NICE National Institute for Health and Care Excellence

NICE guidance

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

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 Olaparib (alone or with endocrine therapy) is recommended, within its marketing authorisation, as an option 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. It is only recommended if the company provides it according to the commercial arrangement.

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.

The cost-effectiveness estimates for olaparib are within what NICE considers to be an acceptable use of NHS resources. So, olaparib is 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 January 2023).

2.4 The company has a commercial arrangement. This makes olaparib 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 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 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 they were able to continue their usual daily activities and maintain a good quality of life while having it, although they 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 breast 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-pathological 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 histological 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.

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 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.

Extrapolating recurrence

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. 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, but this only had 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

3.8 For people with hormone receptor-positive HER2-negative 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 year 5 and year 8, while uncertain, was reasonable.

Extrapolating survival

3.9 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

3.10 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 two 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. The committee was also 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 those 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

3.11 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

3.12 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 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 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

3.13 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

3.14 The base-case ICERs originally submitted by the company for olaparib

compared with routine monitoring were 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 (QALY) gained. This was true for both the triple-negative and the hormone receptor-positive HER2-negative early breast cancer populations. 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 3.13). Incorporating the committee's preferred assumptions on utility values (see section 3.10 and section 3.11), and on risk of recurrence in the triple-negative early breast cancer population (see section 3.8), increased the company's ICERs further. After the first committee meeting, the company updated its commercial arrangement and submitted a new analysis using the committee's preferred assumptions. The change to the commercial arrangement resulted in ICERs that were substantially below £30,000 per QALY gained. The ICERs cannot be reported here because of confidential commercial arrangements for subsequent treatments in the pathway. The committee concluded that olaparib is a cost-effective adjuvant treatment for BRCA mutation-positive HER2-negative high-risk early breast cancer after chemotherapy.

Conclusion

Olaparib is recommended

3.15 The committee recognised 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 agreed that olaparib is an effective treatment (see section 3.4). After the first committee meeting, the company updated its cost-effectiveness analysis, adopting the committee's preferred assumptions and including a revised commercial arrangement. This reduced the ICERs to substantially below £30,000 per QALY gained. The committee concluded that olaparib is a cost-effective adjuvant treatment for BRCA mutation-positive HER2-negative high-risk early breast cancer after chemotherapy.

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 BRCA mutation-positive HER2-negative high-risk early breast cancer and the doctor responsible for their care thinks that olaparib 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 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 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.

Thomas Jarratt
Technical lead

Zoe Charles
Technical adviser

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