond 5 years but this is standard of care recommendation in the clinic for those who will benefit. We can use the CTS5 tool to identify these patients beyond the obvious ones (Grade 3, any nodal involvement). But if we imagine a 51 yo with 5 nodes positive, big (45mm)primary tumour & g3 then run that in CTS5 we read less  than a  40% relapse (see below, 31.7) if endocrine stops at 5 years.  That relapse rate can be improved further with extended endocrine*



*With talazoparib there will undoubtedly be some additional BRCA tests. I think scenario A is incorrect in assuming all with prior EBC pts will have been tested. However, the modelling in scenario B feels to me to overestimate the BRCA test requirement in terms of estimated relapse rates and with current access to testing the proportion who will hit a metastatic relapse without prior testing (as this is reducing)*

**The difference in quality of life for people having talazoparib or chemo before disease progression:**

The committee recognised that having talazoparib or chemo may affect how a person feels and there may be factors affecting patient's quality of life such as red blood cell transfusion and hospital visits. Would you be able to comment on this or any other differences if there is any in this health state?

Response

*1. At the talazoparib meeting earlier this year I hope the messaging from the pt, Professor Tutt and myself helped the committee understand that having chemo is burdensome for patients and units in terms of attendances for blood testing, nurse review, line care (weekly flushes if PICC). Most of these happen 24-48 hrs prior to the day of treatment. The value of the QOL benefit with talazoparib cf standard of care chemo should not be underestimated.*

*2. Also to reiterate, those on chemo will also have a transfusion requirement . However the over recent years the uk oncology community has moved to more restrictive blood transfusion strategies- thus (Hb level 7 and 8 g/dL) have been gradually adopted over the past few years because of the lack of clinical evidence demonstrating an improved outcome when compared with more liberal practices. This is supported by international guidance's, for example European Society for Medical Oncology (ESMO) advocating a threshold of 7–8 g/dL and recommending that transfusions are only used in anaemic patients with severe symptoms in need of rapid Hb improvement. Usually we prescribe a single unit transfusion only and adjust in prescribed dose to reduce repeat. NICE should note that the original data for palliative chemo will have come from an era where less restrictive transfusion approaches was the norm (2 units if Hb <12 was entirely normal 5-10 yrs ago) and we do not see reduced efficacy of palliative vinorelbine/Taxol etc with lower threshold. We feel the talazoparib transfusion protocol was set at an inappropriately high threshold and we have no reason to think using this drug with transfusion thresholds and dose modification approaches will have detrimental efficacy impact.*

**Pfizer response to NICE request 19 September 2023**

**The EAG identified questions regarding how the PFS and OS curves were chosen in the subgroups by hormone receptor status. Can you please provide additional information about which curves were used, how they were chosen, and the rationale for the selected curves?**

Talazoparib is a targeted treatment for BRCA mutated advanced breast cancer, and Pfizer would like to reiterate the testimonies from clinicians present in the first appraisal committee meeting on 4th July 2023, who explained that there is no statistical basis for exploring subgroups, and furthermore no biological mechanism that would predict that hormone receptor status would affect the treatment effect of talazoparib in people with advanced breast cancer. Furthermore, the EMBRACA trial was not powered for consideration of these subgroup and considering them increases the decision uncertainty. Despite this we have provided exploratory subgroup analyses, which we hope the committee finds informative for their decision making. Please find additional clarification below as to how the PFS and OS curves were selected for the HR+/HER2- and TNBC subgroups.

**Progression free survival**

Trial data from EMBRCA are mature (less than 10% of patients remained progression-free at the end of the trial follow up). Survival curves were fitted to PFS data for the ITT population only as this is the focus of the company submission. For analysis of PFS in the HR+/HER2- and TNBC subgroups, PFS KM curves derived from EMBRACA IPD were directly used to estimate patients in PF for talazoparib and PCT.

**Overall survival**

As the OS data are less mature, and following recommendations by the National Institute for Health and Care Excellence (NICE) Decision Support Unit (NICE DSU TSD 14) on survival data extrapolation, five parametric distributions were fitted to model PFS and OS data, and were implemented in the model.

Long-term projection of the survival curve was assessed with visual inspection, on statistical goodness-of-fit and the clinical plausibility of the longer-term projected tail. Statistical goodness-of-fit is assessed based on test statistics Akaike Information Criteria (AIC) and Bayesian Information Criteria (BIC).

Parametric fittings providing the best goodness of fits and reasonable long-term projections were selected to model OS. Given 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. Overall, given the mature data from EMBRACA, mean survival predicted by various distributions are within a reasonable range. The best fitting parametric curves for each subgroup are presented in Table 1 below and Figure 1 and Figure 2 for HR+/HER2- and TNBC respectively. Table 2 shows the median OS observed in EMBRACA and modelled. AIC/BIC for all distributions are presented in Appendix A.

