NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal document

Olaparib plus bevacizumab for maintenance treatment of advanced ovarian, fallopian tube or primary peritoneal cancer

1 Recommendations

1.1 Olaparib plus bevacizumab is recommended for use within the Cancer Drugs Fund as an option for maintenance treatment of advanced (International Federation of Gynecology and Obstetrics [FIGO] stages 3 and 4) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer in adults when:

- there has been a complete or partial response after first-line platinum-based chemotherapy plus bevacizumab, and
- the cancer is associated with homologous recombination deficiency (HRD).

It is recommended only if the conditions in the managed access agreement for olaparib are followed.

1.2 This recommendation is not intended to affect treatment with olaparib plus bevacizumab that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

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Why the committee made these recommendations

Low-dose bevacizumab or olaparib monotherapy are available through the Cancer Drugs Fund as maintenance treatment options for some people with advanced ovarian, fallopian tube or primary peritoneal cancer. When these treatments are not an option, maintenance is routine surveillance.

There is an ongoing clinical trial comparing maintenance treatment with olaparib plus bevacizumab with placebo plus bevacizumab in people whose cancer has responded to first-line platinum-based chemotherapy plus bevacizumab. Early results suggest that it improves how long people live without their cancer getting worse. The evidence suggests that the treatment effect is bigger in people whose disease is HRD-positive. However, there is uncertainty about how olaparib plus bevacizumab affects the length of time people live.

The uncertainty in the clinical evidence means that the cost-effectiveness estimates are very uncertain, so the treatment is not recommended for routine use in the NHS.

If the treatment does increase the length of time people live, it has the potential to be cost effective. Further trial results will help to address the uncertainties in the clinical- and cost-effectiveness estimates. Therefore, olaparib plus bevacizumab maintenance treatment is recommended for use within the Cancer Drugs Fund while further data are collected.

2 Information about olaparib

Marketing authorisation indication

2.1 Olaparib in combination with bevacizumab is indicated for 'the maintenance treatment of adult patients with advanced (FIGO stages III and IV) 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 (HRD) positive status defined by either a BRCA1/2 mutation and/or genomic instability'.

Dosage in the anticipated marketing authorisation

2.2 The dosage schedule for olaparib is available in its summary of product characteristics. The dosage schedule for bevacizumab is available in its summary of product characteristics.

Price

2.3 The list price for olaparib tablets is £2,317.50 for 56x150 mg tablets (excluding VAT; BNF online accessed September 2020).

The company has a commercial arrangement for olaparib tablets. The commercial arrangement additionally forms part of the managed access agreement for use of olaparib tablets in the Cancer Drugs Fund. 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 appraisal committee (section 6) considered evidence submitted by AstraZeneca, a review of this submission by the evidence review group (ERG), NICE's technical report and responses from stakeholders. See the committee papers for full details of the evidence.

Ovarian cancer treatment pathway and scope of the appraisal

Olaparib plus bevacizumab maintenance treatment should be appraised in sequence with first-line treatment

3.1 In routine practice, first-line treatment for advanced ovarian cancer is surgery and platinum-based chemotherapy, followed by routine surveillance until the cancer progresses or comes back. Bevacizumab (15 mg/kg) is licenced for first-line treatment with platinum plus paclitaxel,

but this is not recommended in NICE technology appraisal guidance. Bevacizumab, at a dose lower (7.5 mg/kg) than the marketing authorisation may be used first line with platinum-based chemotherapy and as a subsequent maintenance treatment through the Cancer Drugs Fund when 1 or more of the following eligibility criteria apply:

- International Federation of Gynecology and Obstetrics (FIGO) stage 3 debulked but residual disease of more than 1 cm
- stage 4 disease
- stage 3 disease at presentation and needing neo-adjuvant chemotherapy.

Olaparib monotherapy is also available through the Cancer Drugs Fund as a maintenance treatment for cancer that has responded to first-line platinum-based chemotherapy, but only if there are BRCA mutations (NICE technology appraisal guidance on olaparib monotherapy). The treatment under appraisal here is olaparib plus bevacizumab maintenance treatment for all stage 3 and 4 cancer that:

- has responded to first-line platinum-based chemotherapy plus bevacizumab and
- is associated with homologous recombination deficiency (HRD) positive status defined by either a BRCA1 or 2 mutation or genomic instability (from now, referred to as HRD-positive disease).

