

**NATIONAL INSTITUTE FOR HEALTH AND CARE  
EXCELLENCE**

**Draft guidance consultation**

**Olaparib for adjuvant treatment of BRCA  
mutation-positive HER2-negative high-risk  
early breast cancer after chemotherapy**

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using olaparib 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?

**Note that this document is not NICE's final guidance on this technology. 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After considering these comments, the committee will prepare the final draft guidance.

1 Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using olaparib in the NHS in England.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: 1 December 2022

Second evaluation committee meeting: To be confirmed

2 Details of membership of the evaluation committee are given in section 4

## 1 Recommendations

- 1.1 Olaparib (alone or with endocrine therapy) is not recommended, within its marketing authorisation, for the adjuvant treatment of HER2-negative high-risk early breast cancer that has been treated with neoadjuvant or adjuvant chemotherapy in adults with germline BRCA1 or 2 mutations.
- 1.2 This recommendation is not intended to affect treatment with olaparib 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

People with BRCA mutation-positive HER2-negative high-risk early breast cancer usually have chemotherapy followed by surgery (neoadjuvant chemotherapy), or surgery followed by chemotherapy (adjuvant chemotherapy).

Clinical trial evidence shows that, compared with placebo, olaparib after neoadjuvant or adjuvant chemotherapy decreases the chance of the cancer returning or getting worse, and increases the length of time people live.

But the cost-effectiveness estimates for olaparib are above what NICE considers to be an acceptable use of NHS resources. So, olaparib cannot be recommended.

## 2 Information about olaparib

### Marketing authorisation indication

- 2.1 Olaparib (Lynparza, AstraZeneca) has a marketing authorisation as a 'monotherapy or in combination with endocrine therapy for the adjuvant treatment of adult patients with germline BRCA1/2-mutations who have HER2-negative, high risk early breast cancer previously treated with neoadjuvant or adjuvant chemotherapy'.

## Dosage in the marketing authorisation

- 2.2 The dosage schedule is available in the [summary of product characteristics for olaparib](#).

## Price

- 2.3 The list price is £2,317.50 per 56-pack of 150 mg tablets (excluding VAT; BNF online accessed October 2022).
- 2.4 The company has a commercial arrangement. This makes olaparib available to the NHS with a discount and it would have also applied to this indication if the technology had been recommended. 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 AstraZeneca, 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.

## Clinical need

### BRCA mutation-positive HER2-negative high-risk early breast cancer

- 3.1 The patient experts explained that BRCA mutation-positive HER2-negative high-risk early breast cancer is an aggressive form of cancer with poor outcomes. They also explained that it can be very distressing for people with the condition. It includes hormone receptor-positive and triple-negative breast cancer, the latter having the poorest prognosis. The patient experts explained that there are limited treatment options available for the condition, particularly for triple-negative breast cancer. They thought that many people who have had olaparib appreciated having access to an extra treatment option that has been shown to improve survival. People with HER2-negative high-risk early breast cancer often worry about the increased risk of their cancer returning after treatment.

Also, people with BRCA mutation-positive breast cancer have concerns about whether their relatives have the BRCA1 or 2 mutations, and so have an increased risk of developing cancer. Having a treatment that has been shown to improve outcomes has a positive effect on mental health. One of the patient experts who had had olaparib highlighted that it is a convenient oral treatment, and only infrequent hospital visits are needed for monitoring. They explained that olaparib's side effects were manageable. They also said that she was able to continue her usual daily activities and maintain a good quality of life while having it, although she did have fatigue. The committee concluded that olaparib would be a welcome adjuvant treatment option to improve outcomes in people with BRCA mutation-positive HER2-negative high-risk early breast cancer.

