NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Talazoparib for treating HER2-negative advanced breast cancer with germline BRCA mutations

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using talazoparib in the NHS in England. The evaluation committee has considered the evidence submitted by the company and the views of non-company stakeholders, clinical experts and patient experts.

This document has been prepared for consultation with the stakeholders. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the stakeholders for this evaluation and the public. This document should be read along with the evidence (see the committee papers).

The evaluation committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- 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 age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Issue date: July 2023

Note that this document is not NICE's final guidance on talazoparib. The recommendations in section 1 may change after consultation.

After consultation:

- The evaluation committee will meet again to consider the evidence, this evaluation consultation document and comments from the stakeholders.
- At that meeting, the committee will also consider comments made by people who are not stakeholders.
- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using talazoparib in the NHS in England.

For further details, see NICE's manual on health technology evaluation.

The key dates for this evaluation are:

- Closing date for comments: 18 August 2023
- Second evaluation committee meeting: 5 September 2023
- Details of the evaluation committee are given in section 4

1 Recommendations

1.1 Talazoparib is not recommended, within its marketing authorisation, for treating HER2-negative, locally advanced or metastatic breast cancer with germline BRCA1 or BRCA2 mutations in adults who have had:

- an anthracycline or a taxane, or both, unless these treatments are not suitable, and
- endocrine therapy if they have hormone receptor (HR)-positive breast cancer, unless this is not suitable.

1.2 This recommendation is not intended to affect treatment with talazoparib that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

For most people with HER2-negative, locally advanced or metastatic breast cancer with germline BRCA mutations, talazoparib, if recommended, would be used instead of chemotherapy.

Evidence from a clinical trial shows that talazoparib increases how long people live without their cancer getting worse compared with chemotherapy. But, the trial does not show any difference in how long people live.

When considering the condition's severity, and its effect on quality and length of life, the most likely cost-effectiveness estimates for talazoparib are above what NICE considers an acceptable use of NHS resources. So, talazoparib is not recommended. The committee requests further analyses.

2 Information about talazoparib

Marketing authorisation indication

2.1 Talazoparib (Talzenna, Pfizer) is indicated 'as monotherapy for the treatment of adult patients with germline BRCA1/2-mutations, who have HER2-negative locally advanced or metastatic breast cancer. Patients should have been previously treated with an anthracycline and/or a taxane in the neo/adjuvant, locally advanced or metastatic setting unless patients were not suitable for these treatments. Patients with hormone receptor (HR)-positive breast cancer should have been treated with a prior endocrine-based therapy, or be considered unsuitable for endocrine-based therapy'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for talazoparib.

Price

2.3 £4,965 for a 30 pack of 1 mg capsules and £1,655 for a 30 pack of 0.25 mg capsules (excluding VAT; BNF online accessed July 2023).

2.4 The company has a commercial arrangement, which would have applied if talazoparib had been recommended.

3 Committee discussion

The evaluation committee considered evidence submitted by Pfizer, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

Details of the condition

3.1 Advanced breast cancer includes cancer that has grown directly into nearby tissues and cannot be completely removed by surgery (locally advanced) and cancer that has spread to other parts of the body (metastatic). There is no cure for advanced breast cancer. There are 2 types of HER2-negative breast cancer, based on hormone receptor status: hormone receptor-positive (HR-positive), HER2-negative breast cancer and triple negative breast cancer. BRCA mutations arise in 5% of HR-positive, HER2-negative breast cancers and 10% of triple negative cancers. The patient experts explained that a diagnosis of advanced breast cancer with BRCA mutations is devastating and leads to constant worry about the future and potential impacts on other family members. Triple negative advanced breast cancer has a worse prognosis than HR-positive, HER2-negative advanced breast cancer. But the clinical experts explained that HER2-negative advanced breast cancer with germline BRCA mutations is a small group of breast cancers that are somewhat similar because of the BRCA gene mutation. The committee understood that there is a high disease burden for people with HER2-negative advanced breast cancer with germline BRCA mutations.