Implementing olaparib plus bevacizumab maintenance treatment in the NHS would therefore need changes to be made to the first-line treatment pathway. Specifically, all patients with stage 3 and 4 HRD-positive disease would have to be offered first-line bevacizumab plus platinum chemotherapy. The committee noted that the change to first-line treatment would be associated with increased costs. Also, it noted that the consequences in terms of the clinical outcomes with additional first-line treatments were unclear. The committee concluded that, in line with the appraisal scope, olaparib plus bevacizumab maintenance treatment

needs to be appraised as part of a treatment sequence that includes first-line platinum-based chemotherapy plus bevacizumab.

Both comparators in the scope are relevant

3.2 The comparator in the scope was first-line platinum-based chemotherapy followed by routine surveillance. In addition, for people having bevacizumab through the Cancer Drugs Fund (see section 3.1), the scope included first-line platinum-based chemotherapy plus bevacizumab (7.5 mg/kg every 3 weeks), followed by bevacizumab maintenance therapy at the same dose, as another comparator. The committee considered whether both comparators were relevant. It noted that treatments in the Cancer Drugs Fund are not normally included as comparators. Also, NICE's position statement on appraising new cancer products states that products recommended for use in the Cancer Drugs Fund after 1 April 2016 should not be considered as comparators. The committee heard from the Cancer Drugs Fund clinical lead that bevacizumab 7.5 mg/kg has been available through the Cancer Drugs Fund since at least 2012. He also stated that it is widely used and provides benefits to the high-risk group for whom it is available. The committee acknowledged that the NICE position statement did not apply to technologies in the Cancer Drugs Fund before 2016. It concluded that both comparators were relevant because they were established in NHS clinical practice.

HRD testing is potentially implementable in the NHS

3.3 As noted in section 3.1, the anticipated marketing authorisation for olaparib plus bevacizumab is specific to people with HRD-positive disease. Therefore, HRD testing would be needed before olaparib plus bevacizumab maintenance treatment is started. HRD testing is not routinely done in the NHS. The only available validated test is the Myriad myChoice test, for which samples need to be sent to the US. The clinical experts supported implementing HRD testing in routine NHS practice because genetic mutations can be an important factor in determining

treatment decisions and in prognosis. They considered that implementation was potentially feasible, given the similarities with the somatic (tumour) BRCA testing pathway. They also agreed with the company's comment at technical engagement that the availability of new treatments that need specific tests have previously provided an incentive for test development and introduction. They noted that HRD and somatic BRCA testing should be done at the same time, so that tissue biopsy could be aligned to maximise the chance of enough tissue being available for accurate testing. They also considered using the Myriad myChoice test processing facilities in the US to be a reasonable interim option until an NHS-specific pathway could be set up. The committee concluded that routine HRD testing could be developed and implemented in the NHS.

Clinical need for new treatments

People would welcome new treatments that prolong life and reduce the need for further chemotherapy

3.4 The patient experts explained that advanced ovarian cancer is a devastating condition with a poor prognosis. Most people are diagnosed after it is already advanced and, even when initial treatment is successful, the cancer usually comes back. Living under its shadow and not knowing when it will recur can be very traumatic for patients and their families. Given the effect of the condition on life expectancy, people would welcome new treatments. This clinical need is made greater by the effects of the current treatments on quality of life. For most people, a diagnosis of advanced ovarian cancer means multiple rounds of chemotherapy and having to endure its potentially gruelling side effects. Chemotherapy also has to be delivered in hospital, so it can severely disrupt daily life and work. It can also negatively affect quality of life, family and social relationships. The interval between rounds of chemotherapy can be very short. One expert described her personal experience of having 3 rounds of chemotherapy treatment over 3 years. An added benefit of olaparib is that it can be taken orally. Also, both olaparib and bevacizumab have side

effects that are more manageable than those associated with chemotherapy. The committee concluded that there is a high unmet need for new treatments to delay or prevent recurrence of advanced ovarian cancer.

