NICE National Institute for Health and Care Excellence

NICE guidance

Rucaparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy

Technology appraisal guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

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1 Recommendations

1.1 Rucaparib is recommended as an option for the 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 after complete or partial response to first-line platinum-based chemotherapy in adults, only if:

- it is BRCA mutation-negative and homologous recombination deficiency (HRD)-positive, or
- it is BRCA mutation-negative, and HRD status is negative or unknown, and bevacizumab is not a treatment option because:
- NHS England's BEV3 and BEV10 commissioning approval criteria for having it are not met, or
- it is contraindicated or not tolerated, and
- the company provides rucaparib according to the commercial arrangement.

1.2 These recommendations are not intended to affect treatment with rucaparib 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 healthcare professional consider it appropriate to stop.

Why the committee made these recommendations

For this evaluation, the company asked for rucaparib to be considered only for BRCA mutation-negative and HRD-positive or HRD-negative advanced high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer (from now, described as advanced ovarian cancer) after complete or partial response to first-line platinum-based chemotherapy. This does not include everyone who it is licensed for.

Standard treatment for the HRD-positive type is olaparib plus bevacizumab, bevacizumab alone or routine surveillance if these are not suitable or not tolerated. For the HRD-negative type, it is bevacizumab alone or routine surveillance if this is not suitable or

not tolerated.

Clinical trial evidence shows that rucaparib increases how long people have before their cancer gets worse compared with placebo. It is unclear whether they also live longer because the trial is still ongoing, so there is not enough long-term evidence. Rucaparib has only been indirectly compared with olaparib plus bevacizumab or bevacizumab alone. The results suggest that rucaparib is likely to work as well as bevacizumab alone, but is not as effective as olaparib plus bevacizumab.

BRCA mutation-negative HRD-positive advanced ovarian cancer

The most likely cost-effectiveness estimates for rucaparib compared with olaparib plus bevacizumab and bevacizumab alone are within what NICE normally considers to be an acceptable use of NHS resources for BRCA mutation-negative advanced ovarian cancer that is HRD positive. So, rucaparib is recommended for routine use for this type of cancer. People should be informed that rucaparib is less effective than olaparib plus bevacizumab. But the availability of rucaparib will provide more treatment choices.

BRCA mutation-negative, HRD-negative or HRD-unknown advanced ovarian cancer

The most likely cost-effectiveness estimates for rucaparib compared with routine surveillance are within what NICE normally considers to be an acceptable use of NHS resources for BRCA mutation-negative advanced ovarian cancer that is HRD negative or HRD unknown in people who cannot have bevacizumab. So, it is recommended for routine use for the type of cancer in people who cannot have bevacizumab.

For BRCA mutation-negative advanced ovarian cancer that is HRD negative or HRD unknown in people who can have bevacizumab, the results of further data collection in the Cancer Drugs Fund are unlikely to sufficiently support recommending rucaparib. Also, rucaparib is unlikely to be cost effective compared with bevacizumab maintenance for this group. So, it is not recommended for this type of cancer in people who can have bevacizumab.

2 Information about rucaparib

Marketing authorisation indication

2.1 Rucaparib (Rubraca, pharma&) is indicated 'as monotherapy 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'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for rucaparib.

Price

2.3 The list price for rucaparib is £3,562.00 per 60-tablet pack of 300 mg, 250 mg or 200 mg tablets (excluding VAT; BNF online, accessed January 2025). The company estimates that the average cost per year of rucaparib is £105,869 (estimated from the deterministic base-case economic analysis using the list price).

2.4 The company has a commercial arrangement. This makes rucaparib available to the NHS with a discount. The size of the discount is commercial in confidence.