Clinical management and unmet needs

3.2 The aim of treatment for advanced breast cancer is to extend the length of life, while providing a good quality of life. The treatment pathway differs between HR-positive, HER2-negative and triple negative breast cancer. Treatment options also depend on several other factors, including genetic and biological markers (BRCA, PIK3CA, PD-L1), the extent of disease and previous treatments. The patient experts explained that chemotherapy, currently a common treatment option for people with advanced breast cancer, is often administered intravenously. This means that they need to spend lots of time in and out of the hospital and are not able to lead normal lives. Clinicians prefer to use the most effective

treatments earlier in the treatment pathway. Re-treatment with these therapies is usually not appropriate, leaving few effective treatment options. The clinical and patient experts highlighted that although the landscape for breast cancer treatment has been quickly evolving in recent years, no BRCA-targeted treatments are available in the advanced setting in the NHS. Also, treatment options are limited, especially for triple negative breast cancer. The committee concluded that there is an unmet need for effective treatments for HER2-negative advanced breast cancer with germline BRCA mutations.

Treatment pathways

HR-positive, HER2-negative advanced breast cancer

3.3 The clinical experts explained that for HR-positive, HER2-negative advanced breast cancer with BRCA mutations, the established first-line treatments are CDK4/6 inhibitors with endocrine therapy (see the NICE's technology appraisal guidance on palbociclib, ribociclib with an aromatase inhibitor, abemaciclib with an aromatase inhibitor, ribociclib with fulvestrant, abemaciclib with fulvestrant and palbociclib with fulvestrant). Second and later line options include alpelisib plus fulvestrant for cancer with PIK3CA mutations, everolimus plus exemestane, and single-agent chemotherapies including anthracyclines, taxanes, capecitabine, vinorelbine (NICE's clinical guideline on advanced breast cancer: diagnosis and treatment, from now CG81), eribulin as an option after at least 2 chemotherapy regimens or platinum-based chemotherapy (chemotherapy treatments available depending on whether they were used previously or not).

Triple negative advanced cancer

3.4 For people with triple negative advanced cancer with BRCA mutations, first-line therapies include immunotherapy plus chemotherapy when the cancer is PD-L1 positive (atezolizumab with nab-paclitaxel and pembrolizumab with paclitaxel or nab-paclitaxel). Another first-line option

is single-agent chemotherapy including anthracyclines, taxanes, capecitabine, vinorelbine (CG81) or platinum-based chemotherapy. Second-line and later lines of therapy are single-agent chemotherapy that has not been used yet (CG81), eribulin as an option after at least 2 chemotherapy regimens, and sacituzumab govitecan after at least 2 systemic therapies.

Company's proposed positioning for talazoparib

3.5 The marketing authorisation for talazoparib specifies its use after an anthracycline or a taxane, or both, unless these treatments are not suitable for the cancer. Also, HR-positive breast cancer should have been treated with a previous endocrine-based therapy, unless this is not suitable. The company proposed that talazoparib would be used:

- for HR-positive, HER2-negative advanced breast cancer with BRCA mutations: second or third line, after first-line CDK4/6 inhibitors and second-line anthracycline or taxane-based therapy (if not previously used for early breast cancer)
- for triple negative advanced breast cancer with BRCA mutations: first or second line, after immunotherapy, anthracycline or taxane-based therapy (if not previously used for early breast cancer).

The clinical experts agreed with the company's proposed positioning for talazoparib. They noted that most people with HER2-negative breast cancer with germline BRCA mutations are diagnosed in the early setting. They expected that everyone with positive hormone receptor status would have had an endocrine-based therapy, and up to 50% of them would have had a combination of anthracyclines or taxanes, or both, in early breast cancer. Similarly, almost everyone with triple negative advanced breast cancer would have had anthracyclines or taxanes, or both, in early breast cancer. The committee concluded that the company's proposed positionings for talazoparib were appropriate in HR-positive, HER2-

negative and triple negative advanced breast cancer with BRCA mutations.

