NICE National Institute for Health and Care Excellence

NICE guidance

Olaparib for maintenance treatment of BRCA mutation-positive advanced ovarian, fallopian tube or peritoneal cancer after response to first-line platinum-based chemotherapy

Technology appraisal guidance
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www.nice.org.uk/guidance/ta962

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

This guidance replaces TA598.

1 Recommendations

1.1 Olaparib is recommended, within its marketing authorisation, as an option for maintenance treatment of BRCA mutation-positive, advanced (FIGO stages 3 and 4), high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer that has responded to first-line platinum-based chemotherapy in adults. It is only recommended if the company provides it according to the commercial arrangement.

Why the committee made these recommendations

This evaluation reviews the evidence for olaparib for maintenance treatment of BRCA mutation-positive advanced ovarian, fallopian tube or primary peritoneal cancer after response to first-line platinum-based chemotherapy (NICE technology appraisal guidance 598). It also reviews new evidence collected as part of the managed access agreement. The new evidence includes data from clinical trials and from people having treatment in the NHS in England.

The new clinical evidence shows that people having olaparib live longer and have more time before their cancer gets worse compared with people having placebo.

The most likely cost-effectiveness estimate for olaparib is within the range that NICE considers an acceptable use of NHS resources. So, it is recommended for routine use.

2 Information about olaparib

Marketing authorisation indication

2.1 Olaparib (Lynparza, AstraZeneca) is indicated for 'the maintenance treatment of adult patients with advanced (FIGO stages III and IV) BRCA1/2-mutated (germline and/or somatic) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based 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 for olaparib is £2,317.50 (56 x 150 mg tablets) per 14-day pack and £4,635.00 per 28-day cycle (excluding VAT; BNF online accessed January 2024).

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.

The condition

Details of condition

3.1 The patient expert explained that people with advanced ovarian, fallopian tube or peritoneal cancer have an underlying fear of the cancer recurring which can affect their quality of life. The patient expert noted that because olaparib is specifically given to people with BRCA mutation-positive ovarian cancer, knowing that the treatment is targeted for this indication and is effective, is reassuring. They would like to be able to access olaparib first-line treatment routinely, having been able to use it through the Cancer Drugs Fund. The company noted in its submission that late diagnosis of the disease is common and contributes to the poor outcomes. It noted that although most people's cancer responds to first-line platinum-based chemotherapy, many experience a relapse or disease progression. Response to platinum-based chemotherapy reduces with subsequent rounds of treatment, leading to the cancer becoming platinum resistant in some people. The company noted that there is an unmet need for effective maintenance treatments that achieve long-term remission. The committee concluded that there is an unmet need for routine access to first-line maintenance treatments for advanced ovarian, fallopian tube and peritoneal cancer.

Clinical management

Treatment options

3.2 The usual first-line treatment for BRCA mutation-positive advanced ovarian,

fallopian tube or peritoneal cancer is platinum-based chemotherapy. After a response, first-line maintenance treatment with a poly-ADP-ribose (PARP) inhibitor is offered. These include:

- niraparib, which is available through the Cancer Drugs Fund (CDF; see NICE's technology appraisal guidance on niraparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy [TA673])
- olaparib with bevacizumab (see NICE's technology appraisal guidance on olaparib with bevacizumab for maintenance treatment of advanced high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer [TA946]), and
- olaparib monotherapy, through the CDF.

PARP inhibitors are also available as second- and third-line maintenance treatments after response to platinum-based chemotherapy for people who have not had them previously. But the CDF clinical lead explained that retreatment with PARP inhibitors is currently not NHS practice. The clinical expert noted that this is because there is limited evidence for improved outcomes from retreatment with a PARP inhibitor. The committee concluded that positioning olaparib as a first-line maintenance treatment is appropriate.

Comparators

3.3 The company's submission included routine surveillance as the only comparator, in line with the final scope. Niraparib is only available through the CDF, and olaparib with bevacizumab was only recently recommended for routine commissioning (see section 3.2), so neither could be considered established clinical practice. The committee concluded that routine surveillance was the appropriate comparator.

