NICE National Institute for Health and Care Excellence

NICE guidance

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

Technology appraisal guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations

1.1 Talazoparib is recommended, within its marketing authorisation, for treating HER2-negative, locally advanced or metastatic breast cancer with germline BRCA1 or BRCA2 mutations in adults who have had:

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

Talazoparib is only recommended if the company provides it according to the commercial arrangement.

Why the committee made these recommendations

For most people with HER2-negative, locally advanced or metastatic breast cancer with germline BRCA mutations, talazoparib 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 within the range that NICE considers an acceptable use of NHS resources. So, talazoparib is recommended.

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. This makes talazoparib available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

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 (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 the comments from the patient experts on the impact of advanced breast cancer on patients and their families, and recognised 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 HR-positive cancer 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 3.5). 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 of 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 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; hazard ratio 0.47 (95% CI 0.32 to 0.71) for HR-positive and hazard ratio 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 a 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. EMBRACA was powered to detect a significant difference in overall survival. 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 (hazard ratio 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 (hazard ratio 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 were still 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 (hazard ratio 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 hazard ratio suggested a numerical benefit associated with talazoparib (hazard ratio 0.90, 95% CI 0.63 to 1.28). 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 agreed that additional evidence or analysis from the trial could have provided further insight into talazoparib's effect on overall survival in the overall population and subgroups. 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. During consultation, the company provided Kaplan–Meier curves for overall survival in the subgroups, but no further evidence or analyses were provided. The committee concluded that the subgroup analyses are uncertain and should be interpreted with caution.

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 in NICE's health technology evaluation manual. The committee concluded that the model was suitable for decision making.

Overall population and subgroups

3.13 The company presented the results of the economic analysis for the overall population as assessed in EMBRACA (in the original submission) and for HR-positive, HER2-negative and triple negative subgroups (during consultation). It explained that given the unmet need and improvement in progression-free survival associated with talazoparib, subgroups analyses were 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 (see section 3.1). But it also recalled the differences in prognosis between HR-positive, HER2-negative and triple negative cancer (see section 3.1); the different treatment pathways for HR-positive, HER2-negative and triple negative advanced cancer (see sections 3.3 and 3.4); the potential heterogeneity in the trial's population (see section 3.8); and the difficulties in interpreting talazoparib's treatment effect on overall survival in EMBRACA (see section 3.11). The committee noted that even small differences in prognosis could make a large difference in cost effectiveness. Indeed, in the subgroup analyses, talazoparib seemed more cost effective in the HR-positive, HER2-negative subgroup than in the overall population, and less cost effective in the triple negative subgroup. The evidence for the subgroups is uncertain and should be interpreted with caution (see section 3.11). The committee concluded that analyses for both the overall population and the subgroups by hormone receptor status are potentially relevant for 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 (see 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 In its original submission, 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 were 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 the progression-free survival extrapolations. The committee agreed with the EAG that the company's extrapolation was not a good fit to the data. The committee noted that more flexible methods may result in a better fit with data in the talazoparib arm. In its revised analyses at consultation, the company used Kaplan–Meier curves directly from the trial to estimate time to treatment discontinuation. The committee noted that the company did not explore more flexible methods, but concluded that the company's approach to modelling time to treatment discontinuation is acceptable for decision making.

Overall survival modelling

3.16 In the original submission the company fitted a parametric survival distribution using a log-normal curve to the talazoparib arm of EMBRACA to model overall survival in people having talazoparib. It then applied a hazard ratio, 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 twice in the trial. It noted that because the proportional hazards assumption 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 for talazoparib and physician's choice of treatment. 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 company followed this approach in its revised analyses during consultation. The committee agreed that modelling separate curves was better than applying a hazard ratio to the talazoparib curve, because the proportional hazards assumption was violated. But it was aware of the evidence from EMBRACA that did not show that talazoparib improved overall survival compared with the physician's choice of treatment (see section 3.10), and noted that the separately fitted curves implicitly included a survival benefit for talazoparib. It also recalled the difficulties in interpreting talazoparib's effect on overall survival (see section 3.10 and 3.11). The committee took into account this evidence, and its conclusion that there was no evidence of a survival benefit with talazoparib despite EMBRACA being powered to show a statistically significant difference (see section 3.10). It concluded that it was appropriate to consider scenarios that assumed no survival difference for talazoparib compared with physician's choice of chemotherapy.