Comparators

HR-positive, HER2-negative advanced breast cancer with BRCA mutations

3.6 The clinical experts explained that chemotherapies including capecitabine, vinorelbine and eribulin are the key comparators for HR-positive, HER2-negative advanced breast cancer, based on the company's proposed positioning (see section 3.35). The clinical experts explained that although platinum-based chemotherapy can be used for people who have not had it in early breast cancer, not many people would have it as a second-line treatment. They also explained that many people with BRCA mutations are young, so clinicians prefer to minimise the use of treatments such as alpelisib or everolimus because of the related toxicities and the impact on patients' functioning and quality of life. The Cancer Drugs Fund clinical lead noted that not many people had started these 2 treatments recently in the NHS. He also agreed that capecitabine, vinorelbine and eribulin are the key comparators for talazoparib in this setting. Both the clinical experts and Cancer Drugs Fund clinical lead noted that the later-line treatments can only be considered if people are well enough to have them and that it may not be the case in the advanced setting. Considering the current practice in place, the toxicity of some available treatments and the small number of people using some treatment options, the committee concluded that capecitabine, vinorelbine and eribulin are relevant comparators for talazoparib in HR-positive, HER2-negative advanced breast cancer with BRCA mutations in this appraisal.

Triple negative advanced breast cancer with BRCA mutations

3.7 The clinical experts explained that chemotherapies including capecitabine, vinorelbine and eribulin are the key comparators for talazoparib in triple negative advanced breast cancer, based on the company's proposed

positioning (see section 3.5). The clinical experts noted that platinum-based chemotherapy is unlikely to be used in the advanced setting because most people would have it in early breast cancer. They noted that about one third of breast cancers are PD-L1 positive, and they would expect most of them to have immunotherapy before talazoparib. But there is no evidence on sequencing of treatments or comparative evidence between immunotherapies and talazoparib. The clinical experts explained that sacizutumab govitecan would be used at a later line and should not be considered a comparator. The committee concluded that capecitabine, vinorelbine and eribulin are relevant comparators for talazoparib in triple negative advanced breast cancer with BRCA mutations in this appraisal.

Clinical effectiveness and population

Data sources and generalisability

3.8 The clinical evidence came from EMBRACA, an open label, phase 3 randomised controlled trial (n=431). It was conducted worldwide and included a small number of people from the UK (the number cannot be reported here because it is confidential). The trial compared talazoparib with physician's choice of therapy (gemcitabine, eribulin, capecitabine or vinorelbine) in people with HER2-negative locally advanced or metastatic breast cancer with germline BRCA mutations. The key inclusion criteria were:

- locally advanced breast cancer that cannot be treated with curative radiation or surgical cure or metastatic breast cancer appropriate for single cytotoxic chemotherapy
- HER2-negative, HR-positive breast cancer or triple negative breast cancer with germline BRCA mutations
- previous taxane or anthracycline use, or both, unless contraindicated
- maximum of 3 previous cytotoxic treatments for advanced breast cancer

- the condition was stable for at least 6 months after platinum-based chemotherapy for early breast cancer, or it had not progressed on platinum-based chemotherapy for advanced cancer.

Most breast cancers were metastatic (94%) and the split between HR-positive, HER2-negative and triple negative cancer was similar (56% compared with 44%, respectively). The EAG noted that only a few people in the trial have had treatments currently available to the NHS, such as CDK4/6 inhibitors, immunotherapy and platinum-based chemotherapy. But the clinical experts all agreed that there is no evidence that previous treatments would influence talazoparib's treatment effect and that the trial patient characteristics are similar to what they would expect in the NHS. The EAG also stated that the population in EMBRACA is heterogeneous because of the differences in treatment pathways for HR-positive, HER2-negative advanced breast cancer and triple negative breast cancer, and the previous treatments patients in each group had before talazoparib. The committee concluded that the population of EMBRACA may be representative to those who would have talazoparib in the NHS, but there may be heterogeneity in the population and it would take this into account during decision making.

