NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Olaparib with bevacizumab for maintenance treatment of advanced ovarian, fallopian tube or primary peritoneal cancer [managed access review of TA693]

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

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

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

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Issue date: June 2023

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

After consultation:

- The evaluation committee will meet again to consider the evidence, this evaluation consultation document and comments from the stakeholders.
- At that meeting, the committee will also consider comments made by people who are not stakeholders.
- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using olaparib with bevacizumab in the NHS in England.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: 18th July 2023
- Second evaluation committee meeting: 1st August 2023
- Details of the evaluation committee are given in section 4.

1 Recommendations

1.1 Olaparib with bevacizumab is not recommended, within its marketing authorisation, for maintenance treatment of high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer in adults whose cancer:

- has completely or partially responded after first-line platinum-based chemotherapy with bevacizumab
- is advanced (International Federation of Gynecology and Obstetrics [FIGO] stages 3 and 4) and
- is homologous recombination deficiency (HRD) positive (defined as having either a BRCA1 or BRCA2 mutation or genomic instability).

1.2 This recommendation is not intended to affect treatment with olaparib with bevacizumab that was funded with managed access before final guidance was published. If this applies, NHS England and the company have an arrangement to make sure people who started treatment during the period of managed access will continue to have olaparib with bevacizumab until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

This evaluation reviews the evidence for olaparib with bevacizumab for maintenance treatment of HRD-positive, advanced high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer (NICE technology appraisal guidance 693). It also reviews new evidence collected as part of the managed access agreement.

New clinical trial evidence shows that people taking olaparib with bevacizumab have more time before their cancer comes back than those having bevacizumab only, and they also live longer. But the economic evidence is very uncertain. When taking into account the committee's preferred assumptions, the cost-effectiveness estimates are not within what NICE considers an acceptable use of NHS resources. So, olaparib is not recommended for routine use in the NHS.

2 Information about olaparib

Marketing authorisation indication

2.1 Olaparib (Lynparza, AstraZeneca) with bevacizumab (Avastin, Roche) is indicated for 'maintenance treatment of adult patients with advanced (FIGO stages 3 and 4) 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 in combination with bevacizumab and whose cancer is associated with homologous recombination deficiency positive status defined by either a BRCA1/2 mutation and/or genomic instability'.

Dosage in the marketing authorisation

2.2 The dosage schedules are available in the summary of product characteristics for olaparib and the summary of product characteristics for bevacizumab.

Price

2.3 The list price for olaparib tablets is £2,317.50 per 14-day pack (56 150-mg tablets); £4,635.00 per 28-day cycle (excluding VAT; BNF online, accessed May 2023).

2.4 The company has a commercial arrangement. This makes olaparib with bevacizumab 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 and current management

Advanced ovarian, fallopian tube and peritoneal cancer

3.1 The patient experts explained that advanced ovarian, fallopian tube and peritoneal cancer (hereafter described as ovarian cancer) has a substantial impact on quality life. Most people are diagnosed with ovarian cancer at an advanced stage (stage 3 or 4), where the disease has already spread outside of the pelvis. Even when initial treatment is successful, those living with advanced ovarian cancer often live with the anxiety of possible recurrence and further rounds of chemotherapy. As a result, the time between treatments can be extremely difficult, and people with ovarian cancer are concerned that treatment options will become exhausted as the disease progresses. The clinical and patient experts explained that there are high rates of recurrence after initial surgery and platinum-based chemotherapy. Therefore, it is very important to offer a maintenance treatment following first-line treatment. The committee concluded that there is a high disease burden and need for new treatments for people with advanced ovarian cancer.

Use of PARP inhibitors

3.2 The clinical experts explained that the use of PARP inhibitors such as olaparib is well-established across multiple lines of treatment for ovarian cancer. The specific PARP inhibitor available depends on how many courses of chemotherapy the person has had before, and some are only available through the Cancer Drugs Fund. Also, they are only available for people who have not had treatment with a PARP inhibitor before. The clinical and patient experts highlighted that olaparib with bevacizumab is the only first-line combination maintenance treatment available. They explained that having a first-line maintenance treatment offers significant psychological and physical health benefits and provides a sense of hope that recurrence can be prevented. Having a targeted treatment for homologous recombination deficiency (HRD)-positive disease, which affects around 50% of people with advanced ovarian cancer, is also of

great value. The clinical and patient experts also highlighted that olaparib with bevacizumab has manageable side effects. The committee concluded that the continued availability of olaparib with bevacizumab as a first-line maintenance treatment, to extend periods of remission and improve quality of life, is extremely important to people with advanced ovarian cancer.

