NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Summary of consultation responses

Review of TA762; Olaparib for treating BRCA mutation-positive HER2-negative advanced breast cancer after chemotherapy

1. Final decision post consultation

A review of the guidance will be carried out, which will follow the cost comparison process.

2. Proposal put to consultees and commentators

A review of the guidance should be planned into the appraisal work programme, which will follow the cost comparison process.

3. Rationale for selecting this proposal

Since publication of the terminated guidance, there have been changes to the treatment pathway for BRCA mutation-positive HER2-negative advanced breast cancer with the recommendation of talazoparib (TA952) in the same population as in TA762.

Talazoparib is in the same drug class as olaparib (PARP inhibitor) and indirect treatment comparisons provide some evidence that olaparib and talazoparib provide similar health benefits. Therefore olaparib could potentially be appraised in this indication using the cost comparison approach with talazoparib as a key comparator. The company would need to demonstrate that olaparib provides similar or greater health benefits to talazoparib, at a similar or lower cost.

4. Summary of responses received

Comments received in the course of consultations carried out by NICE 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 submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Respondent: AstraZeneca **Response to proposal:** Agree **<u>Efficacy of olaparib versus talazoparib</u>** Olaparib is expected to have similar clinical effectiveness as talazoparib. Both treatments are PARP inhibitors[1,2] and therefore have the same mechanism of action. Whilst there is no published head-to-head evidence comparing the efficacy of olaparib and talazoparib in this indication, the results from two published indirect treatment comparisons (ITCs) of data from the OlympiAD and EMBRACA trials comparing olaparib and talazoparib respectively reported that there were no statistically significant differences in progression free survival (PFS), overall survival (OS) or overall safety profile between the two interventions.[3,4] Clinical validation from experts in treating BRCA mutation-positive HER2-negative locally advanced or metastatic breast cancer (HER2− aBC with gBRCAm) confirmed that they would expect olaparib and talazoparib to have similar efficacy, in line with the ITCs. AstraZeneca would like to highlight that Olaparib has a more favourable safety profile in terms of haematological events. This was highlighted in Wang 2021: 'Regarding safety, olaparib had reduced risk for both grade 3-4 anemia (OR = 0.34, 95% CrI = 0.003-34.94) and any-grade anemia (OR = 0.37, 95% CrI = 0.02-6.81) compared with talazoparib. Olaparib also showed a low risk for grade 3-4 neutropenia (OR = 0.57, 95% CrI = 0.06-5.75) compared with talazoparib.[4] McCrea 2021 reported a trend favouring olaparib for any serious adverse event (SAE) or treatment-related SAE, although not statistically significant. The ORs for alopecia and anaemia indicated higher risk in talazoparib-treated patients than olaparib-treated patients, while those of nausea and vomiting indicated higher risk in olaparib-treated patients.[3] Clinicians have further validated that they consider talazoparib could lead to more haematological adverse events compared to olaparib. As a result, despite being similar in effectiveness, olaparib may be considered to have a more favourable safety profile. Treatment with olaparib over talazoparib may therefore lead to improved health outcomes	**Comment from Technology Appraisals** Thank you for your comments. This topic has been selected to be appraised as a cost comparison. The comparators have been amended so that talazoparib is now the only comparator for this appraisal. The final scoping table outlines that the economic modelling should include the costs associated with diagnostic testing for BRCA1 or BRCA2 mutations in people with locally advanced or metastatic breast cancer who would not otherwise have been tested.

for patients. Clinicians have validated that they would expect resource use to be the same between the two treatments.

The cost-comparison approach is an appropriate method for this topic, as outlined it is anticipated that olaparib is likely to provide similar or greater health benefits at similar or lower cost than talazoparib. Therefore, it is appropriate to evaluate olaparib through a cost-comparison appraisal.

Positioning of olaparib

Talazoparib (TA952) has recently been recommended for treating patients with HER2− aBC with gBRCAm.[5] In line with the marketing authorisation for talazoparib, such patients will have previously been treated with an anthracycline or a taxane, or both, unless these treatments are not suitable, and endocrine therapy if they have HR+ BC, unless this is not suitable. Talazoparib is positioned for treating HR+/HER2− aBC with gBRCAm as a second-line treatment, whilst it is positioned for the treatment of TNBC with gBRCAm in both first and second-line settings.