Progression-free survival

3.9 Progression-free survival was the primary outcome in EMBRACA. Evidence showed that at the median follow up of 11.2 months at the September 2017 data cut, the median progression-free survival was 8.6 months with talazoparib and 5.6 months with the physician's choice of treatment in the overall population. Talazoparib was associated with improved progression-free survival compared with physician's choice of treatment in the overall population, and the difference was statistically significant (hazard ratio [HR] 0.54, 95% confidence interval [CI] 0.41 to 0.71). Similar results were reported in subgroups based on hormone receptor status in the trial; HR 0.47 (95% CI 0.32 to 0.71) for HR-positive and HR 0.60 (95% CI 0.41 to 0.87) for triple negative breast cancer. The

patient and clinical experts highlighted the importance of progression-free survival for patients and their families even if there is no survival benefit. They explained that people with breast cancer with BRCA mutations are often young, and would value the ability to lead as normal life as possible for as long as possible. The patient expert also explained how difficult and exhausting intravenous chemotherapy could be. For example, the need to attend hospital multiple days a week for blood tests and treatments for weeks. So, people with the condition would value treatments that can delay progression and reduce the need to go to hospital. The committee concluded that talazoparib was associated with delayed disease progression in people with HER2-negative advanced cancer with germline BRCA mutations. It also noted that delaying progression was important for people with the condition.

Overall survival

3.10 Overall survival was a secondary outcome in EMBRACA. At the September 2019 data cut, evidence showed that the median overall survival was 19.3 months in the talazoparib arm at median 44.9 months follow up; and 19.5 months in the physician's choice of treatment arm at median 36.8 months follow up. The difference was not statistically significant (HR 0.85, 95% CI 0.67 to 1.07). The company also presented the results adjusted for subsequent treatments that would not be used in the NHS (PARP inhibitors) and they also did not show statistically significant difference in the overall population (HR 0.82, 95% CI 0.62 to 1.05). The EAG explained that the Kaplan–Meier curves for overall survival crossed twice in the overall population and that the proportional hazard assumption does not hold. It also noted that at the end of 5 years, only 4.4% of people may still be on talazoparib and no one was on the physician's choice of treatment in the trial, so the data on overall survival was relatively complete. The clinical experts agreed that the results from the trial showed no evidence of difference in overall survival between the 2 arms. The committee concluded that the evidence did not show that

talazoparib improved overall survival in people with HER2-negative advanced cancer with germline BRCA mutations.

Overall survival in subgroups

3.11 Subgroups by hormone receptor status and by previous line of treatments (0, 1, or 2 and above) were pre-planned in EMBRACA. Similar to the overall population, there were no statistically significant differences between the 2 arms in the subgroups based on hormone receptor status, or based on previous lines of treatment. The EAG stated that talazoparib's treatment effect may differ by subgroups stratified by hormone receptor status and by previous line of treatments, and noted that the overall survival results are difficult to interpret. For example, in the HR-positive, HER2-negative subgroup, the median survival was 23.1 months for talazoparib compared with 22.4 months in the physician's choice of treatment arm (HR 0.83, 95% CI 0.60 to 1.14). In the triple negative subgroup, the median survival was numerically longer with physician's choice of treatment than with talazoparib (18.6 months compared with 13.4 months), but the HR suggested a numerical benefit associated with talazoparib (HR 0.90 [less than 1]). The company explained that EMBRACA was not powered to detect differences between talazoparib and physician's choice of treatment in subgroups. It also noted that the differences in median overall survival may be driven by subsequent treatments people had in the physician's choice of treatment arm. 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. The committee noted that subgroup analyses should be interpreted with caution. 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. These may include, but are not limited to, evidence or analysis examining the

similarities and differences in prognosis by hormone receptor status, and Kaplan–Meier curves for overall survival in the subgroups.