Clinical effectiveness

Data sources and generalisability

3.4 The key clinical-effectiveness evidence for olaparib was from SOLO-1, a randomised, double-blind, phase 3 clinical trial. The trial included adults with advanced (stage 3 or 4) ovarian, fallopian tube or peritoneal cancer whose condition was responding to first-line platinum-based chemotherapy. The committee recalled that data from SOLO-1 was considered during the original appraisal, and that although olaparib showed favourable progression-free survival, the overall survival results were uncertain because of data immaturity (21% maturity) and lack of statistical significance. The most recent SOLO-1 data cutoff (March 2022) has a median follow-up period of 84 months (7 years) with 38.1% maturity. The company also reported data from the Systemic Anti-Cancer Therapy (SACT) database, for people who had olaparib through the CDF. The CDF clinical lead noted that the average age of people in SOLO-1 was lower than in the SACT dataset (53 years compared with 61 years, respectively). They were concerned about the impact of age on the generalisability of the SOLO-1 results to NHS clinical practice. The committee acknowledged the concerns about generalisability, and would have preferred a similar average age for both datasets. It concluded that although SOLO-1 data was sufficient for decision making, it would have preferred further analysis to understand the impact of age on its recommendation (see section 3.14).

Survival outcomes

3.5 Progression-free survival was the primary outcome in SOLO-1. The most recent data cutoff (March 2022) showed that olaparib delayed disease progression compared with placebo. The company considers the exact magnitude of the delay to be confidential, so it cannot be reported here. The median overall survival was not reached for the olaparib arm, but was 75.2 months for the placebo arm (hazard ratio [HR] 0.55, confidence interval [CI] 0.40 to 0.76). The company noted that overall survival benefits were still seen despite around 44% of people in the placebo arm having a PARP inhibitor after disease progression. The EAG and the company considered that the SACT overall survival results were

similar to the SOLO-1 results. The EAG was concerned that overall survival was similar for olaparib and placebo until about 42 months, after which the curves diverged. The committee asked the company to provide a compelling clinical rationale for the divergence in the overall survival curves from month 42 onwards. The company responded that a robust and accurate rationale would be difficult to provide. The committee concluded that although the survival data for olaparib remained immature, the most recent data cutoff (March 2022) suggested that it improves overall survival compared with placebo.

Economic model

Company's modelling approach

3.6 The company used the same partitioned survival model from the original appraisal (TA598). The model included 4 health states: progression free, progressed disease 1, progressed disease 2, and death. Progression free was assumed to be the entry health state. The model included half-cycle correction, assumed a 47-year time horizon, and applied the non-reference case discount (1.5%) for costs and quality-adjusted life years (QALYs; see section 3.11). The committee was satisfied with the company's modelling approach.

Modelling of progression-free survival

3.7 The company considered olaparib maintenance treatment to have curative potential for some people. It noted that people whose cancer had not progressed within 5 years were likely to remain in long-term remission. It stated in its submission that the SOLO-1 progression-free survival Kaplan–Meier curve plateaued, which meant that the risk of disease progression or death was close to zero (and comparable to that of the general population). So, the company used mixture cure models for extrapolating progression-free survival. Its preferred base-case model was log-logistic. The EAG noted that the company's progression-free survival estimates were not generated with the most recent data cutoff (March 2022). In response to this, the company highlighted that it used an earlier data cutoff (March 2020) due to a protocol change in SOLO-1 that

allowed people who had stopped treatment or were in remission to reduce their hospital visits (from every 3 months to every 6 months) and to only assess their tumour if their clinician judged it necessary. The EAG preferred using the most recent data cutoff for generating all survival estimates, for consistency and because this reduced the need for extrapolation. It requested updated mixture cure models from the company using the most recent data cutoff. The company provided the updated mixture cure models for progression-free survival, but noted that only some could be clinically validated because of time limitations. The company considered the models to be statistically and clinically appropriate. Based on the updated model, the EAG preferred to generate progression-free survival estimates using generalised gamma curves. The committee considered that the change in hospital visits in SOLO-1 would not markedly impact the progression-free survival results. It agreed with the EAG that the most recent data cutoff (March 2022) should be used for estimating progression-free survival because this reduced the need for extrapolation. It also preferred the generalised gamma curves because these provided the most plausible estimates.

Overall survival

3.8 The company generated its base-case long-term overall survival estimates by fitting a standard parametric model (generalised gamma) to the SOLO-1 Kaplan–Meier curve. The EAG was concerned about this approach. It noted that in SOLO-1 the definition of overall survival included progression-free survival. So, if progression-free survival was estimated using a mixture cure model (see section 3.6), then overall survival should include a cure fraction that was either equal to or greater than the progression-free survival cure fraction. The EAG highlighted that the company's base-case modelling approach required fixes (constraints) to prevent it from generating illogical estimates. The EAG had requested additional analyses from the company, noting that it believed these fixes would not be needed if a mixture cure model were used for estimating overall survival. The company provided the mixture cure models using the most recent data cutoff for overall survival as requested, but noted that only some could be clinically validated because of time limitations. For its base case, the company maintained its initial standard parametric approach to modelling overall survival. The EAG felt that the mixture cure models with the most recent data cutoff generated more robust survival estimates. It preferred log-logistic models

for extrapolating overall survival. The committee concluded that the most recent data cutoff (March 2022) should be used for estimating overall survival to reduce the need for extrapolation. It also preferred the log-logistic curves because these provided the most plausible estimates.