The positioning of olaparib will be consistent with the population for which talazoparib has received a recommendation for (TA952).[5] As both olaparib and talazoparib are targeted treatments for patients with BRCA1/2 mutations, it is anticipated that they will be used in the same place within the treatment pathway. Clinicians have validated that they will prioritise treatment with a PARP inhibitor if patients have a known BRCA mutation. Clinical experts have validated that talazoparib is likely to become standard of care for patients with HER2− aBC with gBRCAm and as such, talazoparib represents the only relevant comparator for olaparib.

Efficacy of olaparib versus chemotherapy

The efficacy of olaparib versus chemotherapy is not clinically similar. The OlympiAD trial demonstrates that olaparib monotherapy significantly improved the outcomes of patients with HER2– metastatic breast cancer and gBRCAm when compared to treatment of physician's choice (TPC) chemotherapy (vinorelbine, capecitabine and eribulin).[1,6]

• Patients in the olaparib group had a statistically significant and clinically meaningful improvement in PFS compared to patients in the TPC group (median PFS: 7.0 months versus 4.2 months, respectively; hazard ratio (HR) for disease progression or death: 0.58 (95% CI: 0.43–0.80; P<0.001) as assessed by blinded independent central review (BICR) • A statistically and clinically meaningful benefit in objective response rate (ORR) was also observed for patients treated with olaparib (59.9%) compared to TPC (28.8%) • OlympiAD was not powered to assess differences in OS between treatment groups, and whilst OS numerically favoured olaparib, there was no statistically significant demonstration of improvement for olaparib (median OS: 19.3 months) compared to TPC (median OS: 19.3 months vs 17.1 months; HR: 0.90; 95% CI: 0.66–1.23; P=0.513). • Safety analysis demonstrated olaparib is well tolerated, with the rate of grade 3 or higher AEs being lower (38.0%) for olaparib than TPC (49.5%) The OlympiAD trial did not compare olaparib versus gemcitabine, however AstraZeneca does not consider gemcitabine, or any of the chemotherapy regimens outlined review proposal paper, to be a relevant comparator for olaparib. Gemcitabine was a comparator within the physician's choice of treatment arm of the EMBRACA trial. However, during the talazoparib appraisal TA952 5, the comparator arm in the model was adjusted to remove gemcitabine because it is rarely used in NHS. Resource use is expected to decrease with olaparib versus chemotherapy. This is due to an increase in resource associated with treating toxicity adverse events associated with chemotherapy treatment. Furthermore, olaparib is orally administered and does therefore not require patients to attend clinic. It would not be suitable to conduct a cost-comparison of olaparib versus chemotherapy due to differences in efficacy and patient outcomes. However, clinicians have validated that they would prioritise treatment of BRCA positive patients with a PARP inhibitor. Talazoparib is therefore the most relevant direct comparator, due to being the only reimbursed PARP inhibitor in this space. **<u>BRCA mutations testing in locally advanced or metastatic breast cancer</u>** BRCA testing is already well established in clinical practice.	

The National Genomic Test Directory (NGTD) has defined specific eligibility criteria for routine gBRCAm testing according to multiple factors which influence pre-test carrier probability, such as age, family history, and tumour characteristics. These criteria currently drive clinical practice, the two NGTD criteria most applicable to this appraisal are:[7] • gBRCAm testing offered to women aged <60 years with TNBC • gBRCAm testing offered to women aged <40 years for other breast cancer types (including HR+/HER2− patients) The NGTD defines specific criteria for gBRCAm testing to determine eligibility for NICE-recommended PARP inhibitor treatment. Detection of gBRCAm informs the management plan the patient, allowing for targeted treatment using a PARP inhibitor. Accordingly, clinical experts consulted during the talazoparib appraisal (TA952) noted that there had been an increased uptake in BRCA testing following the NICE recommendation of BRCA-targeted olaparib treatment in early breast cancer in 2022.5 Talazoparib has recently been reimbursed for HER2− aBC with gBRCAm. Therefore, there are not anticipated to be any changes in testing volumes resulting from the reimbursement of olaparib in this setting. **Health-related benefits beyond the QALY calculation** It should be noted that several benefits of olaparib in the proposed setting cannot be fully reflected in health economic models. Such uncaptured benefits include: the impact of extending remission on patient's social life, ability to work, mental health and emotional well-being, the value of having a longer time free from treatment, and the positive impact for family members and carers. **Equality** No equality considerations have been identified at this stage. **Talazoparib Market Share**	

We would like to highlight that the population for consideration within this appraisal is 'HER2-negative locally advanced or metastatic breast cancer with germline BRCA1/2-mutations that has previously been treated with:

- an anthracycline and a taxane in the (neo)adjuvant or metastatic setting, unless these treatments would not be suitable.
- endocrine therapy in the case of hormone receptor (HR)-positive breast cancer, unless endocrine therapy is not suitable.'