Economic model

3.12 The company used a cohort partitioned-survival model with 3 states, progression-free, post-progression survival and death. It compared talazoparib with physician's choice of treatment in people with HER2-negative advanced breast cancer with germline BRCA mutations. The EAG described the model as largely aligned with NICE's methods for economic evaluation. The committee concluded that the model was suitable for decision making.

Overall population and subgroups

3.13 The company presented the results for the overall population as assessed in EMBRACA. It explained that given the unmet need and improvement in progression-free survival associated with talazoparib, subgroups analysis was not relevant. The EAG disagreed with this. The committee understood that to some extent HER2-negative advanced breast cancer with germline BRCA mutations may be similar (section 3.1). But it also recalled the differences in prognosis between HR-positive, HER2-negative and triple negative cancer (section 3.1); the different treatment pathways for HR-positive, HER2-negative and triple negative advanced cancer (sections 3.3 and 3.4) and the potential heterogeneity in the trial's population (section 3.8); and the difficulties in interpreting talazoparib's treatment effect on overall survival in EMBRACA (section 3.11). The committee noted that even small differences in prognosis could make a large difference in cost effectiveness. Considering this and other uncertainties, the committee concluded that analyses for both the overall population and the subgroups by hormone receptor status are needed to inform decision making.

Physician's choice of treatment

3.14 The company's economic model compared talazoparib with physician's choice of treatment, consisting of capecitabine, vinorelbine and eribulin. Capecitabine, vinorelbine and eribulin are relevant comparators for this appraisal (sections 3.6 and 3.7). The company based the comparator on the physician's choice of treatment arm in EMBRACA, adjusted to remove gemcitabine because it is rarely used in NHS. To do so, the company assumed similar effectiveness for capecitabine, eribulin, vinorelbine and gemcitabine. The clinical experts agreed with the company that treatment effects are unlikely to be substantially different between these treatments. The committee concluded that the adjusted physician's choice of treatment in the company's submission is an appropriate comparator for HR-positive, HER2-negative and triple negative advanced breast cancer with BRCA mutations in the economic analysis.

Modelling time to treatment discontinuation

3.15 The modelling of time to treatment discontinuation was a key driver of the cost-effectiveness results. The company fitted parametric survival curves to time to treatment discontinuation. But the EAG noted that for the physician's choice of treatment arm the data was complete, and that only 4.4% of people in the talazoparib arm may be taking the treatment in the trial at the end of 5 years. Because all the company's fitted extrapolations were a poor fit to the Kaplan–Meier curves, the EAG preferred to use the Kaplan–Meier curves from the trial directly, noting that it may still slightly underestimate the cost of talazoparib in the model. The committee questioned why the company extrapolated the time to treatment discontinuation while the data was relatively complete. The company explained that it was to smooth the curves from the trial and to align them with progression-free survival's extrapolations. The committee agreed with the EAG that the company's extrapolation was not a good fit to the data. The committee concluded that from the approaches available, the EAG's approach of using Kaplan–Meier curves directly from the trial to estimate

time to treatment discontinuation was preferred. It noted that more flexible methods may result in a better fit with data in the talazoparib arm.

Red blood cell transfusions

3.16 The rate of red blood cell transfusions was a key driver of the cost-effectiveness results. To model the NHS transfusion rate, the company used a rate of 8.3% as published in Mahtani et al. 2022 because the rate of transfusions in the EMBRACA trial (38.1%) was too high and did not reflect anticipated UK clinical practice. The EAG considered that the EMBRACA rates should be used because there was uncertainty in the correlation between the rate of red blood cell transfusion, dose modifications, and the efficacy of talazoparib. The clinical experts agreed with the company that 38.1% is too high. They also explained that many people in the trial had a one-off transfusion early in the trial, so they did not consider that the transfusion rate would significantly affect the treatment effect of talazoparib as noted by the EAG. The patient expert explained that, although the transfusion rate seems high, they felt it would be acceptable to people, especially since talazoparib does not require weekly hospital visits. The clinical experts noted that in practice they would manage anaemia with dose reduction first instead of red blood cell transfusion, because transfusion is associated with risks. They were confident that the difference in their approach to transfusions would not affect the clinical effectiveness of talazoparib. They also noted that patients in the trial may have stayed on the reduced dose longer than what would be seen in clinical practice. The company explained that the trial's protocol required transfusion when haemoglobin fell below the threshold of 10 g/dL, later amended to 9 g/dL. It explained that 9 g/dL was closer to the NHS transfusion criteria. Talazoparib's summary of product characteristics states that treatment should be stopped if haemoglobin falls below 8 g/dL (treatment would be resumed at a lower dose when the haemoglobin value is 9 g/dL or higher). The company explained that the transfusion rate after the threshold amendment in the trial dropped to 32% from 42% (the average rate across the trial duration is 38.1%). The clinical