**Table 1. Best parametric fits**

| Population | Talazoparib | PCT |
|---|---|---|
| ITT | Log-normal | Weibull |
| HR+/HER2- | Log-logistic | Weibull |
| TNBC | Gen gamma | Exponential |

**Figure 1. HR+/HER2- overall survival – best parametric fits**

**Figure 2. TNBC overall survival – best parametric fits**

**Table 2. Median OS by treatment from trials and model**

| Population | Treatment | OS reported from trial (median, months) | OS modelled (median, months) | Source |
|---|---|---|---|---|
| ITT | Talazoparib | 19.3 | 20.4 | EMBRACA IPD |
| | PCT | 19.5 | 20.4 | |
| HR+/HER2- | Talazoparib | 23.1 | 23.8 | |
| | PCT | 22.4 | 22.4 | |
| TNBC | Talazoparib | 13.4 | 15.5 | |
| | PCT | 18.6 | 14.8 | |

Pfizer would further like to clarify that we have not proposed that the 1.7 severity modifier should be applied for TNBC but suggested that it is arguable. If severity of disease is considered on continuum, TNBC is close in proximity to the 0.95 proportional shortfall threshold cliff edge. Committee's have broader discretion and flexibility to consider the severity of TNBC holistically in

the context of HER2-negative advanced breast and the lack of currently available targeted treatment options in their decision making.

Scenario analyses are presented in Table 3 and Table 4 below showing the model results generated using a range of alternative parametric survival curves for the HR+/HER2-negative and TNBC populations respectively. Parametric survival distributions in the scenario analyses were selected based on next best fitting curves according to the AIC/BIC results in Appendix A.

**Table 3. Alternative survival distributions in HR+/HER2- population**

| | Talazoparib | | | PCT | | | Incremental | | | Deterministic |
|---|---|---|---|---|---|---|---|---|---|---|
| **Distribution** | **Cost** | **QALYs** | **LYs** | **Cost** | **QALYs** | **LYs** | **Cost** | **QALYs** | **LYs** | **ICER at [redacted] PAS** |
| Talazoparib (log-logistic)<br>PCT (Weibull) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £18,355 |
| Talazoparib (gen gamma)<br>PCT (log-logistic) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | Dominant |
| Talazoparib (log-normal)<br>PCT (Gompertz) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £20,988 |

**Table 4. Alternative survival distributions in TNBC population (1.2 severity modifier)**

| | Talazoparib | | | PCT | | | Incremental | | | Deterministic |
|---|---|---|---|---|---|---|---|---|---|---|
| **Distribution** | **Cost** | **QALYs** | **LYs** | **Cost** | **QALYs** | **LYs** | **Cost** | **QALYs** | **LYs** | **ICER at [redacted] PAS** |
| Talazoparib (gen gamma)<br>PCT (exponential) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £32,229 |
| Talazoparib (log-normal)<br>PCT (Weibull) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £29,860 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Talazoparib (log-logistic)<br>PCT (Gompertz) | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | £28,579 |

**The EAG was unable to determine exactly how OS was varied in the probabilistic sensitivity analysis in the company model provided in response to draft guidance. OS does not appear to have been varied for the ITT population and varied by changing distributional shape parameters for the subgroups. Can you please provide full details describing how OS is varied in the PSA for both the ITT population and the TNBC and HR+/HER2- subgroups?**

Second-order stochastic sensitivity analyses were performed to account for the joint uncertainty of the underlying parameter estimates in the ITT population and subgroup analyses. The model included Cholesky decomposition matrix calculation fields for modelling pairs of input parameters for which the covariance structure between two variables was known. All survival curve function parameters (OS, PFS) were varied using this method to account for the correlation between the scale and shape parameters of the two-parameter survival functions. The variance and covariance matrix of the survival function parameters were obtained from the curve-fitting procedure completed using statistical software.

It is possible to verify that the OS does indeed vary for the ITT population by setting the model to a base configuration, particularly setting “select.Population” on the “Settings” sheet to “HER2- (TNBC & HR+), All Lines”, and ensuring that “Best Fit Parametric” projection approaches are used on the “Clinical Inputs” sheet. One may then disable PSA sampling on all parameters bar those informing the ITT tala OS model by setting all values in column J on the “Parameters” sheet to 0 excepting rows 127:129. Running the PSA for a small number of iterations will reveal that the incremental QALYs vary with none but the OS parameters for talazoparib set to be sampled. Conversely, setting all values in “Parameters” column J to 0 and running the PSA will show no variation in outcome. Please note that the deterministic reference point does not have the severity modifier applied to QALYs.

The scatter plot of 1,000 iterations of the PSA was presented in the ACD response (18th August 2023) and reproduced in Figure 1 below to illustrate the variability in results.