Comparators

3.3 The comparators in the scope were bevacizumab maintenance therapy at an 'off-label' dose of 7.5 mg per kg every 3 weeks (the 15 mg per kg licensed dose is not recommended in the NHS) and routine surveillance. The company excluded routine surveillance from its submission, after being advised by medical oncologists that it is increasingly uncommon for people with advanced ovarian cancer to have no active treatment in this setting. The EAG's clinical experts agreed that routine surveillance is not a relevant comparator. The committee concluded that the relevant comparator for this evaluation was bevacizumab maintenance therapy at a dose of 7.5 mg per kg.

HRD testing

3.4 The marketing authorisation for olaparib with bevacizumab is specific to HRD-positive disease. As a result, HRD testing is needed to determine whether a tumour is HRD-positive before starting treatment. Currently, the Myriad myChoice HRD plus test is used to determine HRD status. But, the company calculated its HRD-testing cost using a unit cost for an 'in-house lab' HRD test, while the EAG used the list price of the Myriad test. The company disagreed with using the list price because it does not reflect the true cost paid by the NHS. The Cancer Drugs Fund lead explained that NHS England anticipates that its Genomic Laboratory Hubs will be responsible for all HRD testing within the next few months and agreed with the cost used in the company's model. The committee concluded that the cost used by the company reflected the cost that would be used in clinical practice and should be used in the modelling.

Clinical effectiveness

Data sources

3.5 The clinical effectiveness evidence for olaparib with bevacizumab was from the PAOLA-1 trial. This was a phase 3, double-blind, randomised controlled trial in 806 people with advanced (stages 3 and 4) ovarian cancer. It compared olaparib (300 mg twice daily, n=537) to placebo (n=269). Everyone also had bevacizumab (15 mg per kg every 3 weeks) as maintenance treatment. People with HRD-positive disease were a prespecified subgroup, totalling 47% of the olaparib arm and 49% of the placebo arm. At the time of the original submission (NICE technology appraisal guidance 693, from here TA693), approximately 3 years of follow-up data was available from PAOLA-1. The final analysis of PAOLA-1 provides approximately 2 extra years of follow-up data. The committee recalled that the trial did not include anyone from the UK. It also acknowledged that maintenance bevacizumab was given at a dose of 15 mg per kg, which is a higher dose than defined in the scope (see section 3.3). The committee concluded that PAOLA-1 provided the best available evidence for use in the evaluation.

Baseline characteristics

3.6 The EAG's clinical experts noted that the age of people in PAOLA-1 was lower than seen in clinical practice, with the mean age of people in PAOLA-1's HRD-positive subgroup reported as 58.1 years. As a result, the EAG decided to use the median age of people with HRD-positive disease having olaparib with bevacizumab from the Systemic Anti-Cancer Therapy (SACT) data. The company disagreed with this approach, stating that baseline characteristics used in the model should reflect the source of evidence on which efficacy, costs and utilities are based. Other baseline characteristics, including weight and height, were derived from PAOLA-1's intention-to-treat population as the values were unavailable for the HRD-positive subgroup. The company and EAG both agreed that the choice of baseline age used in the model had a negligible impact on the incremental

cost-effectiveness ratios (ICERs). Therefore, the committee did not consider this issue further.

Subsequent treatments in PAOLA-1

3.7 Crossover from the placebo arm to the olaparib arm was not permitted during PAOLA-1. But, upon discontinuation of either intervention, people could have other treatments at the investigators' discretion. The EAG raised concerns that retreatment with PARP inhibitors was present in both arms because of several subsequent treatment regimens. Retreatment with PARP inhibitors is not recommended in UK clinical practice. To assess whether this affected the trial outcomes, the EAG requested an analysis from the company in which people in the trial were split according to whether they had a PARP inhibitor or not. But, the company believed that this analysis was not appropriate because it would break randomisation. The company believed that retreatment with PARP inhibitors would have a negligible impact on the clinical effectiveness results because it only occurred in a small proportion of people in both arms. The clinical experts agreed with the company that the low rates of retreatment in the study population would have a trivial impact on the results. The committee concluded that the likely impact of retreatment with PARP inhibitors on the relative clinical effectiveness of olaparib with bevacizumab compared with bevacizumab alone in PAOLA-1 would be small.