Using PARP inhibitors early in the treatment pathway is likely to maximise the potential benefits of these treatments

3.5 The clinical and patient experts agreed that introducing poly-ADP-ribose polymerase (PARP) inhibitors, such as olaparib, for ovarian cancer has been a significant advance in treating the condition. The patient expert, who had started taking olaparib after surgery and 4 lines of chemotherapy, described olaparib as transformative. She explained that it had prolonged her life and allowed her to live an almost normal life after years of debilitating chemotherapy. She also explained that, before olaparib, bevacizumab had been an effective and manageable treatment in her experience, so it seemed logical to use both drugs as early as possible. The clinical experts noted that the patient's personal testimony was reflective of their clinical experience. They also stressed that using effective treatments as early as possible is important. This is because treatments given first line can make a dramatic difference to survival and quality of life, whereas the possibility of a cure is very low after subsequent lines of treatment. Also if treatment is delayed, people may die before becoming eligible to have it, or may not meet the eligibility criteria for having a PARP inhibitor. The committee concluded that there are compelling reasons for using therapies such as olaparib and bevacizumab early in the ovarian cancer treatment pathway when the possibility of a cure is greatest.

People without a BRCA mutation have the greatest unmet need for new maintenance treatments

3.6 As noted in section 3.1, olaparib monotherapy is available through the Cancer Drugs Fund as a maintenance treatment after response to first-line platinum-based chemotherapy but only for people with BRCA

mutation-positive disease. In addition, PARP inhibitor treatments are available after later lines of chemotherapy, either through the Cancer Drugs Fund or in routine commissioning (see NICE technology appraisal guidance on rucaparib, niraparib and olaparib). Retreatment with PARP inhibitors is very unusual in the NHS, so there is normally only 1 opportunity to access them. The committee acknowledged that access to PARP inhibitors varies by BRCA status. It recognised that the ovarian cancer treatment pathway means that people without BRCA mutations have to wait until the cancer has come back, when the prognosis is worse, to gain access to a PARP inhibitor. The committee noted that the population covered by the anticipated marketing authorisation for olaparib plus bevacizumab maintenance treatment is people with HRD-positive disease. This includes some (but not all) people without BRCA mutations. The clinical experts noted that around half of people with HRD-positive disease have a BRCA mutation. The committee concluded that people without a BRCA mutation have the greatest unmet need for new maintenance treatments. It added that olaparib plus bevacizumab would therefore provide a potential new treatment option for some people in this group.

Clinical evidence

The clinical trial does not fully reflect the scope

3.7 The clinical evidence presented by the company comes from PAOLA-1, a randomised controlled trial in 806 people with advanced (stages 3 and 4) ovarian cancer. The trial compared the efficacy of olaparib (300 mg twice daily) for up to 2 years (n=537) with a matching placebo (n=269). Everyone also had bevacizumab (15 mg/kg every 3 weeks) as maintenance treatment for up to 15 months. People with HRD-positive disease were a prespecified subgroup, amounting to 48.0% of the intention-to-treat population. HRD testing was done after randomisation. A similar proportion of people were HRD-positive in each arm (47.5% in the olaparib plus bevacizumab arm and 49.1% in the placebo plus

bevacizumab arm). The committee noted that the trial did not include anyone from the UK and did not fully reflect the scope in terms of the population, intervention or comparators of interest. Specifically:

- The people in PAOLA-1 had cancer that had already responded to first-line platinum-taxane chemotherapy plus bevacizumab whereas the population in the scope was people with newly diagnosed advanced ovarian cancer.
- The intervention in the trial was olaparib plus bevacizumab maintenance treatment, whereas the intervention in the scope included first-line treatment (see section 3.1).
- The comparator in the trial was bevacizumab monotherapy (15 mg/kg every 3 weeks) maintenance treatment, whereas the 2 comparators in the scope were platinum-based chemotherapy followed by routine surveillance and platinum-based chemotherapy plus bevacizumab (7.5 mg/kg every 3 weeks) followed by bevacizumab maintenance treatment (see section 3.2).