**Figure 3. Scatter plot of PSA**

**Testing**

Pfizer acknowledge that this was not specifically requested by NICE however we wanted to take the opportunity to respond to the last-minute comments from NHS England around BRCA testing.

It was disappointing from a process perspective to receive these comments so late in the process, especially given the opportunity for these to the provided by NHS Rngland at submission, at technical engagement and at the first committee meeting (where NHS England were represented). I imagine other stakeholders will be equally disappointed have not had the opportunity to respond to these comments.

With regard to NHS England's estimations around the extra population that will require BRCA testing, we note the clinical expert's statements that this is a large overestimation.

Much of the talazoparib eligible population is already covered by the current NHS genomic directory testing criteria and the issue is that of low awareness and education of testing which is improving.

More importantly however, BRCA testing is standard of care that is already routinely provided by the NHS for many beneficial reasons, both for public health and individual breast cancer patients (e.g. familial risk, prognostication) independent of the treatment decision for talazoparib. Furthermore the expansion of genomic testing is a UK wide government initiative as stated in the "Genome UK: the future of healthcare" published in 2020 for the NHS to "become the most advanced genomic healthcare system in the world". As part of this initiative, one of their key actions is "NHS England will continue to introduce new clinical indications for genomic testing through the national genomic test directory so that more patients can benefit from genomic testing" as stated in the implementation plan (Genome UK: 2022 to 2025 implementation plan for England - GOV.UK (www.gov.uk)). This is reflected in the fact that the NHS genomic testing directory is constantly changing (for e.g. the latest BRCA testing criteria was updated in June 2023.

Additionally, in the NICE manual section 4.8 it states "if a diagnostic test to identify patients or establish the presence or absence of a particular biomarker is **not routinely** used in the NHS but is **introduced** to support the treatment decision for the specific technology, include the associated costs of the diagnostic in the assessments of clinical and cost effectiveness". We would argue that BRCA testing is already routinely used and not being "introduced" as a new test.

In the NICE manual section 4.4.15 it states that the committee should consider the specific circumstances and context of the evaluation when there is an established plan to change practice or service delivery in the NHS. As mentioned above, there is a government implementation plan to expand genomic testing.

The committee, in TA886, considered a similar issue of whether to include BRCA testing costs and with similar principles as above, where committee concluded that the BRCA testing costs should not be included.

Therefore because 1. BRCA testing is already a routinely available standard of care for breast cancer patients independent of talazoparib treatment decision and 2. the genomic testing criteria is constantly changing, and the estimations of scenarios will likely be inaccurate and irrelevant, we believe as was concluded in ACM1 with the clinical experts agreement, that BRCA testing costs should not be included in the talazoparib submission.

**Appendix A. Goodness of Fit for Parametric Fitting to OS for Talazoparib and PCT Combined in All Populations in the EMBRACA Trial**

| **ITT** | | | | |
|---|---|---|---|---|
| Analysis | AIC | BIC | AIC | BIC |
| **Weibull** | 1876.446 | 1883.723 | **903.423** | **909.277** |
| **Log-normal** | **1850.412** | **1857.688** | 919.562 | 925.416 |
| Log-logistic | 1851.914 | 1859.190 | 910.924 | 916.778 |
| Exponential | 1896.078 | 1899.723 | 918.786 | 921.727 |
| Generalized gamma | 1852.246 | 1863.140 | 905.445* | 914.183* |
| Gompertz | 1894.653 | 1901.929 | 907.250 | 913.105 |
| **TNBC** | | | | |
| Analysis | AIC | BIC | AIC | BIC |
| Weibull | 867.227 | 872.867 | 385.478 | 389.456 |
| Log-normal | 841.299 | 846.939 | 387.359 | 391.337 |
| Log-logistic | 843.543 | 849.184 | 387.837 | 391.815 |
| **Exponential** | 867.329 | 870.165 | **385.463** | **387.488** |
| **Generalized gamma** | **833.956** | **842.368** | 387.453 | 393.307 |
| Gompertz | 867.591 | 873.232 | 386.531 | 390.509 |
| **HR+/HER2-** | | | | |
| Analysis | AIC | BIC | AIC | BIC |
| **Weibull** | 1000.240 | 1006.274 | **514.840** | **519.553** |
| Log-normal | 999.726 | 1005.760 | 527.529 | 532.243 |
| **Log-logistic** | **993.525** | **999.559** | 517.721 | 522.435 |
| Exponential | 1027.311 | 1030.342 | 533.409 | 535.791 |
| Generalized gamma | 997.815 | 1006.827 | 516.991* | 523.983 |
| Gompertz | 1014.811 | 1020.846 | 519.101 | 523815 |
| *Non-convergence of the generalised gamma distribution for the PCT arm | | | | |

EAG RESPONSE

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

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

## EAG response to additional evidence provided by the company in response to a request by NICE following the postponed ACM2

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

Completed 21st September 2023

CONTAINS COMMERCIAL IN CONFIDENCE DATA



UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

# 1 EAG RESPONSE

This appendix contains the EAG response to the company response to the additional information, requested by NICE, following the postponement of ACM2. The company provided the following additional information:

- company rationale for the choice of distributions used to model OS, PFS and TTD for the HR+/HER2- and TNBC subgroups
- methods used by the company to vary OS in PSA
- company view on the inclusion of *BRCA* testing in the cost effectiveness analysis.