## **Treatment pathway**

### **Relevant comparator**

3.2 The committee noted that current standard care for BRCA mutation-positive HER2-negative high-risk early breast cancer is neoadjuvant chemotherapy followed by surgery and surveillance, or surgery followed by adjuvant chemotherapy. The most common chemotherapy regimen is an anthracycline taxane combination plus a platinum therapy. People with hormone receptor-positive HER2-negative cancer may also have adjuvant endocrine therapy after surgery. The committee noted that olaparib would be used after neoadjuvant or adjuvant chemotherapy, either as:

- monotherapy in triple-negative early breast cancer, or
- with endocrine treatment in hormone receptor-positive HER2-negative early breast cancer.

Because olaparib would be used in addition to any current therapies, the committee agreed that the relevant comparator was routine monitoring for cancer recurrence.

## Clinical evidence

### Generalisability of OlympiA

3.3 The clinical evidence came from [OlympiA](#), a randomised double-blind placebo-controlled trial (n=1,836). It was done in 23 countries worldwide and included 106 people from the UK. The trial compared olaparib with placebo in people with (germline) BRCA mutation-positive HER2-negative high-risk early breast cancer. People in the trial had either had neoadjuvant or adjuvant treatment at the point of randomisation. The criteria for defining high risk in OlympiA were:

- for people with triple-negative breast cancer who had neoadjuvant chemotherapy: residual invasive cancer in the breast, the resected lymph nodes (non-pathologic complete response) or both at the time of surgery
- for people with hormone receptor-positive HER2-negative breast cancer who had neoadjuvant chemotherapy: residual invasive cancer in the breast, the resected lymph nodes (non-pathologic complete response) or both at the time of surgery, and a score of 3 or more based on pretreatment clinical and post-treatment pathological stage, receptor status and histologic grade
- for people with triple-negative breast cancer who had adjuvant chemotherapy: node-positive or node-negative cancer with a primary tumour of 2 cm or more
- for people with hormone receptor-positive HER2-negative breast cancer who had adjuvant chemotherapy: 4 or more pathologically confirmed positive lymph nodes.

The clinical experts explained that the criteria for defining high risk were representative of how olaparib would be used in the NHS. They also explained that people with hormone receptor-positive HER2-negative breast cancer (17.7%) in OlympiA were selected as having cancer with an equivalent high risk of relapse as people with triple-negative breast cancer

(82.3%). The clinical experts explained that, in clinical practice, a higher proportion of people would have hormone receptor-positive HER2-negative breast cancer. They said that the proportions in the trial reflected the lower prevalence of BRCA mutations in people with hormone receptor-positive HER2-negative breast cancer, and their later enrolment into the trial. The committee agreed that the definition of high-risk early breast cancer in OlympiA was appropriate. It concluded that the trial was broadly generalisable to people who would have olaparib in the NHS.

### Clinical effectiveness

3.4 The primary outcome in OlympiA was invasive disease-free survival. Secondary outcomes included distant disease-free survival and overall survival. A statistically significant difference in all 3 outcomes was shown with olaparib compared with placebo:

- Invasive disease-free survival at 4 years was 82.7% in the olaparib arm and 75.4% in the placebo arm (a difference of 7.3%, 95% confidence interval [CI] 3.0% to 11.5%).
- Distant disease-free survival at 4 years was 86.5% in the olaparib arm and 79.1% in the placebo arm (a difference of 7.4%, 95% CI 3.6% to 11.3%).
- Overall survival at 4 years was 89.8% in the olaparib arm and 86.4% in the placebo arm (a difference of 3.4%, 95% CI -0.1 to 6.8%).

The committee noted that event rates were low: 82.7% of people in the olaparib arm and 75.4% in the placebo arm were alive and cancer-free after 4 years. But it concluded that, in the full trial population, adjuvant treatment with olaparib had been shown to improve invasive disease-free survival, distant disease-free survival and overall survival compared with placebo. Also, it agreed that low rates are expected in people who have recently had surgery and chemotherapy with curative intent.

## Efficacy of olaparib in subgroups

3.5 For the subgroup of people in OlympiA who had triple-negative breast cancer, olaparib statistically significantly improved invasive disease-free survival compared with placebo. For the subgroup of people with hormone receptor-positive HER2-negative breast cancer, the results were consistent with the overall population but were not statistically significant. The clinical experts advised that this was because:

- of the smaller sample size and lower number of events in that subgroup (see section 3.3)
- OlympiA was not powered to detect differences in subgroups at the latest data cut-off (median 3.5-year follow up).