The committee concluded that PAOLA-1 provided the best available evidence for use in the appraisal, but the results did not directly reflect the decision problem. It considered this a significant limitation of the evidence base that would need to be addressed in the modelling to ensure that the cost-effectiveness estimates were relevant to the NHS.

Olaparib plus bevacizumab maintenance treatment improves progression-free survival in people with HRD-positive ovarian cancer

3.8 The primary end point in PAOLA-1 was investigator-assessed progression-free survival (PFS). In the intention-to-treat population, people who had olaparib plus bevacizumab had longer median PFS than people who had placebo plus bevacizumab (22.1 months compared with 16.6 months). The difference between the groups was statistically significant (hazard ratio [HR] 0.59, 95% confidence interval [CI] 0.49 to 0.72; p<0.0001). A PFS benefit was also seen in the HRD-positive

subgroup and the effect size was bigger than in the intention-to-treat population (median PFS 37.2 months compared with 17.7 months, unstratified HR 0.33, 95% CI 0.25 to 0.45]). In contrast, no difference in PFS was found between the treatment arms in the HRD-negative subgroup (median PFS 16.9 months compared with 16.0 months, unstratified HR 0.92, 95% CI 0.72 to 1.17]). The clinical experts noted that the PFS results provide compelling evidence that olaparib plus bevacizumab is more effective in people with HRD-positive disease than in those with HRD-negative disease. The committee agreed with the clinical experts. It concluded that olaparib plus bevacizumab maintenance treatment improves PFS in people with HRD-positive ovarian cancer that has completely or partially responded after first-line platinum-taxane chemotherapy plus bevacizumab.

The overall-survival data are promising but uncertain

3.9 Overall survival is a secondary end point in PAOLA-1. The company submission included early results for the HRD-positive subgroup based on the number of events that had occurred at the time of the primary PFS analysis. These estimates favoured olaparib plus bevacizumab maintenance 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 clinical experts acknowledged the uncertainty in the current estimates given the data maturity. However, they stated that the more mature data from SOLO1 on using olaparib monotherapy in the first-line maintenance setting provided some reassurance that the PFS benefit observed in PAOLA-1 may translate into an overall-survival benefit in the long-term. The committee agreed that the current overall-survival data are promising but concluded that the survival benefit remains uncertain.

It is unclear whether olaparib plus bevacizumab maintenance treatment is curative

3.10 The committee recognised that a key consideration for the appraisal is whether olaparib plus bevacizumab maintenance treatment is likely to prevent recurrence or only delay it. The clinical experts noted that survival outcomes are heterogenous in the population of interest (they cited ICON5, CHORUS and ICON7 as reporting outcomes after first-line treatment that support this observation). They explained that, based on previous studies and experience of using PARP inhibitors, any potential overall-survival benefit is likely to be driven by a subgroup with particularly good treatment outcomes. The clinical experts anticipate that olaparib plus bevacizumab will increase the proportion of people who have long-term PFS and overall survival. They also explained that maintaining PFS for 5 years is widely considered to be a good indicator of long-term survival. The cancer will progress after 5 to 10 years in only a small proportion of people who are progression free at 5 years. The clinical experts noted that they do not tell people after 5 years of PFS that they are 'cured', but tell them that their cancer is very unlikely to come back. This is reflected in the British Gynaecological Cancers Society ovarian cancer guidelines, which recommend stopping follow up if the cancer has not come back within 5 years. The committee noted that the clinical experts' comments were consistent with those made by clinical experts for NICE's technology appraisal guidance on olaparib for maintenance treatment of BRCA mutation-positive advanced ovarian, fallopian tube or peritoneal cancer after response to first-line platinum-based chemotherapy. The experts for that appraisal made the following comments in relation to a trial of olaparib for relapsed ovarian cancer (Study 19):

- After 10 years, 10% of people are disease free (indicating a cure).
- This 10% are more likely to be people whose cancer had a complete response to platinum-based chemotherapy.