experts commented that a value between the trial and Mahtani study may be more appropriate. The committee was aware that the post threshold amendment rate in the trial may be more consistent with the NHS practice compared with the overall average rate from the trial, but this was uncertain. The committee understood that the trigger for transfusion and how transfusion is managed are likely to impact on the treatment effect of talazoparib, patients' quality of life, and costs associated with talazoparib. But the information presented was not sufficient to fully understand the potential effects. It concluded 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. But because of the uncertainties, it would also like see additional 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.

Progression-free survival utility

3.17 The utility values for progression-free survival were a key driver of the cost-effectiveness results. The company used the health-related quality-of-life data measured by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) in EMBRACA, mapped to the EQ-5D-3L. It estimated the utility value for the talazoparib and physician choice of treatment arms separately in the progression-free survival health state (the values cannot be presented here because they are confidential). The EAG explained that because EMBRACA was an open-label trial it is not appropriate to use utilities that differ according to treatments people had. Instead, the EAG used the talazoparib utility for everyone in the progression-free state in the model. The committee agreed with the EAG approach although it noted that there may be other factors that could affect how a person feels when having talazoparib or the comparator treatment, for example, needing red blood transfusions and hospital visits associated with the chemotherapies. Given the available evidence, the committee concluded that the utility value for talazoparib for the progression-free state in the model was

preferred. It noted that additional analyses could explore how additional factors affect health-related quality of life (for example, using disutilities).

Relative dose intensity

3.18 The application of a relative dose intensity multiplier was another key driver of the cost-effectiveness results. The company adjusted the doses of talazoparib and physician's choice of treatment drugs in its base case using a relative dose intensity multiplier. The EAG explained that the application of the multiplier could underestimate the cost of talazoparib. But it was unclear how the relative dose intensity multiplier was calculated because the company did not provide detailed dosing data. So the EAG removed the relative dose intensity multiplier from all treatments in the model. The committee considered it inappropriate to apply multipliers in the model without detailed dosing data or information provided. It noted that dose reductions were frequently used in the trial. The committee concluded that it would like to see a detailed analysis from the company on how it applied the relative dose intensity multipliers in the model. In the absence of the analysis, the EAG's approach of removing the modifier was preferred.

Overall survival modelling

3.19 To model overall survival in people having talazoparib, the company fitted a parametric survival distribution using a log-normal curve to the talazoparib arm of EMBRACA. It then applied a HR, adjusted for subsequent use of PARP inhibitors using a rank preserving structural failure time model, of 0.82 to model the overall survival in the physician's choice of treatment arm. The EAG explained that the proportional hazards assumption does not hold because the Kaplan–Meier curves of the 2 arms crossed at least twice in the trial. It noted that because the proportional hazard function was violated, the hazard ratio for overall survival is not an appropriate measure of talazoparib's treatment effect. The EAG considered that separate functions are needed to estimate overall survival. So, the EAG used a log-normal curve to model overall

survival in the talazoparib arm, and a Weibull curve in the physician's choice of treatment arm. The committee recalled that the evidence from EMBRACA suggested that talazoparib did not improve overall survival compared with the physician's choice of treatment (see section 3.10), but noted that the company's modelling approach implicitly included a survival benefit. It also recalled the difficulties in interpreting talazoparib's effect on overall survival. Given the evidence and the uncertainties, the committee concluded that the EAG's approach of fitting independent curves is more appropriate than the company's approach. But it acknowledged that it is possible that different models may be considered. The committee considered that, given the absence of evidence for overall survival benefit, it would like to see a scenario analysis assuming no overall survival benefit associated with talazoparib in the model for decision making.