They also explained that they did not expect to see any difference in treatment effect between the 2 HER2-negative subgroups in the trial. Also, the committee noted the company's comment that there was no evidence of statistical heterogeneity between subgroups. The committee accepted these comments. It concluded that additional data from the trial would provide further insight into the efficacy of olaparib in the subgroup with hormone receptor-positive HER2-negative breast cancer.

## Economic model

### Model design

3.6 The company presented a 5-state semi-Markov model to estimate the cost effectiveness of adjuvant treatment with olaparib compared with routine monitoring in people with BRCA mutation-positive HER2-negative high-risk early breast cancer previously treated with adjuvant or neoadjuvant chemotherapy. The 5 health states were: disease-free, non-metastatic breast cancer (local recurrence), early-onset metastatic breast cancer (recurrence within 2 years), late-onset metastatic breast cancer (recurrence after 2 years) and death. The model estimated the cost effectiveness of olaparib in people with triple-negative breast cancer and



people with hormone receptor-positive HER2-negative cancer breast cancer separately. The EAG described the model as high-quality and largely aligned with [NICE's methods for economic evaluation](#). The committee concluded that the model was suitable for decision making.

### Assumptions in economic model

3.7 There was no long-term data from OlympiA to use in the economic model. So, the company and the EAG had to extrapolate the data and make assumptions about recurrence using expert opinion and the published literature. To model recurrence in the triple-negative breast cancer subgroup, the company used the data for this subgroup from OlympiA. For the hormone receptor-positive HER2-negative cancer subgroup, the company used the full trial population as a proxy. This was because of the smaller sample size of this subgroup and the relatively low number of observed events. The EAG thought that this approach was acceptable. But it thought that it may have over- or underestimated the true risk in this subgroup because the full trial population was dominated by the triple-negative breast cancer subgroup (see section 3.3). The committee acknowledged that data was limited for the hormone receptor-positive HER2-negative cancer group (see section 3.3 and section 3.5), and that this presented challenges for the modelling. It concluded that this added greater uncertainty to the cost-effectiveness results for the hormone receptor-positive HER2-negative cancer subgroup.

### Extrapolating recurrence

3.8 The company used a log-normal distribution to model the risk of recurrence in both the triple-negative and hormone receptor-positive HER2-negative breast cancer populations. The EAG agreed with the log-normal distribution for the triple-negative population but thought that this was too optimistic for the hormone receptor-positive HER2-negative population. It preferred the generalised gamma distribution. This gave the smallest difference in long-term invasive disease-free survival for this subgroup. It also resulted in there being an equal risk of recurrence in the

olaparib and placebo groups at an earlier time point (5.4 years compared with 14.5 years in the company's model). The company provided scenario analyses varying the time point at which the risk of recurrence was equal, this had only a small effect on incremental cost-effectiveness ratios (ICERs). The committee agreed that there was insufficient evidence to make an informed decision about whether a log-normal or generalised gamma distribution was more suitable without further follow up from the trial. It noted the clinical experts' opinion that, for long-term invasive disease-free survival, there was little difference between the 2 distributions.

### **Risk of recurrence in triple-negative breast cancer population**

3.9 For people with hormone receptor-positive HER2-negative cancer breast cancer, the company and EAG assumed that the risk of recurrence remained elevated throughout the lifetime horizon of the model. But, for people with triple-negative breast cancer, the company and EAG made different assumptions. The company assumed that, after 5 years, there was a 0% chance of recurrence while the EAG assumed a 5% risk from year 5 to year 15. The clinical experts explained that most recurrences in people with triple-negative breast cancer occur in the first 2 to 3 years after diagnosis. They also said that the risk of recurrence after 5 years is very low, although it is not likely to be 0%. They estimated that there may be a 2% to 3% risk of recurrence between year 5 and year 8, and 0% after 8 years. The committee concluded that assuming a 2% to 3% risk of recurrence between years 5 and year 8, while uncertain, was reasonable.