The committee considered that other olaparib studies and the trials of other PARP inhibitors provided useful clinical context, and showed that a long-term treatment effect that could be indicative of cure is plausible. However, the committee also noted that although median PFS has been reached in PAOLA-1, the median length of follow up in the olaparib plus bevacizumab arm was 22.7 months (less than 2 years), and the treatment was given for up to only 15.0 months. The limited follow up means that there are insufficient data to show whether the treatment can maintain remission up to the clinically important 5-year threshold. It also noted there was no obvious plateau in the intervention arm of the Kaplan–Meier plot to confirm a levelling off of the risk of progression and, given the numbers remaining at risk of progression, this was unlikely to be observed in future. The committee concluded that it is unclear whether olaparib plus bevacizumab maintenance treatment can cure ovarian cancer.

Cost effectiveness

The company's maintenance-only analysis is not appropriate

3.11 The company presented a 4-state partitioned survival model to estimate the cost effectiveness of olaparib plus bevacizumab (15 mg/kg) maintenance treatment in people with HRD-positive disease whose cancer had responded to first-line platinum-based chemotherapy plus bevacizumab (15 mg/kg). The company presented 2 analyses, a maintenance-only analysis and an extended-regimen analysis (see section 3.12). In the maintenance model, the company compared olaparib plus bevacizumab (15 mg/kg) maintenance treatment with routine surveillance and bevacizumab (7.5 mg/kg). It also included bevacizumab (15 mg/kg) alone as a comparator. However, this was not in the scope and is not a standard treatment in the UK, so this comparison is not discussed further. The committee considered that the company's maintenance analysis did not address the full appraisal question in the scope because it focused on the maintenance period only. It did not consider the associated costs or clinical outcomes of having bevacizumab

(15 mg/kg) plus platinum-based chemotherapy first line (see section 3.1). Therefore, the committee concluded that this analysis was not appropriate.

The extended-regimen analysis is appropriate

3.12 The company's extended-regimen analysis compared first-line platinum-based chemotherapy plus bevacizumab (15 mg/kg) followed by olaparib plus bevacizumab (15 mg/kg) maintenance treatment for people whose cancer had responded with:

- first-line platinum-based chemotherapy followed by routine surveillance
- first-line platinum-based chemotherapy plus bevacizumab (7.5 mg/kg) followed by bevacizumab (7.5 mg/kg) as maintenance treatment for people whose cancer had responded
- first-line platinum-based chemotherapy plus bevacizumab (15 mg/kg) followed by bevacizumab (15 mg/kg) as maintenance treatment for people whose cancer had responded (which was not in the scope and is not routine treatment in the UK, so is not discussed further).

The company included the cost of having bevacizumab (15 mg/kg) plus first-line platinum-based chemotherapy but assumed that all the first-line treatment options were equally effective. The ERG identified some errors in the company's extended-regimen analyses. It considered that the analysis did not capture the full costs or the clinical outcomes of first-line treatment. The ERG included the additional costs and the outcomes in its own exploratory analyses. This analysis assumed that, in 69% of people, the cancer had completely or partially responded after first-line treatment, was stable in 23% and would progress in 8%. The clinical experts considered that these assumptions were clinically plausible. The committee agreed with the ERG that the company's extended-regimen analysis was limited because it did not capture the full costs or the health benefits of first-line treatment. It concluded that the ERG's extended-regimen analysis was more appropriate because it included both of these.