BRCA testing

3.20 The company assumed that everyone has routine BRCA testing and did not include the cost of BRCA testing in the model. The committee discussed whether BRCA testing costs should be included for people with HER2-negative, HR-positive breast cancer. The clinical experts explained that there has been an increased uptake in BRCA testing following the NICE recommendation of BRCA-targeted treatment in early breast cancer in 2022 (in NICE technology appraisal guidance on olaparib). They explained that most people eligible for talazoparib meet the current BRCA testing criteria. The committee concluded that the cost of BRCA testing does not need to be included in the model.

Health state resource use

3.21 The company assumed that resource use in the progression-free survival health state differed depending on whether people had a response (complete or partial) or stable disease. The EAG explained that no evidence supporting differential resource use depending on response type was provided. It also noted that there was no precedent in using this approach in previous appraisals for advanced breast cancer. So, it

explored a scenario in which resource use does not differ by response type. The committee concluded that resource use that does not differ by response type was appropriate for decision making.

Cost of subsequent treatments

3.22 The company used the physician's choice of treatment arm cost and applied it to everyone in the progressed disease health state. The EAG considered that not everyone would choose to have a subsequent treatment and it was unlikely that subsequent treatments would continue until death. So, it considered that it would be more appropriate to model subsequent treatments as a one-off cost applied at the time of progression. But, this could not be done given the lack of information in the company submission. The EAG noted that the company's model has a micro-costing option that uses EMBRACA's per arm subsequent treatment data, which are adjusted by removing PARP inhibitors. So, it reweighted this micro-costing approach and applied it in its preferred base case. The committee agreed with the EAG and concluded that the EAG's reweighted micro-costing approach was appropriate for decision making.

Cost of neutropoenia

3.23 The company modelled the cost of treating neutropenia using an NHS outpatient appointment cost and the cost of treatment with an immunostimulant (filgrastim) in the progression-free disease health state. The EAG used the cost of a 14-day single course of filgrastim for treating an episode of neutropenia because filgrastim posology is a daily dose for no more than 14 days. The committee concluded that the cost of a 14-day course of filgrastim for treating an episode of neutropenia was appropriate for decision making.

Progressed disease utilities

3.24 The company used a utility value of 0.626 for the progressed disease health state, which is the midpoint between Huang 2020 (0.601) and Lambert-Obry 2018 (0.650). The EAG explained that the Huang

publication is only an abstract with unclear population information. So, it used a utility value of 0.650 from peered reviewed paper Lambert-Obry 2018 instead. The committee agreed with the EAG's consideration and concluded that the utility value of 0.650 for the progressed disease health state was appropriate for decision making.

Severity

3.25 The committee considered the severity of the condition (the future health lost by people living with the condition and having standard care in the NHS). The committee may apply a greater weight to quality-adjusted life years (QALYs; a severity modifier) if technologies are indicated for conditions with a high degree of severity. The company provided absolute and proportional QALY shortfall estimates in line with NICE's health technology evaluations manual. The EAG agreed with the company's calculation of the severity modifier. The committee concluded that the severity weight of 1.2 applied to the QALYs was appropriate.

Cost-effectiveness estimates

3.26 The exact cost-effectiveness results cannot be reported here because of confidential discounts for talazoparib, comparators and follow-up treatments. But when all the confidential prices and the severity modifier are applied, both the company's and EAG's preferred cost-effectiveness estimates for talazoparib compared with physician's choice of treatment in the overall population were higher than what NICE considers a cost-effective use of NHS resources.