### **Extrapolating survival**

3.10 The company and the EAG used different extrapolation curves for estimating survival after early metastatic recurrence. The company used an exponential distribution and the EAG used the Gompertz distribution. The EAG argued that using an exponential distribution is unsuitable when the data violates the proportional hazards assumption. It highlighted that the company had presented evidence that hazards between arms were

non-proportional. Both Kaplan–Meier curves and log-cumulative hazards indicated violation of proportional hazards. The EAG thought that the Gompertz distribution gave the most plausible survival difference between arms and, given the long-term uncertainty, was more conservative. The clinical experts noted that the latest publication of the OlympiA data showed that the proportional hazards assumption was met for survival. The committee noted that the choice of extrapolation method had a small effect on the ICER, so did not discuss this further.

### **Company's utility values**

3.11 The utility values used in the modelling were a key driver of the cost-effectiveness results, particularly the values for the disease-free health state. The company used health-related quality-of-life data from the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) in OlympiA, mapped to EQ-5D-3L to estimate the utility value for the disease-free health state. It set the non-metastatic breast cancer (local recurrence) utility value to be the same as that for the disease-free health state because the difference between the 2 was non-significant in the trial. The metastatic breast cancer utility value was sourced from external literature. The EAG had 2 issues with the company's approach. Firstly, it believed that there was a risk of bias because of low completion rates of the EORTC QLQ-C30 questionnaires. Secondly, it had concerns about the algorithms used to map the data to EQ-5D-3L. The EAG highlighted that older algorithms, such as the Crott and Briggs algorithm used in the company's base case, have been shown to produce biased estimates. It also explained that newer algorithms have had insufficient external validation. The committee noted these limitations and questioned whether the company's estimates were plausible. It noted that these were 0.869 for the disease-free and the non-metastatic breast cancer health states and 0.685 for the metastatic breast cancer health state. The committee appreciated that the utility values were estimated from the health-related quality-of-life data in OlympiA. But it was concerned that the values were unrealistically high because the disease-

free value was only slightly lower than that of age-matched people in the general population (0.877). The committee considered this to be implausible because people taking olaparib would recently have had both surgery and chemotherapy. Also, this value was not consistent with other technology appraisals of treatments for triple-negative breast cancer. Also, the committee was not convinced that it was realistic to assume the same utility for the disease-free and non-metastatic breast cancer (local recurrence) health states. This was because of the anxiety associated with having a local recurrence and probable further surgery, possibly including mastectomy. The committee was also aware that the utility values used by the company for metastatic breast cancer were generally higher than used in some other technology appraisals. For these reasons, the committee concluded that the company's utility values were not appropriate.

### **EAG's utility values**

3.12 The EAG used utility values from an external UK study ([Verrill et al. 2020](#)) in people with HER2-positive breast cancer (108 with early and 102 with metastatic breast cancer). This study directly measured health-related quality of life using the EQ-5D questionnaire. The values were 0.732 for the disease-free, 0.668 for non-metastatic breast cancer and 0.603 for metastatic breast cancer health states. The EAG chose a value for non-metastatic breast cancer that was the midpoint between the disease-free and metastatic breast cancer health states. The committee noted that the estimates were much lower than the company's estimates, possibly because of the older population in Verrill et al. compared with OlympiA. The EAG also presented a sensitivity analysis adjusting for the age difference between Verrill et al. and OlympiA. This increased the utility values to 0.770 for the disease-free, 0.702 for non-metastatic breast cancer and 0.634 for metastatic breast cancer health states. The committee accepted that using the utilities from Verrill et al. had some limitations because of differences in the populations. But it concluded that the utility values from the EAG's age-adjusted estimates using Verrill et al.

were the most appropriate of the ones presented by the company and EAG.