## *1.1 EMBRACA trial HR+/HER2 and TNBC subgroup analyses*

The company has provided cost effectiveness results for the HR+/HER2- and TNBC patient subgroups using EMBRACA trial PFS, OS and TTD data.

For PFS and TTD, the company has used EMBRACA trial PFS and TTD K-M data directly in the company model. Given the maturity of the EMBRACA trial data for these two endpoints, the EAG considers this approach is reasonable.

For OS, the company has fitted standard parametric curves to the EMBRACA trial OS K-M data and then selected distributions based on AIC/BIC test statistics and consideration of whether long-term survival projections were reasonable. The company's definition of reasonable was not provided.

The EAG considers that the distributions chosen by the company to model survival for the HR+/HER2- and (especially) for the TNBC subgroups are overly reliant on the tails of the EMBRACA trial OS K-M data where numbers at risk are very small. In the ITT population, at 36 months, there were only 18 patients still at risk in the PCT arm, meaning that single events had large impacts on the EMBRACA trial OS K-M curves. This means that:

- any long-term OS gains (the key driver of cost effectiveness results) for a minority of patients treated with talazoparib, rather than PCT, are highly uncertain (as was the case for the ITT population)
- model OS predictions produce conclusions that seem optimistic compared to EMBRACA trial OS K-M data.

HR+/HER2- subgroup EMBRACA trial OS K-M data suggest that survival is essentially the same for patients treated with talazoparib or PCT for around the first 30 months of the trial, over which period OS K-M data are robust. However, the company model predicts that, compared with patients treated with PCT, at 30 months, [redacted]% more patients treated with talazoparib will still be alive; this proportion rises to [redacted]% at 5 years.

For patients with TNBC, the company model predicts a median OS gain of 0.7 months for patients treated with talazoparib compared with patients treated with PCT. However, EMBRACA trial median OS results show that patients treated with PCT gain 5.2 months compared to patients treated with talazoparib. Further, EMBRACA trial results show that the absolute difference in survival at 2 years is [redacted] and favours PCT; however, company model results suggest that [redacted] more patients will be alive at 2 years if treated with talazoparib rather than PCT.

The EAG considers that the fitted OS distributions presented by the company that have associated AIC/BIC statistics that are within 5 points of the distribution with the lowest AIC/ BIC statistics are statistically indistinguishable. None of the distributions selected by the company meaningfully improved the proximity of projected OS to EMBRACA trial OS K-M data over the first 2 years. The EAG considered using the EMBRACA trial OS K-M data directly in the model, but this would have resulted in no long-term survivors (beyond about 7 years) in either arm; the EAG did not consider this approach was reasonable given that long-term survival is the key driver of the cost effectiveness of talazoparib versus PCT.

As is the case with the ITT population, the existence or magnitude of any survival benefit for patients treated with talazoparib compared to PCT in the HR+/HER2- and TNBC subgroups is uncertain. The additional evidence provided by the company appears to show that survival benefits, and therefore the cost effectiveness of talazoparib versus PCT, for the HR+/HER2- and TNBC subgroups, are likely to be different. The OS projections chosen by the company are uncertain and appear to favour treatment with talazoparib, particularly for the TNBC subgroup; the EAG therefore considers that the company ICERs per QALY gained should be considered optimistic.

## *1.2 Company PSA: varying OS*

The EAG thanks the company for providing information on how OS was varied in the PSA. Varying survival curves directly in PSA in the way described by the company is problematic. When selecting base case OS distributions, the company methods included an exploration of the plausibility of long-term projections generated by the model. The distribution chosen to model OS for the ITT population treated with talazoparib (the log-normal) generated a prediction that, at 10 years, [redacted]% of patients treated with talazoparib would still be alive. However, in 1,000 runs of the PSA, 10-year survival varied between [redacted]% and [redacted]%. The EAG considers that, if a base case distribution was considered plausible based on 10-year survival estimates, then a variation of this same distribution which generates survival estimates that are two to three times higher or lower than the base case distribution cannot also be considered plausible. As, in some runs, the PSA is generating survival estimates that

are not plausible, this renders the PSA confounded and PSA results should not be used to inform decision making.

### *1.3 BRCA testing*

The EAG considers that the issues raised around the inclusion of BRCA testing are reasonable; the decision for inclusion rests with NHS England/NICE.