Progression-free survival

3.8 The primary end point in PAOLA-1 was investigator-assessed progression-free survival (PFS). As part of the current review, the company provided more mature PFS data. This continued to show a statistically significant benefit in PFS for olaparib with bevacizumab in the HRD-positive subgroup compared with placebo with bevacizumab. People who had olaparib with bevacizumab had longer median PFS than those who had placebo with bevacizumab, and the difference between the 2 groups was statistically significant. Also, fewer people in the olaparib with

bevacizumab group had progressed after 5 years of treatment (the results, including the number of events that had occurred at the time of the analysis, cannot be reported because they are not yet in the public domain). The committee concluded that olaparib with bevacizumab maintenance treatment improves PFS in people with HRD-positive ovarian cancer that has completely or partially responded after first-line platinum-based chemotherapy with bevacizumab.

Overall survival

3.9 Overall survival (OS) was a secondary end point in PAOLA-1. The company's submission for TA693 included early results for the HRD-positive subgroup, which the committee concluded were promising but uncertain due to their immaturity. Median OS had not been reached in the data cut used as part of TA693. As part of this current review, the company provided more mature OS data. These results show a clinically meaningful benefit in OS for olaparib with bevacizumab in the HRD-positive subgroup compared with placebo plus bevacizumab. Those who had olaparib with bevacizumab had longer median OS. Also, more people in the olaparib with bevacizumab group were alive after 5 years (the results, including the number of events that had occurred at the time of the analysis, cannot be reported because they are not yet in the public domain). The committee noted that this more mature data maintained the promising findings from the first data-cut in TA693. The committee concluded that olaparib with bevacizumab maintenance treatment improves OS in people with HRD-positive ovarian cancer that has completely or partially responded after first-line platinum-based chemotherapy with bevacizumab.

Modelling approach and structure

Model structure

3.10 The company presented a partitioned survival model with 4 health states to estimate the cost effectiveness of olaparib with bevacizumab compared

with bevacizumab monotherapy. The 4 health states were progression free, first disease progression, second disease progression and death. The model was accepted by the committee as part of TA693 and has been updated with the mature PAOLA-1 trial data. The committee concluded that the model was appropriate for decision making.

Company's approach to survival modelling

3.11 The modelling of survival was a key driver of the cost-effectiveness results. The company modelled PFS using a mixture cure model (MCM) whereas the EAG used a spline model. For OS, both the company and EAG used a standard parametric approach (log-normal curve), which was set to equal PFS once the 2 curves crossed. Therefore, differences in long-term survival estimates occurred due to the differences in PFS modelling, not the OS curves. The company's MCM assumed that the model population consisted of 2 groups: a 'cured' population and a population whose cancer would progress. People predicted to be progression free at 5 years were considered 'cured' and were assumed to have the same mortality as the UK general population. In the original evaluation of olaparib with bevacizumab, the committee considered that the use of a MCM was not justified and may have overestimated survival gain. It was concerned that the length of follow up in PAOLA-1 was not sufficient to support the conclusion that a proportion of people were cured at 5 years. The company believes that the committee's concerns have been addressed by the more mature PFS data now available. It explained that compared with published empirical evidence, all standard parametric modelling approaches underpredicted PFS after 5 years for people on standard care and did not capture the plateauing effect observed in the final PAOLA-1 PFS data. The EAG raised concerns about the use of the MCM. It did not consider that the updated data from PAOLA-1, or any external sources cited by the company, justified the use of a MCM in advanced ovarian cancer. It also did not feel that the company provided any evidence to support the existence of a separate survival trajectory for people who could be 'cured'. It also highlighted that there was no

observable plateau in the olaparib with bevacizumab PFS curve, which would be expected for a curative treatment, and the PFS data was still not mature enough to demonstrate this effect. The EAG also noted that the company's approach to modelling OS (log-normal, followed by MCM) resulted in survival estimates at 25 years and 30 years that the EAG determined as implausible. Clinical experts said that it would be plausible for 5% to 10% of people to be alive 30 years after diagnosis, which is lower than the company's survival estimates. The committee agreed with the EAG, noting that it was only appropriate to use a MCM when there is clear evidence of a cure. It considered that while the presence of a plateau within the olaparib with bevacizumab curve was not implausible, the data provided by the company was still not mature enough to justify the use of a MCM in this disease area. It also expressed concerns regarding the sustained survival benefit observed in the olaparib with bevacizumab arm when using the MCM approach. The committee felt this may be a statistical artefact arising from OS being set to equal PFS. Taking these factors into account, the committee concluded that the company's modelling of PFS using a MCM was not suitable for decision making.