Treatment sequence

3.9 In SOLO-1, 31% of people who had a subsequent treatment in the olaparib arm had a PARP inhibitor after disease progression. In the placebo arm, around 60% had a PARP inhibitor as a subsequent treatment. The committee recalled that PARP inhibitor retreatment is not current NHS practice (see section 3.2). The company said that in its model, subsequent PARP inhibitor use in the olaparib arm was set at 0%. The EAG noted that in SOLO-1, it was unclear what proportion of people in the placebo arm had treatment in line with the NHS pathway, that is, had a PARP inhibitor after response to second-line platinum-based chemotherapy. It was concerned that some people may have had a PARP inhibitor as standalone maintenance treatment without initially having second-line platinum-based chemotherapy. In response to clarification, the company noted that treatment sequencing data was not collected in SOLO-1 and it would be statistically inappropriate to derive it. The company provided an updated model with improved functionality for modelling subsequent treatment. The EAG noted that the company's updated model did not link subsequent treatment with previous platinum-based chemotherapy, but acknowledged that the improved functionality allowed it to do additional exploratory analyses. The exploratory analyses used clinical expert input to estimate the proportion of people likely to have a PARP inhibitor at second and third line, in line with NHS practice (that is, after platinum-based chemotherapy). Additionally, a separate analysis explored using an exponential decrease in the number of people eligible for olaparib. This is because the EAG felt that the company's approach, which used a constant estimate of people experiencing non-fatal survival events as being eligible for treatment, to be an overestimate. The committee was concerned that in addition to the key issues raised by the EAG, health outcomes related to subsequent PARP inhibitor treatment were not captured in the model. The clinical expert explained that a recent study showed a very small but not clinically relevant improvement in progression-free survival after retreatment with a PARP inhibitor. They did not think that subsequent PARP inhibitor treatment would impact health outcomes

significantly for the olaparib arm. But in the placebo arm, olaparib would have an impact on both second progression-free survival and overall survival. The committee asked the company if it performed an analysis for the subgroup that did not have subsequent PARP inhibitor treatment. The company responded that this had not been possible because of a lack of data and methodological concerns, but that other PARP inhibitor appraisals have explored this. Regardless of the potential methodological concerns, the committee would have preferred to see the data for this subgroup. It concluded that it preferred the EAG's approach to modelling subsequent treatment because this approach more closely matched how olaparib would be used in NHS clinical practice.

Time on subsequent PARP inhibitor treatment

3.10 The company's model used data from a different clinical trial (SOLO-2) to estimate time on subsequent PARP inhibitor treatment for the placebo arm. Time on treatment data was not collected in SOLO-1. The committee understood that SOLO-2 assessed the effectiveness of olaparib in people whose ovarian cancer had relapsed after 2 or more lines of chemotherapy. This population differed to the population in SOLO-1. The EAG noted that the time on subsequent PARP inhibitor treatment in SOLO-2 was longer than the time between first and second disease progression generated in the company's model using SOLO-1 data. The EAG highlighted that after disease progression, people in the placebo group would be expected to have platinum-based chemotherapy, then PARP inhibitor maintenance treatment until the second disease progression. So, it would be reasonable to assume that time on treatment would not exceed the time between the first and second disease progression. In its cost-effectiveness estimates, the EAG applied this assumption. The company considered the EAG's approach to be inappropriate because it constrained the model by making the time in the progressed disease state the same as the time on subsequent PARP inhibitor treatment. It noted that the population was heterogenous, with different outcomes, and some people would not necessarily have treatment after progression. The clinical expert confirmed that the population would be heterogenous and that they expected the time on treatment to be longer than the EAG estimate. The EAG explained that in the absence of further evidence, SOLO-2 time on treatment data was useful. But the magnitude of difference between the model-generated estimate and the SOLO-2 estimate suggested that

the latter lacked face validity for this population. The committee acknowledged the EAG's concerns but took into account the clinical expert's perspective. It concluded that in the absence of further evidence, the company's estimate was reasonable.