3 Committee discussion

The evaluation committee considered evidence submitted by pharma&, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

Details of condition

3.1 The patient expert explained that advanced ovarian, fallopian tube and peritoneal cancer (from now, described as advanced ovarian cancer) has a substantial impact on quality of life. Even when initial treatment is successful, people with advanced ovarian cancer often live with the anxiety of possible recurrence. Concerns include the toxicity and side effects from further rounds of chemotherapy when the cancer recurs. So, the time between treatments can be extremely difficult, and people with advanced ovarian cancer are concerned that treatment options will become exhausted as the cancer progresses. Statements submitted by 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 patient and clinical experts explained that rucaparib would give people another option for maintenance treatment after first-line treatment. This would give healthcare professionals and people with the condition more choice if a treatment is not tolerated. The patient experts also explained that there are fewer treatment options for people with BRCA mutation-negative advanced ovarian cancer, particularly for people with HRD-negative ovarian cancer. The committee understood that there is a particularly high unmet need in this group of people. It concluded that there is a high disease burden and a need for new treatments for people with advanced ovarian cancer.

Positioning of rucaparib

3.2 The company noted in its submission that maintenance treatment with olaparib is well established in people with a BRCA mutation (see 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). So, it focused its submission for rucaparib on 2 subgroups in which it thought there is greater clinical need:

- people with BRCA mutation-negative advanced ovarian cancer that is HRD positive (also known in the company submission as non-tBRCA with high loss of heterozygosity) after complete or partial response to first-line platinum-based chemotherapy
- people with BRCA mutation-negative cancer that is HRD negative (also known in the company submission as non-tBRCA with low loss of heterozygosity) after complete or partial response to first-line platinum-based chemotherapy.

  The company explained that people routinely have tests for HRD and BRCA mutation status in the NHS. But it noted that there is expected to be a subset of people with BRCA mutation-negative cancer with unknown HRD status. The clinical experts explained that this is because of sampling and technical issues, and people with unknown HRD status are not a clinically or biologically distinct group in clinical practice. The committee concluded that positioning rucaparib as a first-line maintenance treatment for people with BRCA mutation-negative advanced ovarian cancer that is HRD positive or HRD negative was appropriate.

Clinical management

Treatment pathway and comparators

3.3 The usual first-line treatment for advanced ovarian cancer is platinum-based chemotherapy, which may be combined with bevacizumab. After a response, first-line maintenance treatment with a poly ADP ribose polymerase (PARP)

inhibitor or bevacizumab alone is offered. These include:

- niraparib, which is recommended through the Cancer Drugs Fund for people with advanced ovarian cancer regardless of BRCA mutation or HRD status (see NICE's technology appraisal guidance on niraparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy)

- olaparib alone, which is licensed for people whose cancer is BRCA mutation-positive (see 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), so is not relevant to the company's positioning of rucaparib for people whose cancer is BRCA mutation-negative

- olaparib plus bevacizumab, which is licensed for people whose cancer is HRD positive (see NICE's technology appraisal guidance on olaparib with bevacizumab for maintenance treatment of advanced high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer)

- bevacizumab alone, which is routinely commissioned in the NHS for people who meet the BEV3 and BEV10 commissioning approval criteria (see the NHS England National Cancer Drugs Fund list).

  Routine surveillance is also an option if maintenance treatment is not suitable or cannot be tolerated. The company included olaparib plus bevacizumab, bevacizumab alone and routine surveillance as comparators for people with BRCA mutation-negative advanced ovarian cancer that is HRD positive. It included bevacizumab alone and routine surveillance for people with BRCA mutation-negative advanced ovarian cancer that is HRD negative. Both the company and the clinical experts expected niraparib to be the main alternative for rucaparib in clinical practice. But niraparib is only available through the Cancer Drugs Fund, so could not be considered established clinical practice. The committee noted that some people will be unable to have maintenance treatment with bevacizumab if they:

- do not meet the commissioning approval criteria

- cannot tolerate bevacizumab, or

- have not had induction treatment with bevacizumab.

The NHS England Cancer Drugs Fund clinical lead (from here, Cancer Drugs Fund lead) explained that bevacizumab alone is used in about 17% of people having first-line maintenance treatment. Olaparib is used in 11% of people (BRCA positive population), olaparib plus bevacizumab in 24% of people (HRD positive population) and niraparib in 48% of people through the Cancer Drugs Fund.