Committee's preferred assumptions

3.27 The committee had preferred analysis and assumptions, specifically:

- both the analysis for the overall population and analysis for the subgroups by hormone receptor status are needed for decision making (section 3.13)

- the EAG's approach of using Kaplan–Meier curves directly from the trial to model time to treatment discontinuation (section 3.15)
- the rate of red cell blood transfusions for talazoparib in the NHS is likely to be a value between the trial and Mahtani study (section 3.16)
- the utility value for talazoparib for the progression-free survival state (see section 3.17)
- the EAG's approach of removing the relative dose intensity multiplier from the model (section 3.18)
- fitting independent curves to extrapolate overall survival in the model (section 3.19)
- BRCA testing does not need to be included in the model (section 3.20)
- the EAG's approach of not differing resource use by response type for the progression-free survival state (section 3.21)
- the EAG's reweighted micro-costing approach for the costs of subsequent treatments (section 3.22)
- the costs of filgrastim as a 14-day course for treating an episode of neutropenia (section 3.23)
- the utility value of 0.650 from Lambert-Obry 2018 for the progressed disease health state (section 3.24)
- a severity weight of 1.2 applied to the incremental QALYs (section 3.25).

Uncertainties and additional analyses needed

3.28 The committee noted some uncertainties in the evidence and in company's modelling assumptions and required further analyses, specifically:

- Talazoparib's treatment effect on overall survival and difficulties in interpreting its treatment effect in subgroups by hormone receptor status. Additional evidence or analysis from the trial is needed that explores talazoparib's effect on overall survival in the overall population and subgroups, for example, the similarities and differences in

prognosis by hormone receptor status, and Kaplan–Meier curves for overall survival in the subgroups (section 3.11).

- Only using the overall population to inform the model. Both the analysis for the overall population and analysis for subgroups by hormone receptor status are needed (3.13).
- Exploring more flexible methods for modelling of time to treatment discontinuation (see section 3.15).
- The trigger of red cell blood transfusion in EMBRACA and the correlations between dosing, dose reduction, red cell blood transfusion and treatment effect of talazoparib. Additional information or analysis of these are needed (section 3.16).
- Exploring how additional factors may affect quality of life in the progression-free survival health state, for example, using disutilities. (section 3.17).
- There is a lack of accurate dosing data from the trial. A detailed analysis from the company is needed on how it applied the relative dose intensity multiplier in the model (section 3.18).
- There is uncertainty in talazoparib's treatment effect on the overall survival. A scenario analysis assuming no overall survival benefit associated with talazoparib is needed (section 3.19).

Equality

3.29 The committee was aware that some people with HER2-negative advanced breast cancer with BRCA mutations may be younger and from Black family backgrounds. It was also aware that triple negative breast cancer is more common in some ethnicities and patient groups. The committee noted that HER2-negative advanced cancer with BRCA mutations is a condition of high unmet need (see section 3.2) but that the higher prevalence of the condition in some population groups cannot be addressed by a technology appraisal. If recommended, the recommendation would be applied to all ages and family backgrounds.

The committee agreed that these were not potential equality issue for this appraisal.

Conclusion

Recommendation

3.30 The company's base case, EAG's preferred analysis and the committee's preferred cost-effectiveness estimates for talazoparib compared with physician's choice of treatment were all higher than what NICE considers a cost-effective use of NHS resources (section 3.26). So, the committee did not recommend talazoparib for treating HER2-negative locally advanced or metastatic breast cancer with germline BRCA mutations. The committee requested further analyses from the company (section 3.28).

4 Evaluation committee members and NICE project team

Evaluation committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee A.

Committee members are asked to declare any interests in the technology being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Radha Todd

Chair, technology appraisal committee A

NICE project team

Each evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical adviser and a project manager.

Marcela Haasova
Technical lead

Yelan Guo
Technical adviser

Jeremy Powell
Project manager

ISBN: [to be added at publication]