A mixture cure model is not justified and may overestimate survival gain

3.13 The company and the ERG used different methods to model survival. This was the key driver of the cost-effectiveness results. The company used a mixture cure model to estimate long-term survival. This 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. To predict overall survival, the company used standard parametric models up to 5 to 6 years and then overall survival was set to equal PFS. The ERG had several concerns about the company's modelling approach. It disagreed with using the mixture cure model in principle because PAOLA-1 data are not mature enough to show a cure effect. It noted that a wide range of cure fractions had been reported across the different mixture cure models tested by the company. It also noted that the difference in the cure fractions used by the company in its base case, combined with its decision to set overall survival to equal PFS, resulted in a large and very long predicted overall-survival effect for olaparib plus bevacizumab. The ERG considered the company's approach of setting the overall-survival curves equal to the PFS curves methodologically flawed and to have a major effect on the relative effectiveness of the treatments. The committee agreed with the ERG's concerns. It noted that, at present, PAOLA-1 does not provide sufficient evidence to support the company's assumption that a proportion of patients would be cured at 5 years. This is because there are only 3 years of PFS data. The specific cure fractions used in the company's mixture cure model are therefore not supported by the trial data. The committee was also concerned about the lack of a plateau in the Kaplan–Meier curve for PFS, which would be expected for a curative treatment. It appreciated that clinical trials for other PARP inhibitors have shown a plateau in the curves and that a subgroup are cancer free after 10 years, indicating a cure. However, this has so far not been proven for olaparib plus bevacizumab. It also noted that the small proportion of

people whose cancer progresses between 5 and 10 years (see section 3.10) are not accounted for in the company's mixture cure model. The committee considered that these points undermined the company's justification for using a mixture cure model. It agreed that using a mixture cure model, and the specific cure fractions preferred by the company, may have overestimated the survival gain for olaparib plus bevacizumab. It concluded that it is not possible to resolve the uncertainties about overall survival until further data are available from PAOLA-1.

The ERG's exploratory analyses show the high uncertainty in the survival modelling

3.14 The ERG initially preferred to use standard parametric models to estimate long-term PFS and overall survival. However, it updated its approach after the clinical experts suggested at technical engagement that the PFS projections were not plausible. The ERG's updated modelling used the company's mixture cure model to estimate PFS, but predicted the survival trajectory from the overall-survival data rather than the PFS data. The clinical experts explained that the overall-survival projections for the routine surveillance arm were much higher than in clinical studies. The ERG acknowledged that the absolute overall-survival values were optimistic in both arms of the model and that its updated analysis had included some simplified modelling techniques. It explained that the aims of its updated approach were to:

- show the substantial effect of using different survival modelling approaches on the cost-effectiveness results
- provide an estimate of the relative survival benefit associated with olaparib plus bevacizumab maintenance treatment, which could be considered more realistic than the company's.

The committee appreciated that the ERG's updated analysis was an exploratory analysis designed to show the uncertainty in the company's approach. It noted that the incremental cost-effectiveness ratios (ICERs)

increased substantially when the ERG's original and updated survival modelling approaches were used. The committee concluded that the ERG's analyses showed the high level of uncertainty in the survival modelling.

Subsequent treatment costs should reflect routine NHS practice

3.15 The company and ERG used different treatment costs in their modelling, and this was also a driver of cost effectiveness. The company incorporated a hypothetical 50% discount to the bevacizumab list price to reflect the loss of exclusivity in 2020. The committee was aware that a confidential discount for bevacizumab had been agreed in a patient access scheme, and that the correct discounted price would be used in its decision making. The committee noted that the company and ERG also had different approaches to costing subsequent treatments. The company's approach was a hybrid between reflecting the treatments given in PAOLA-1 and what is available routinely in UK clinical practice and through the Cancer Drugs Fund. By contrast, the ERG's costs were matched to NHS routine practice, whereby routinely commissioned treatments were included but not those available through the Cancer Drugs Fund. The committee noted the NICE position statement on consideration of products recommended for use in the Cancer Drugs Fund as comparators, or in a treatment sequence, in the appraisal of a new cancer product. The committee agreed that the costing of subsequent treatments should reflect routine NHS practice in line with the position statement. It therefore considered that the ERG's approach was more appropriate.

HRD-testing costs should be included in the modelling

3.16 The company did not include HRD-testing costs in its analyses. The ERG's exploratory analyses showed that including the costs of HRD testing would increase the cost-effectiveness estimate by around £5,000 per quality-adjusted life year (QALY) gained. The committee was aware that HRD testing is not standard practice, so an uplift in resources directly

related to using olaparib plus bevacizumab would be needed to introduce it into the NHS. The committee concluded that HRD-testing costs should be included in the cost-effectiveness modelling.