### **BRCA testing costs**

3.13 The company assumed that olaparib was not associated with additional costs for BRCA testing, which is needed to determine eligibility for olaparib. The rationale for this was that most people with HER2-negative high-risk early breast cancer will have routine BRCA screening as part of standard care in the NHS. The EAG questioned whether this was the case for people with hormone receptor-positive HER2-negative cancer early breast cancer and preferred to include BRCA testing costs for this group. The company submitted data suggesting that most people with hormone receptor-positive HER2-negative cancer high-risk early breast cancer who are potentially eligible for olaparib would already be identified for BRCA testing if the current National Genetic Test Directory criteria were uniformly implemented in clinical practice. This was because OlympiA only recruited people with breast cancer at high risk of recurrence. The clinical experts agreed that most people with hormone receptor-positive HER2-negative high-risk early breast cancer would be eligible for testing and that training for clinicians would increase implementation. The committee accepted that most people with HER2-negative early breast cancer at high risk of recurrence meet the current testing criteria, so BRCA testing costs did not need be included in the model.

### **Discount rates**

3.14 The company argued that discount rates of 1.5% for costs and outcomes should be applied for the triple-negative breast cancer population instead of rates of 3.5%. The company presented a scenario analysis using the lower rates and this reduced the ICER in the triple-negative breast cancer population substantially. But the committee noted that, for the 1.5% rates to be applicable, the treatment would have to:

- be used in people who would otherwise die or have a very severely impaired life
- restore those people to full or near-full health
- have benefits that are sustained over a very long period.

The EAG argued that the immaturity and long-term uncertainty of the data meant that it was unclear whether olaparib will restore people to full health or provide sustained benefits. The committee agreed with this. It also noted that 75.4% of people in the placebo arm of OlympiA had not had an invasive disease-free survival event by 4 years. This indicated that the first criterion was also not met. The committee concluded that olaparib did not meet the eligibility criteria needed for a reduced discount rate to be used.

## **Cost effectiveness**

### **Cost-effectiveness estimates for olaparib**

3.15 The company's base-case ICERs for olaparib compared with routine monitoring are above the range normally considered a cost-effective use of NHS resources. That range is £20,000 to £30,000 per quality-adjusted life year gained. This was true for both the triple-negative and the hormone receptor-positive HER2-negative early breast cancer populations. The ICERs were higher and the results more uncertain for hormone receptor-positive HER2-negative breast cancer than for triple-negative breast cancer (see section 3.7). None of the company's scenario analyses substantially changed the results apart from an analysis that used 1.5% discount rates for costs and outcomes. But the committee had concluded that was not appropriate (see section 3.14). Incorporating the committee's preferred assumptions on utility values (see section 3.11 and section 3.12), and on risk of recurrence in the triple-negative early breast cancer population (see section 3.9), increased the company's ICER further. The ICERs cannot be reported here because of confidential commercial arrangements for subsequent treatments in the pathway. The

committee concluded that adjuvant treatment with olaparib had not been shown to be cost effective.

## Conclusion

### Olaparib is not recommended

3.16 In the company's analysis, olaparib was not cost effective compared with routine surveillance. The company's cost-effectiveness estimates were also likely to have been an underestimate. This was largely because the model included utility values that the committee did not consider plausible. Incorporating the committee's preferred assumptions (see section 3.9, section 3.11, and section 3.12) increased the ICERs. Also, there was greater uncertainty about the modelling in the hormone receptor-positive HER2-negative subgroup (see section 3.7 and section 3.8). The committee appreciated the unmet need for treatment options for people with BRCA mutation-positive HER2-negative high-risk early breast cancer (see section 3.1). It also concluded that olaparib was an effective treatment in the overall trial population (see section 3.4). But it was unable to recommend adjuvant treatment with olaparib because it had not been shown to be cost effective.

## 4 Evaluation committee members and NICE project team

### Evaluation committee members

The 4 technology appraisal evaluation 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**

### **Jane Adam**

Chair, Technology appraisal evaluation committee

## **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.

### **Thomas Jarratt**

Technical lead

### **Zoe Charles**

Technical adviser

### **Thomas Feist**

Project manager

ISBN: [to be added at publication]