Such that patients must harbour a BRCA mutation to receive treatment with olaparib. Clinicians have validated that if a patient had a known BRCA mutation then they would prioritise treatment with a PARP inhibitor. This is due to improved efficacy and reduced toxicity, as is associated with other treatments such as chemotherapy. Talazoparib is the only reimbursed PARP inhibitor in this setting, therefore talazoparib is expected to be the direct comparator and to have substantial market share for treatment of patients who specifically have germline BRCA1/2-mutations.

References

1. Litton JK, Hurvitz SA, Mina LA, et al. Talazoparib versus chemotherapy in patients with germline BRCA1/2-mutated HER2-negative advanced breast cancer: final overall survival results from the EMBRACA trial. Ann Oncol 2020;31:1526-1535.
2. Robson M, Im SA, Senkus E, et al. Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation. N Engl J Med 2017;377:523-533.
3. McCrea C, Hettle R, Gulati P et al (2021) Indirect treatment comparison of olaparib and talazoparib in germline BRCA-mutated HER2-negative metastatic breast cancer. Journal of Comparative Effectiveness Research. 10(13):1021-30.
4. Wang J, Zhang Y, Yuan L et al (2021) Comparative efficacy, safety, and acceptability of single-agent poly (ADP-ribose) polymerase (PARP) inhibitors in

BRCA-mutated HER2-negative metastatic or advanced breast cancer: a network meta-analysis. Aging 1;13(1):450.
5. National Institute of Health and Care Excellence. TA952: Talazoparib for treating HER2-negative advanced breast cancer with germline BRCA mutations. Available at: https://www.nice.org.uk/guidance/TA952 (Accessed:18/04/2024).
6. Robson ME, Tung N, Conte P, et al. OlympiAD final overall survival and tolerability results: Olaparib versus chemotherapy treatment of physician's choice in patients with a germline BRCA mutation and HER2-negative metastatic breast cancer. Ann Oncol 2019;30:558-566.
7. England N. National Genomic Test Directory. Available at: https://www.england.nhs.uk/publication/national-genomic-test-directories/ (accessed 06/01/2022), 2021.

Respondent: Breast Cancer Now **Response to proposal:** Agree Breast Cancer Now welcomes the news that NICE will consider a review of guidance on the use of olaparib for treating BRCA mutation-positive HER2 negative metastatic breast cancer after chemotherapy. We were disappointed that the original appraisal process for this technology indication was terminated. We welcomed the approval of talazoparib in January 2024 for people with HER2 negative locally advanced or metastatic breast cancer with germline BRCA1 or BRCA2 mutations in adults, as it provides an additional treatment option for this group. The appraisal of olaparib in this indication via the cost-comparison approach could potentially add a further treatment option for people with these mutations. We consider it appropriate for olaparib to be evaluated using a cost-comparison approach, using talazoparib as a key comparator. Both olaparib and talazoparib are PARP inhibitors, being considered for use in BRCA mutated HER2 negative secondary breast cancer. The methods of administration for the two drugs are also similar, as both are taken orally, olaparib twice daily, talazoparib once daily. In the OlympiAD trial olaparib achieved a median overall survival of 19.3 months, versus 17.1 months with TPC. In the EMBRACA trial talazoparib did not significantly improve overall survival over chemotherapy. It did prolong progression-free survival (PFS) compared to chemotherapy, with a median PFS of 8.6 months versus 5.6 months. Both treatments have similar side-effect profiles; in the clinical trial olaparib patients reported nausea, anaemia, vomiting, fatigue, cough, decreased appetite, back pain and headache at a relatively higher frequency than the comparator. For talazoparib the most common side effects reported by the group receiving the drug in the clinical trial were anaemia, fatigue, nausea, neutropenia, and headache. Olaparib is a targeted treatment for those with mutations in the BRCA genes. Whether BRCA is tested for in people with secondary breast cancer is dependent on their individual	**Comment from Technology Appraisals** Thank you for your comments. This topic has been selected to be appraised as a cost comparison. The comparators have been amended so that talazoparib is now the only comparator for this appraisal. The final scoping table outlines that the economic modelling should include the costs associated with diagnostic testing for BRCA1 or BRCA2 mutations in people with locally advanced or metastatic breast cancer who would not otherwise have been tested.