No survival benefit scenarios

3.17 During consultation, the company presented scenario analysis assuming no survival benefit for talazoparib compared with physician's choice of chemotherapy, alongside its base case. It used the talazoparib overall survival curve for both talazoparib and physician's choice of treatment for this scenario. The company noted that the final EMBRACA overall survival results suggest a 15% reduction in the risk of death associated with talazoparib compared with physician's choice of chemotherapy. Also, that subsequent higher PARP inhibitor use in the chemotherapy arm is likely to have negatively influenced the results. It also noted that non-significant overall survival benefits have been accepted in other NICE appraisals. The EAG emphasised that the difference in overall survival was not statistically significant even after company's adjustment for subsequent PARP inhibitor use, and that the data was relatively complete (see section 3.10). The committee queried if later overall survival data collection was planned for EMBRACA. The company explained that there is no further data collection. The Cancer Drugs Fund clinical lead noted that trials with no difference in overall survival are not unusual. The committee noted that in some cases no significant

overall survival difference is seen in trials that are not powered for overall survival. In those cases, the appropriate approach to modelling may vary according to the details of the evidence and situation. In this case, EMBRACA was powered to show differences in overall survival and the data was relatively mature, yet the trial did not show that talazoparib improved overall survival (see section 3.10). Taking into account all of the evidence available, the committee concluded that it was most appropriate to consider modelling based on no survival benefit in its decision making. The committee was aware that if the physician's choice of chemotherapy curve was used in the no survival benefit scenarios (instead of the talazoparib curve), the resulting cost-effectiveness results would be slightly higher. But, it accepted that the modelling based on the talazoparib curve was sufficient for decision making.

Red blood cell transfusions

3.18 In the original submission, the company modelled red blood cell transfusions using a rate of 8.3%, as published in Mahtani et al. 2022. This was because it considered that 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 people 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 was 38.1%). The clinical experts commented that a value between the trial and the Mahtani study may be more appropriate. The committee agreed with the experts 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 have liked to see additional information on triggers of blood transfusion from EMBRACA, and analyses exploring the relationship between dosing, dose reduction, red blood transfusion rate and the treatment effect of talazoparib, but this was not provided by the company. In its revised analyses at consultation, the company used the rate of 23.1%, a midpoint of the EMBRACA (38.1%) and Mahtani (8.3%) values, to model the rate of red blood cell transfusions. It also provided a scenario analysis with a post-amendment EMBRACA rate of 32.4%. The EAG reiterated that the treatment effect of talazoparib, patients' quality of life, and costs are all based on the trial data and linked to the rate of transfusions used in the trial, especially if these transfusions had allowed people to stay on a higher dose of talazoparib for longer. The company explained that 53.1% of people having talazoparib in EMBRACA had at least 1 dose reduction, so dose reductions were reflected in study outcomes. The Cancer Drugs Fund clinical lead noted that the Mahtani study had a short follow up so its results may not be reliable. The clinical experts noted that transfusions for breast cancer are rare. They explained that historically, transfusions were more common in the NHS. But they did not see a decrease in effectiveness of chemotherapy regimens once the current, much more restrictive, transfusion approaches were introduced. The committee agreed that the NHS transfusion rate for talazoparib will be lower than the rate in EMBRACA. But it noted that there is an uncertainty in how this lower rate would impact the treatment effect of talazoparib, patients' quality of life and dosing seen in the trial. It concluded that modelling using a value of 23.1% is appropriate for decision making, but noted uncertainty in this assumption.

Progression-free survival utility

3.19 The company modelled utility in the progression-free state using 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's 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. It emphasised that open-label trials like EMBRACA are prone to bias in self-reported outcomes. Instead, the EAG used the talazoparib utility for everyone in the progression-free state in the model. The company argued that using different values for talazoparib and physician's choice of treatment is evidence based and appropriate. It noted a study that showed a difference in utilities between PARP inhibitors and chemotherapy (Mahtani 2022) and stated that some NICE appraisals accepted different progression-free survival utilities by treatment arm. The company also presented 2 scenarios that considered a smaller difference between utilities than seen in EMBRACA. The committee acknowledged the EAG approach. It noted that there may be other factors that could affect how a person feels when having talazoparib or the comparator treatment, for example the need for red blood transfusions or hospital visits. It noted that additional analyses could have explored how additional factors affect health-related quality of life (for example, using disutilities). The patient experts described how quality of life is substantially affected by chemotherapy (see section 3.2 and section 3.9), and highlighted that talazoparib is likely to be associated with better quality of life than chemotherapy. The clinical experts commented that a difference in progression-free survival utility is plausible. The committee was persuaded by the patient and clinical experts that people on talazoparib are likely to have better quality of life than those on chemotherapy. It recognised that there were limitations in the data based on EMBRACA and that the difference in utilities may have been overestimated. The committee concluded that the EMBRACA utilities are acceptable for decision making in this appraisal. But it acknowledged that the progression-free utility values from EMBRACA are uncertain because of its open-label design, which is prone to bias.