The choice of utilities has a small effect on the cost-effectiveness results

3.17 The company and ERG used different utility values in their analyses. The company's utilities were derived from EQ-5D-5L data from PAOLA-1 (mapped to EQ-5D--3L) for the PFS and first disease-progression health states. There were different values for PFS on and off treatment. The ERG was concerned about the appropriateness of having different utilities for PFS on and off treatment, and about the methods used to estimate the utilities. Therefore, the ERG preferred to use mapped EQ-5D-3L values from NICE's technology appraisal guidance on olaparib monotherapy maintenance treatment in its own analyses. The committee noted that the choice of utilities had a very small effect on the cost-effectiveness results and did not discuss this further.

Cost-effectiveness estimate

Olaparib plus bevacizumab maintenance treatment cannot be recommended for routine commissioning

3.18 The company's ICERs, using its extended-regimen analysis, for first-line platinum-based chemotherapy plus bevacizumab (15 mg/kg) followed by olaparib plus bevacizumab maintenance treatment for people whose cancer had responded were:

- £26,268 per QALY gained compared with platinum-based chemotherapy followed by routine surveillance
- £19,925 per QALY gained compared with first-line platinum-based chemotherapy plus bevacizumab (7.5 mg/kg) followed by bevacizumab maintenance treatment for people whose cancer had responded.

Using the company's analysis, but incorporating the ERG's changes to the extended-regimen analysis in line with the committee's preference (see

section 3.12), the ICERs were £34,165 per QALY gained for the routine surveillance arm and £24,726 per QALY gained for the bevacizumab (7.5 mg/kg) arm. All the ICERs are lower when the confidential patient access scheme for bevacizumab is included. The committee noted that the ICERs were based on the company's survival modelling approach and could have substantially overestimated the survival gain for the olaparib plus bevacizumab arm (see section 3.13). Because of the high level of uncertainty in the survival modelling, the committee considered that the ICERs could be much higher. It noted that using the ERG's survival modelling updated after technical engagement, and including other preferred assumptions (see sections 3.16 and 3.17), increased the ICER to £93,350 per QALY gained compared with the routine surveillance arm and £75,476 per QALY gained compared with the bevacizumab (7.5 mg/kg) arm. The committee considered that the ERG's exploratory analyses showed the substantial effect on the ICERs of using different survival modelling. Therefore, the committee could not state with any certainty a most plausible ICER. It concluded that, because of the high level of uncertainty, the ICER had not been shown to be within the range normally considered a cost-effective use of NHS resources (that is, between £20,000 and £30,000 per QALY gained). Therefore, it could not recommend olaparib plus bevacizumab maintenance treatment for routine NHS use.

Cancer Drugs Fund

Further data from PAOLA-1 would help to resolve the uncertainties in the clinical- and cost-effectiveness evidence

3.19 Having concluded that olaparib plus bevacizumab maintenance treatment could not be recommended for routine NHS use, the committee considered whether it could be recommended within the Cancer Drugs Fund. It discussed the arrangements for the Cancer Drugs Fund agreed by NICE and NHS England in 2016, noting NICE's Cancer Drugs Fund methods guide (addendum). The committee recognised that olaparib plus

bevacizumab maintenance treatment is an innovative treatment for advanced ovarian cancer and that there is a high unmet need in this disease area. It therefore considered whether clinical uncertainty associated with the treatment could be addressed through collection of additional data from PAOLA-1. The company explained that further data collection is expected within the next 2 years, including data on PFS, PFS2 and interim overall-survival data. The committee agreed that further data would be a valuable addition to the clinical evidence base and would help to resolve the major uncertainties.

