

Olaparib with bevacizumab for maintenance treatment of advanced high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer

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.

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This guidance replaces TA693.

1 Recommendations

1.1 Olaparib with bevacizumab is 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).

Olaparib 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 with bevacizumab for maintenance treatment of HRD-positive advanced high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer (NICE's 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 people having bevacizumab alone, and that they also live longer.

The most likely cost-effectiveness estimates for olaparib with bevacizumab are within what NICE considers an acceptable use of NHS resources. So, it is 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 the '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) or £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 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 and current management

Advanced high-grade epithelial ovarian, fallopian tube and primary peritoneal cancer

- 3.1 The patient experts explained that advanced high-grade epithelial ovarian, fallopian tube and primary peritoneal cancer (from now, 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), when the cancer has already spread outside of the pelvis. Even when initial treatment is successful, people living with advanced ovarian cancer often live with the anxiety of possible recurrence and further rounds of chemotherapy. So, the time between treatments can be extremely difficult, and people with ovarian cancer are concerned that treatment options will become exhausted as the cancer progresses. The clinical and patient experts explained that there are high rates of recurrence after initial surgery and platinum-based chemotherapy. So, it is very important to offer a maintenance treatment after 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 poly-ADP-ribose polymerase inhibitors

- 3.2 The clinical experts explained that using poly-ADP-ribose polymerase (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. They are also 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 combination maintenance treatment available that can be used first line. 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 cancer, 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 could extend periods of remission and improve quality of life. It added that this is extremely important to people with advanced ovarian cancer.

Comparators

- 3.3 The comparators in the scope were bevacizumab maintenance treatment 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. This was 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 was not a relevant comparator. The committee concluded that the relevant comparator for this evaluation was bevacizumab maintenance treatment 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 cancer. So, 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. So, they 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 cancer 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), about 3 years of follow-up data was available from PAOLA-1. The final analysis of PAOLA-1 provides about 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.

Subsequent treatments in PAOLA-1

3.6 Crossover from the placebo arm to the olaparib arm was not permitted during PAOLA-1. But, on stopping 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 this, people in the trial were split according to whether they had a PARP inhibitor or not. But the

company thought that this analysis was not appropriate because it would break randomisation. It thought that retreatment with PARP inhibitors would have had a negligible impact on the clinical-effectiveness results. This was 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 had 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 have been small.

Progression-free survival

- 3.7 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 a statistically significant increase in median PFS compared with people who had placebo with bevacizumab (46.8 months compared with 17.6 months; hazard ratio [HR] 0.41, 95% confidence interval [CI] 0.32 to 0.54). Also, there was a decrease in the number of people in the olaparib with bevacizumab group whose cancer had progressed after 5 years (46.1% compared with 19.2%). The committee concluded that olaparib with bevacizumab maintenance treatment improved PFS in people with HRD-positive ovarian cancer that has completely or partially responded after first-line platinum-based chemotherapy with bevacizumab.

Overall survival

- 3.8 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 because of 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 with

bevacizumab. People who had olaparib with bevacizumab had longer median OS (75.2 months compared with 57.3 months; HR 0.62, 95% CI 0.45 to 0.85). Also, more people in the olaparib with bevacizumab group were alive after 5 years (65.5% compared with 48.4%). The committee noted that this more mature data maintained the promising findings from the first data cut in TA693. It concluded that olaparib with bevacizumab maintenance treatment improved OS in people with HRD-positive ovarian cancer that has completely or partially responded after first-line platinum-based chemotherapy with bevacizumab.

Evidence of cure

3.9 The company highlighted that there was a compelling body of evidence on the potential for long-term remission in advanced ovarian cancer from:

- external empirical data
- longer follow-up data from PAOLA-1.

The company explained that the updated PAOLA-1 data showed clear plateaus for PFS in both arms of the Kaplan–Meier plot, confirming a levelling-off of the risk of progression. The company also presented evidence from SOLO-1 (a study of olaparib maintenance monotherapy compared with placebo in people with newly diagnosed BRCA-positive advanced ovarian cancer). The company thought that the SOLO-1 7-year follow-up results also showed a plateauing effect in the olaparib arm. So, this validated the expectation of curative potential in advanced ovarian cancer. The EAG considered that the PAOLA-1 data was not mature enough to confirm the existence of a plateau in the olaparib with bevacizumab arm. But it accepted that it was not implausible that it could plateau in a similar way to the bevacizumab arm. The EAG was also not convinced that SOLO-1 showed a plateau in the olaparib arm. The clinical experts did not agree with the EAG's interpretation of the Kaplan–Meier curves. They thought there was evidence of a plateau in both arms of PAOLA-1 and SOLO-1. They also commented that it was not plausible to accept a plateauing effect for PFS for people who have bevacizumab-only maintenance treatment but not for the combination with olaparib. The clinical experts explained that maintaining PFS for 5 years is a good indicator of long-term survival, and that the probability of relapse after

5 years is extremely low. They explained that they do not tell people after 5 years of PFS that they are 'cured'. But they said that they would communicate that there is a very good chance that the cancer will not come back if it has not done so after 5 years. The clinical experts commented that, in the context of this evaluation, it was reasonable to say that a proportion of people are cured. The committee accepted that there is a low probability of relapse after 5 years of being progression free. It was persuaded that it was likely that a plateau would occur in the olaparib with bevacizumab arm of PAOLA-1, meaning a subset of the population would be 'cured'. But uncertainty remained around what proportion of the population this would affect. The committee concluded that there was reasonable evidence for the existence of a 'cure' in a proportion of people with HRD-positive ovarian cancer who have olaparib with bevacizumab maintenance treatment.