Relative dose intensity

3.20 In the original submission, 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 advised 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 its revised analyses at consultation, the company removed the relative dose intensity multiplier from all treatments in the model. It did not provide detailed analysis on how it applied the relative dose intensity multipliers in the model. In the absence of the analyses, the committee concluded that the company's approach of removing the relative dose intensity multipliers is acceptable for decision making.

BRCA testing

3.21 The company assumed that everyone has routine BRCA testing and did not include the cost of BRCA testing in the model. 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 stated that most people eligible for talazoparib meet the current BRCA testing criteria. In its consultation response, NHS England explained that BRCA testing is routinely available for people with triple negative breast cancer, but that the cost of testing should be included for some people with HR positive, HER2 negative breast cancer. It presented 2 scenarios. Scenario A assumed that 19% of the potentially eligible NHS population would need testing, and scenario B assumed that 52% of the potentially eligible NHS population would need testing. The company disagreed and stated that genomic testing is a UK-wide government initiative and that the number of genetic tests available is quickly changing. It also explained that everyone with HR-positive, HER2-negative breast cancer can have testing for

BRCA mutations as a part of panel test for the PIK3CA mutations. It also noted that NICE's technology appraisal guidance on the PARP inhibitor olaparib did not include BRCA testing in the model. The clinical expert agreed with the company that BRCA testing has increased rapidly since olaparib was recommended for early breast cancer in May 2023. The Cancer Drugs Fund clinical lead explained that while testing has increased, not all people with HER2 negative, HR positive breast cancer are currently eligible for routine BRCA testing. The committee accepted that although many people have access to BRCA testing, it may not be routinely available to everyone. So, the cost of BRCA testing needs to be included for a small proportion of people. It noted that scenario A provides a plausible estimate of the number of people who would need additional BRCA testing as a result of introducing talazoparib. The committee concluded that the cost of additional BRCA testing for some people should be included in the modelling, and that the scenario in which 19% of people have an additional test is suitable for decision making.

Health state resource use

3.22 In the original submission, 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. In its revised analyses at consultation, the company changed its approach and did not differ resource use by response type. The committee concluded that this approach to health state resource use is acceptable for decision making.

Cost of subsequent treatments

3.23 In the original submission, 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 is adjusted by removing PARP inhibitors. So, it reweighted this micro-costing approach and applied it in its preferred base case. In its revised analyses at consultation, the company used the EAG's reweighted micro-costing approach. The committee concluded that this approach to subsequent treatments is acceptable for decision making.

Cost of neutropenia

3.24 In the original submission, 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. In its revised analyses at consultation, the company submitted an updated base case and used the cost of a 14-day course of filgrastim for treating an episode of neutropenia. The committee concluded that this approach to modelling cost of neutropenia is acceptable for decision making.

Progressed disease utilities

3.25 In the original submission, 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. In its revised analyses at consultation, the company submitted an updated base case and used the utility value of 0.650 for the progressed disease health state. The committee concluded that this approach to progressed disease utilities is acceptable for decision making.

Innovation

3.26 The committee heard that talazoparib could minimise inpatient attendance and resource use and so could help to improve capacity in oncology departments. The committee also heard that talazoparib can offer substantial benefits to people's quality of life (see section 3.19), but noted that this was captured in the model by the differential progression-free survival utilities. It did not identify additional benefits of talazoparib not captured in the economic modelling.

Severity

3.27 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

Acceptable ICER

3.28 NICE's manual on health technology evaluation notes that above a most plausible incremental cost-effectiveness ratio (ICER) of £20,000 per QALY gained, decisions about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. The committee noted a number of uncertainties, specifically about:

- Talazoparib's treatment effect on overall survival and difficulties in interpreting its treatment effect in subgroups split by hormone receptor

status (see sections 3.10 and 3.11).