Discount rate

3.11

Treatment cost

3.12 The company estimated the acquisition cost of olaparib using the mean dose from SOLO-1. This was lower than the recommended dose in its marketing authorisation (600 mg; see section 2.2). The EAG noted that the lower dose likely took into account adverse event management through dose interruptions and reductions. But it explained that because olaparib was only available as 100 mg and 150 mg tablets, the lower dose would not result in any cost savings for the NHS. So, the EAG applied the fixed recommended dose for its cost-effectiveness estimates. The company highlighted that people having dose interruptions related to adverse events would not incur a cost in practice to the NHS. The CDF clinical lead said that people are typically supplied with the full treatment dose and that adverse events would likely be managed after this. So, the NHS would incur a cost. They noted that wastage is a significant issue in the NHS. The EAG raised an additional issue related to how dose was modelled. It noted that the lower dose (558 mg) was only applied to the olaparib arm but the full dose was used for subsequent lines of treatment. Because subsequent PARP inhibitor treatment (including niraparib) was applied to the placebo arm, this increased the acquisition cost for the placebo arm and biased the results to favour olaparib. The EAG did not have data on dose reduction in other PARP inhibitor trials (such as niraparib) to appropriately apply these. So, it considered that assuming no dose reduction was the best approach. The committee preferred the EAG's method for estimating treatment cost.

Cost-effectiveness estimates

Preferred assumptions

3.13 The committee's preferred assumptions were:

- modelling progression-free survival using the most recent data cutoff (March 2022) with a generalised gamma curve applied to a mixture cure model (see section 3.7)
- modelling overall survival using the most recent data cutoff (March 2022) with a log-logistic curve applied to a mixture cure model (see section 3.8)
- using clinical expert estimates for subsequent PARP inhibitor treatment and applying an exponential decrease in the number of people eligible for olaparib (see section 3.9)
- using SOLO-2 data to estimate time on maintenance PARP inhibitor treatment (see section 3.10)
- applying a 3.5% discount rate to costs and QALYs (see section 3.11)
- using the recommended total daily dose for calculating the treatment acquisition cost (see section 3.12).

Acceptable cost-effectiveness estimates

3.14 NICE's health technology evaluation manual states 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 specifically consider the following factors:

- the degree of certainty and uncertainty around the ICER
- aspects that relate to uncaptured benefits and non-health factors.

The committee noted that there were unresolved uncertainties, including the lack of data about time on treatment and how this was modelled (see

section 3.10). But it felt that the length of follow up in the clinical trial (7 years) was sufficiently long compared with many other trials. It was willing to accept an ICER towards the higher end of the range that is normally considered a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained). With the committee's preferred assumptions and the confidential commercial arrangements for olaparib and the subsequent treatments in the pathway, the cost-effectiveness estimates were within the range considered an acceptable use of NHS resources.

Other considerations

Additional uncertainty

3.15 The committee considered further uncertainty related to the generalisability of SOLO-1 to NHS clinical practice. This included:

- the average age of people in the SACT dataset and SOLO-1 (see section 3.4; 61 years compared with 53 years)
- the proportion of people expected to have olaparib beyond 2 years.

The company had done a scenario analysis to explore the impact of a higher proportion of people having treatment beyond 2 years than in its base case. But the CDF clinical lead noted that in practice, more people continued treatment beyond 2 years than were captured in the company's scenario analysis. The committee asked the EAG to do additional analyses exploring these uncertainties. Based on the results, the committee concluded that the most plausible ICER indicated that olaparib is cost effective.

Equality

3.16 The company's submission noted that the risk of BRCA mutation is higher in Ashkenazi Jewish groups, and that people who do not identify as female may have ovarian or fallopian tube cancer. Submissions from patient organisations

also noted that because of religious beliefs, some people may not want genetic testing for BRCA mutations. Gender reassignment, race and religion are protected characteristics under the Equality Act 2010. The committee acknowledged these issues and agreed that its recommendation would apply equally to all people regardless of their ethnic background or belief. Its recommendation would not have a different impact on people protected by the equality legislation than on the wider population and so it did not need to modify its recommendation to take account of these issues.

Conclusion

Recommendation

3.17 The committee concluded that the most plausible ICER was within the range that NICE considers a cost-effective use of NHS resources. So, it recommended olaparib for routine use for maintenance treatment of BRCA mutation-positive advanced ovarian, fallopian tube or peritoneal cancer that has responded to first-line platinum-based chemotherapy in adults.

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 advanced ovarian, fallopian tube or peritoneal 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 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

Dr Radha Todd
Chair, technology appraisal committee A

NICE project team

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

Raphael Egbu
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Technical adviser

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