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 was updated with the mature PAOLA-1 trial data. The committee concluded that the model was appropriate for decision making.

Baseline age in the model

- 3.11 The EAG's clinical experts noted that the age of people in PAOLA-1 was lower than that seen in clinical practice. The mean age of people in PAOLA-1's HRD-positive subgroup reported as 58.1 years. So, in its modelling, the EAG decided to use the median age of people with HRD-positive cancer having olaparib with bevacizumab from the Systemic Anti-Cancer Therapy (SACT) data. The company disagreed with this approach. It stated that baseline characteristics used in a

model should reflect the source of evidence on which other key parameters such as efficacy, costs, treatment duration and utilities are based. The committee considered that it would be more suitable to use the average age that more closely reflected the anticipated NHS population. PAOLA-1 did not include anyone from the UK, but the SACT data provided real-world evidence from the UK. So, the committee concluded that it was more suitable to use the median age from the SACT data.

Survival modelling

3.12 The modelling of survival was a key driver of the cost-effectiveness results. The company modelled PFS using a mixture cure model (MCM), but 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. The company's MCM assumed that the model population consisted of 2 groups: a 'cured' population who were progression free at 5 years and a population whose cancer would progress. The company explained that there is strong evidence to support the concept of long-term remission after first-line treatment of advanced ovarian cancer (see [section 3.9](#)). It proposed that this supported adopting an MCM for this evaluation. The EAG raised concerns about using the MCM. It did not consider that the updated data from PAOLA-1, or any external sources cited by the company, justified it. The EAG preferred the 3-knot spline model. It thought that it 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. The company argued that the EAG-preferred spline curves failed to effectively capture people whose cancer responded long-term. It also highlighted that the spline models did not provide clinically plausible long-term predictions. For example, the EAG's OS estimates were much lower than general population mortality. Also, it would be unfeasible for OS to drop so substantially between 10 years and 20 years after diagnosis. The clinical experts also expressed concern with the EAG's OS estimates. They stated that there would be no reason to expect estimates for olaparib with bevacizumab to decline any faster than estimates for placebo with bevacizumab. They also stated that the EAG's choice of model was too pessimistic because it assumed an ongoing rate of progression beyond 5 years. The committee acknowledged that the EAG's approach had limitations because it did not reflect the plateau in the olaparib with

bevacizumab PFS curve and potential for 'cure' (see section 3.9). It agreed that it was not plausible for the curves to show a plateau for bevacizumab monotherapy but not for olaparib with bevacizumab. The committee noted the EAG's concerns about the company's MCM. But it was persuaded that there was reasonable evidence for the existence of a 'cure' in a proportion of people who have first-line maintenance treatment (see section 3.9). So, it agreed that an MCM was appropriate. But the committee raised questions around how the cure fraction was generated. It was concerned that the cure fraction may have been an overestimate, and would have liked to have seen more assessment of the uncertainty around this. It was also concerned that the survival estimates from the model were optimistic. It appreciated that the company had provided further scenario analyses after the consultation on the draft guidance to address some of the uncertainty around the long-term survival extrapolations. But it considered that a high level of uncertainty remained. The committee concluded that the company's MCM was suitable for decision making, but that there was a high degree of uncertainty around the cure fraction and the survival estimates generated.

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. This was because, at the time of the analysis, they were only available through the Cancer Drugs Fund. Also, recommendations through managed access are not considered established practice according to [section 6.4.10 of the NICE health technology evaluations manual](#). So, 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 in which 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 incremental cost-effectiveness ratio

3.14 The [NICE health technology evaluations manual](#) notes that, above a most plausible incremental cost-effectiveness ratio (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 considered the company's modelling approach to be suitable for decision making. But it acknowledged that a high level of uncertainty remained about the proportion of people who would be 'cured' (see [section 3.12](#)). The committee also noted that there were several uncaptured benefits, including the impact of HRD testing on the need for somatic BRCA testing in UK clinical practice. Also, the wider benefits for HRD testing were not considered in the model, including increased understanding of genetic drivers of cancer to inform prognosis and optimal management. Because of the high level of uncertainty in the cost-effectiveness estimates, the committee agreed that an acceptable ICER would be below £20,000 per QALY gained.

Committee's preferred assumptions and cost-effectiveness estimates

3.15 The most likely ICER cannot be reported here because of confidential commercial arrangements for olaparib, bevacizumab and subsequent treatments in the pathway. But it was below the acceptable level (see [section 3.14](#)) when the committee's preferred assumptions on the following were incorporated:

- HRD-testing cost (see [section 3.4](#))
- baseline age (see [section 3.11](#))
- subsequent treatments (see [section 3.13](#)) and
- the company's approach to survival modelling (see [section 3.12](#)).

So, olaparib with bevacizumab is recommended for maintenance treatment of HRD-positive advanced high-grade 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 improved 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 incorporated its preferred assumptions was within what NICE considers a cost-effective use of NHS resources. So, olaparib with bevacizumab for maintenance treatment of HRD-positive advanced high-grade ovarian cancer after response to first-line platinum-based chemotherapy with bevacizumab is recommended for routine use in the NHS.

4 Implementation

- 4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication.
- 4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends using 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.
- 4.3 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 homologous recombination deficiency-positive, advanced high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer and the doctor responsible for their care thinks that olaparib with bevacizumab is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Evaluation committee members and NICE project team

Evaluation committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by [committee A](#).

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

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

Chair

Radha Todd

Chair, technology appraisal committee A

NICE project team

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

Emily Leckenby

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