- The trigger of red cell blood transfusion in EMBRACA and the correlations between dosing, dose reduction, red cell blood transfusion and the treatment effect of talazoparib (see section 3.18).
- Progression-free survival health state utilities because EMBRACA is an open-label trial (see section 3.19).

But the committee agreed that although there are some uncertainties, the data was mature. The EAG explained that the company's approach to probabilistic analyses meant that clinically implausible scenarios were included in the analysis. The committee accepted that this meant that the probabilistic analysis had limitations and its results were uncertain. Taking into account the full evidence available, the committee concluded that an acceptable ICER would be towards the higher end of the range normally considered a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained). Because the probabilistic results are uncertain, it would take both the deterministic and probabilistic results into consideration.

Cost-effectiveness estimates

3.29 The committee recalled its preferred assumptions, specifically:

- cost-effectiveness results for the overall population and subgroups by hormone receptor status (see section 3.13)
- using Kaplan–Meier curves directly from the trial to model time to treatment discontinuation (see section 3.15)
- assuming no survival benefit (see section 3.17)
- assuming that 23.1% of people on talazoparib would need red blood cell transfusions (see section 3.18)
- using different progression-free survival state utility values for talazoparib and chemotherapy (EMBRACA values; see section 3.19)

- removing the relative dose intensity multiplier from the model (see section 3.20)
- assuming that 19% of potentially eligible population in the NHS would need BRCA testing (see section 3.21).
- not differing resource use by response type for the progression-free survival state (see section 3.22)
- reweighted micro-costing approach for the costs of subsequent treatments (see section 3.23)
- using the costs of filgrastim as a 14-day course for treating an episode of neutropenia (see section 3.24)
- using the utility value of 0.650 from Lambert-Obry 2018 for the progressed disease health state (see section 3.25).

  The exact cost-effectiveness results cannot be reported here because of confidential discounts for talazoparib, comparators and follow-up treatments. When incorporating all of the committee's preferred assumptions, all the confidential prices and the severity modifier, the cost-effectiveness estimates for talazoparib compared with physician's choice of treatment in the overall population are within the range that NICE considers a cost-effective use of NHS resources.

Equality

3.30 The committee was aware that some people with HER2-negative advanced breast cancer with BRCA mutations may be younger and of a Black ethnicity. It was also aware that triple negative breast cancer is more common in some ethnicities and patient groups. During consultation, it heard that BRCA mutations are more common in people of an Ashkenazi Jewish ethnicity. Also, although breast cancer is rare in men, it is more common in men with BRCA mutations than other men. The committee noted that HER2-negative advanced cancer with BRCA mutations is a condition of high unmet need (see section 3.2), but the higher prevalence of the condition in some population groups cannot be

addressed by a technology appraisal. The recommendation would be applied to all ages and family backgrounds. The committee agreed that these were not potential equality issues for this appraisal.

Conclusion

Recommendation

3.31 Having concluded that talazoparib is cost-effective use of NHS resources for treating HER2-negative locally advanced or metastatic breast cancer with germline BRCA mutations (see section 3.28), the committee recommended it for routine use in the NHS.

4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication.

4.2 Chapter 2 of Appraisal and funding of cancer drugs from July 2016 (including the new Cancer Drugs Fund) – A new deal for patients, taxpayers and industry states that for those drugs with a draft recommendation for routine commissioning, interim funding will be available (from the overall Cancer Drugs Fund budget) from the point of marketing authorisation, or from release of positive draft guidance, whichever is later. Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or cost comparison evaluation), at which point funding will switch to routine commissioning budgets. The NHS England Cancer Drugs Fund list provides up-to-date information on all cancer treatments recommended by NICE since 2016. This includes whether they have received a marketing authorisation and been launched in the UK.

4.3 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final draft guidance.

4.4 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has HER2-negative locally advanced or metastatic breast cancer with germline BRCA mutations and the doctor responsible for their care thinks that talazoparib is the right treatment, it should be available for use, in line with NICE's recommendations.

5 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), 1 or more technical advisers and a project manager.

Marcela Haasova
Technical lead

Ewa Rupniewska and Yelan Guo
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