Olaparib plus bevacizumab maintenance treatment meets the Cancer Drugs Fund inclusion criteria

3.20 The committee recalled that, using the company's analysis but incorporating the ERG's changes to the extended-regimen analysis in line with its preference (see section 3.13), the ICERs were £34,165 per QALY gained compared with the routine surveillance arm and £24,726 per QALY gained compared with the bevacizumab (7.5 mg/kg) arm. It also recalled that the ICERs were lower when the confidential patient access scheme for bevacizumab was included. The company's base case assumed that people will be cured from ovarian cancer if they are progression free at 5 years. Although the clinical experts had explained that a cure is possible, the committee noted that there were only 3 years of PFS data from PAOLA-1 and the overall-survival data were immature (see section 3.9). Therefore, the committee considered that the company's base-case ICER may be an optimistic estimate of cost effectiveness (see section 3.18). It thought that it was plausible the ICER could be much higher, exceeding the range that is usually considered a cost-effective use of NHS resources. The committee accepted that the upper bound of the range of plausible ICERs was highly uncertain. However, it considered that, pending the results from PAOLA-1, there was plausible potential for platinum-based chemotherapy with bevacizumab 15 mg/kg followed by olaparib plus bevacizumab maintenance treatment to be cost effective in routine NHS use. Therefore, it concluded that the treatment meets the

criteria for inclusion in the Cancer Drugs Fund for treating HRD-positive advanced ovarian, fallopian tube or primary peritoneal cancer.

Conclusion

Olaparib plus bevacizumab maintenance treatment is recommended for the Cancer Drugs Fund

3.21 Early results from PAOLA-1 suggest that maintenance treatment with olaparib plus bevacizumab in people with HRD-positive disease that has responded to first-line platinum-based chemotherapy plus bevacizumab (15 mg/kg) improves PFS compared with maintenance treatment with placebo plus bevacizumab. However, mature overall-survival data are not available and the extent to which the PFS benefit will translate into an overall-survival benefit is unclear. Because of the uncertainty about the overall-survival benefit, the estimates of cost effectiveness are very uncertain, and the treatment cannot be recommended for routine use in the NHS. If the treatment does increase survival, it has the potential to be cost effective. Further data from PAOLA-1 will help to address the uncertainties in the clinical and cost effectiveness. Olaparib plus bevacizumab maintenance treatment is therefore recommended as an option within the Cancer Drugs Fund while further data are collected.

4 Implementation

4.1 When NICE recommends a treatment as an option for use within the Cancer Drugs Fund, NHS England will make it available according to the conditions in the managed access agreement. This means that, if a someone has advanced (International Federation of Gynecology and Obstetrics stages 3 and 4) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer that has responded to first-line platinum-based chemotherapy plus bevacizumab and the cancer is associated with homologous recombination deficiency positive status defined by either a BRCA1 or 2 mutation or genomic instability, and the doctor responsible for their care thinks that olaparib plus bevacizumab maintenance treatment is

the right treatment, it should be available for use, in line with NICE's recommendations and the Cancer Drugs Fund criteria in the managed access agreement. Further information can be found in NHS England's Appraisal and funding of cancer drugs from July 2016 (including the new Cancer Drugs Fund) – A new deal for patients, taxpayers and industry.

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 use in the Cancer Drugs Fund, 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. Drugs that are recommended for use in the Cancer Drugs Fund will be funded in line with the terms of their managed access agreement, after the period of interim funding. The NHS England and NHS Improvement 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 the drug or treatment, or other technology, is approved for use within the Cancer Drugs Fund. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, for use within the Cancer Drugs Fund, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document or agreement of a managed access agreement by the NHS in Wales, whichever is the later.

5 Review of guidance

5.1 The data collection period is expected to end as outlined in the data collection arrangement when further data from the PAOLA-1 study are

available. Once enough evidence is available, the process for exiting the Cancer Drugs Fund will begin and the review of the NICE guidance will start.

5.2 As part of the managed access agreement, the technology will continue to be available through the Cancer Drugs Fund after the data collection period has ended and while the guidance is being reviewed. This assumes that the data collection period ends as planned, and the review of guidance follows the standard timelines described in NICE's Cancer Drugs Fund methods guide (addendum).

Jane Adam
Chair, appraisal committee
September 2020

6 Appraisal committee members and NICE project team

Appraisal 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 to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

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

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

NICE project team

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

Juliet Kenny
Technical lead

Zoe Charles
Technical adviser

Thomas Feist
Project manager

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