EAG's approach to survival modelling

3.12 At the clarification stage, the EAG requested that the company explored the use of more flexible models, including splines. The company provided scenario analysis using spline curves at 0, 1, 2 and 3 knots, alongside 1 knot splines with fixed cure points at 5 years, 7 years and 10 years. But, it argued that the spline curves failed to capture long-term responders effectively. The EAG disagreed, stating that the 3-knot spline model provided a good visual fit to the PFS Kaplan–Meier data, capturing any possible plateau in the bevacizumab monotherapy arm and providing more plausible tails. It also highlighted that its own approach remained optimistic when considering OS (log-normal, followed by 3-knot splines), but was more realistic than the company's approach. The company disagreed, highlighting that the EAG's OS estimates were much lower

than general population mortality, and it would be unfeasible for OS to drop so significantly between 10 years and 20 years after diagnosis. Clinical experts also expressed concern with the EAG's OS estimates, stating that there would be no reason to expect estimates for olaparib with bevacizumab to decline any faster than those for placebo with bevacizumab. They also stated that the EAG's choice of model was too pessimistic because it assumes an ongoing rate of progression beyond 5 years. The committee considered that the company's MCM approach was not justified by the available data. But, it acknowledged that the EAG's approach was not ideal, as it also set OS to equal PFS and the results were still uncertain. It highlighted that it would have been helpful to see more detail around how the 3-knot spline model was designed, particularly relating to how the number of knots and their placement were chosen. The committee concluded that both approaches were uncertain. The EAG's approach to survival modelling had limitations but was the more conservative of the 2 approaches presented.

Subsequent treatments in the model

3.13 PARP inhibitors were included as subsequent treatments in the placebo with bevacizumab arm of the model. The company included rucaparib as the most common subsequent PARP inhibitor based on patient initiations data from NHS England, followed by niraparib, then olaparib. The EAG removed rucaparib and olaparib as subsequent treatments from their base case on the advice of NICE, because at the time of the analysis they were only available through the Cancer Drugs Fund, and recommendations through managed access are not considered established practice according to section 6.4.10 of the NICE health technology evaluations manual. Therefore, niraparib was included as the subsequent PARP inhibitor in the EAG's base case. But, because olaparib was due to exit managed access, the EAG provided scenarios where olaparib was included at its anticipated post-Cancer Drugs Fund exit price. The committee noted that this made the cost-effectiveness results for olaparib with bevacizumab less favourable. No scenario analyses were included

for rucaparib because it is not in the process of exiting the Cancer Drugs Fund. The committee agreed that the EAG's approach using niraparib as the subsequent PARP inhibitor in its base case was appropriate.

Cost-effectiveness estimates

Acceptable ICER

3.14 The NICE health technology evaluations manual notes that above a most plausible ICER of £20,000 per quality-adjusted life year (QALY) gained, decisions about the acceptability of the technology as an effective use of NHS resources will specifically consider:

- the degree of certainty and uncertainty around the ICER and
- uncaptured benefits and non-health factors.

The committee noted there were multiple uncertainties within the clinical and economic evidence, especially relating to the survival modelling approach (see section 3.11 and section 3.12). But, they also acknowledged that the EAG's base case ICER was likely to be conservative. Because of this, the committee agreed that an acceptable ICER would be comfortably below £30,000 per QALY gained.

Committee's preferred assumptions and cost-effectiveness estimates

3.15 When incorporating the committee's preferred assumptions on HRD-testing cost (see section 3.4), subsequent treatments (see section 3.13), and the EAG's more conservative survival modelling (see section 3.11 and section 3.12), the ICER was above the acceptable level (see section 3.14). The ICER cannot be reported here because of confidential commercial arrangements for olaparib, bevacizumab and subsequent treatments in the pathway. Therefore, olaparib with bevacizumab is not recommended for maintenance treatment of HRD-positive advanced ovarian cancer that has completely or partially responded after first-line platinum-based chemotherapy with bevacizumab.

Conclusion

Recommendation

3.16 The clinical effectiveness evidence showed that olaparib with bevacizumab improves both PFS and OS in people with HRD-positive ovarian cancer that has completely or partially responded after first-line platinum-based chemotherapy with bevacizumab. The committee concluded that the ICER that incorporates its preferred assumptions is not within what NICE considers a cost-effective use of NHS resources for olaparib with bevacizumab for maintenance treatment of HRD-positive advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy with bevacizumab. So, olaparib is not recommended for routine use in the NHS.

4 Evaluation committee members and NICE project team

Evaluation committee members

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

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

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

Chair

Radha Todd

Chair, technology appraisal committee A

NICE project team

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

Emily Leckenby
Technical lead

Zoe Charles
Technical adviser

Thomas Feist
Project manager

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