history and biology. Testing criteria for BRCA mutations is set out in the NHS England National Genomic Test Directory: R208 sets out testing criteria through which people living with breast cancer may be tested if the individual meets the following criteria: a. Breast cancer (age <40years, OR b. Bilateral breast cancer (age <50years, OR c. Triple negative breast cancer (age <60years, OR d. Assigned male at birth and affected with breast cancer (and age), OR e. Breast cancer (age <45years) and a first degree relative with breast cancer (age <45years), OR f. Combined pathology-adjusted Manchester score ≥15 or single gene pathology adjusted score of ≥10 or BOADICEA/CanRisk score ≥10% OR g. Ashkenazi Jewish ancestry and breast cancer at any age For people with breast cancer who do not meet these criteria R444 sets out additional testing criteria for NICE approved PARP inhibitor treatment 1. For people with triple negative breast cancer who have received neo-adjuvant chemotherapy: residual invasive cancer in the breast, the resected lymph nodes (non-pathological complete response) or both at the time of surgery 2. For people with triple-negative breast cancer having adjuvant chemotherapy: node-positive OR node-negative cancer with a primary tumour ≥ 2 cm 3. For people with hormone receptor-positive, HER2-negative breast cancer who have received neoadjuvant chemotherapy: residual invasive cancer in the breast, the resected lymph nodes (non-pathologic complete response) or both at the time of surgery, AND a CPS + EG score of ≥3 based on pre-treatment clinical and posttreatment pathological stage, receptor status and histological grade	

4. For people with hormone receptor-positive, HER2-negative breast cancer having adjuvant chemotherapy: 4 or more pathologically confirmed positive lymph nodes.	

Respondent: METUPUK **Response to proposal:** Agree We have consulted with patients who have germline BRCA1/2 mutations. Patients would welcome olaparib being made available on the NHS for metastatic breast cancer, in addition to talazoparib. Olaparib and talazoparib have different side effect profiles and patients would like their oncologist to decide which treatment is most appropriate for them. Comments from patients who have accessed olaparib: "I have been taking olaparib since May 2021 and I tolerate it very well. I have had a little nausea, but these occasions I can count on one hand. Occasional tiredness but not too much. Dry mouth does occur, and other mouth issues like ulcers and therefore issues with teeth. The sore mouth has been the worst side effect but it's also relatively recent. Bloods have been good throughout and I've worked constantly. I feel unbelievably lucky to have had access to this drug. Lifesaver." "I am an NHS patient who received olaparib as part of a compassionate access scheme. I was diagnosed with triple negative secondary breast cancer over three years ago, shortly after giving birth. I am incredibly grateful to have received olaparib. It has given me a long period of stability with additional time to spend with my young family and also carry on working. My oncologist has recently changed me to talazoparib, and I am pleased they have the choice to select the most suitable parp inhibitor for me." BRCA testing is already used widely for breast cancer in the NHS. In early breast cancer most high-risk patients are detected via the criteria laid out in National Genetic Test Directory. In TA886 (olaparib in early breast cancer) the cost of BRCA was not included in the modelling. In advanced breast cancer, most patients who have not already been tested for BRCA will be de novo patients or low risk patients who progressed after early breast cancer. In	**Comment from Technology Appraisals** Thank you for your comments. This topic has been selected to be appraised as a cost comparison. The comparators have been amended so that talazoparib is now the only comparator for this appraisal. The final scoping table outlines that the economic modelling should include the costs associated with diagnostic testing for BRCA1 or BRCA2 mutations in people with locally advanced or metastatic breast cancer who would not otherwise have been tested.

TA952 (talazoparib), BRCA testing was included in the modelling to include the small number of patients (19%) who were predicted to have not already been tested. It is reasonable that if olaparib is used for advanced breast cancer, BRCA testing should be modelled in the same way as it was for talazoparib. It is reasonable to use the same comparators that were discussed by the clinical experts in TA952. Gemcitabine was not a comparator in TA952. It is also reasonable that if olaparib is used for advanced breast cancer, it should be positioned in the patient pathway at the same point as talazoparib. No new treatments have been recommended by NICE for advanced breast cancer since TA952 was published (at the time of writing).	

Paper signed off by: Emily Crowe, 01/05/2024

Contributors to this paper:

Technical Lead: Emma McCarthy

Technical Adviser: Claire Hawksworth

Project Manager: Charlotte Downing

Programme Manager: Gavin Kenny