After consultation on the draft guidance, the company reiterated its comments that niraparib would be the main alternative to rucaparib in clinical practice. It also emphasised that, for people whose cancer is HRD negative and who cannot have bevacizumab, the only comparator in this evaluation is routine surveillance. The company said that this does not reflect clinical practice. The committee appreciated that niraparib would be the main alternative for rucaparib in clinical practice. But it maintained its view that niraparib was not an appropriate comparator because it has not been assessed as cost effective or recommended for routine commissioning. The committee also appreciated that, for people with BRCA mutation-negative HRD negative advanced ovarian cancer who cannot have bevacizumab, the only comparator is routine surveillance. The committee concluded that the relevant comparators were:

- olaparib plus bevacizumab, bevacizumab alone and routine surveillance for the BRCA mutation-negative HRD positive population
- bevacizumab alone and routine surveillance for the BRCA mutation-negative HRD negative population.

Bevacizumab dose

3.4 The NICE scope for this evaluation included bevacizumab alone at the unlicensed dose of 7.5 mg/kg every 3 weeks as a comparator. This is because it is routinely funded for maintenance monotherapy treatment of advanced ovarian cancer (see the BEV10 commissioning approval criteria in NHS England's National Cancer Drugs Fund list). The licensed dose of 15 mg/kg every 3 weeks is not routinely

funded for maintenance monotherapy. But the company did not think that bevacizumab alone at a dose of 7.5 mg/kg was a relevant comparator in its submission. It explained that, in NICE's technology appraisal guidance on bevacizumab in combination with paclitaxel and carboplatin for first-line treatment of advanced ovarian cancer, the appraisal committee was unable to consider bevacizumab at a dose of 7.5 mg/kg because the dose was unlicensed. It also noted that it had identified no recent studies assessing survival data for maintenance treatment with bevacizumab at the 7.5 mg/kg dose. So, the company included bevacizumab alone at a dose of 15 mg/kg as a comparator. Further justification from the company for using the 15 mg/kg dose is described in section 3.7. The EAG thought the 7.5 mg/kg dose to be the relevant comparator because its clinical advisers had said that this is what is used in the NHS. The clinical experts at the first committee meeting also confirmed that the 7.5 mg/kg dose is the one used in NHS clinical practice for maintenance monotherapy.

In response to consultation on the draft guidance, the company acknowledged that bevacizumab at a dose of 7.5 mg/kg had the potential to be considered as a comparator. But it remained concerned at the lack of evidence for the efficacy of bevacizumab maintenance treatment at this dose (see section 3.7). The committee recalled section 6.2.4 of NICE's manual on health technology evaluations. This says that a committee can consider as comparators technologies that do not have regulatory approval for the population defined in the scope when they are considered to be part of established clinical practice for the population in the NHS. The committee understood that bevacizumab at a dose of 7.5 mg/kg is unlicensed but is routinely funded and is the dose used for maintenance monotherapy in clinical practice. So, it concluded that bevacizumab alone at a dose of 7.5 mg/kg is the relevant dose for this evaluation.

Previous bevacizumab

3.5 Maintenance treatment of bevacizumab alone is only available in the NHS after completing first-line induction treatment with platinum-based chemotherapy plus bevacizumab (see section 3.3). Maintenance treatment with olaparib plus bevacizumab usually follows induction chemotherapy with bevacizumab. But the committee noted that it is also commissioned in about a third of people who have not had bevacizumab as part of induction chemotherapy. The EAG highlighted

that only a small proportion of people in the ATHENA-MONO study had had induction treatment that included bevacizumab. Clinical advice to the EAG was that inclusion or exclusion of bevacizumab as part of induction treatment does not influence the clinical-effectiveness results in the maintenance setting. The clinical experts at the first committee meeting agreed with this. They thought it was appropriate to combine data for people whose cancer had responded to induction treatment either with or without bevacizumab. The committee noted that a subgroup analysis for people who had previous bevacizumab would be based on a substantially reduced sample size from ATHENA-MONO. So, it concluded that combining data for people whose cancer had responded to induction treatment either with or without bevacizumab is appropriate for decision making.

Clinical effectiveness

Direct data sources

3.6 The clinical-effectiveness evidence for rucaparib came from ATHENA-MONO, a phase 3 double-blind randomised controlled trial. The trial included adults with newly diagnosed advanced ovarian, fallopian tube or primary peritoneal cancer that had responded to first-line platinum-doublet treatment. It provided direct evidence to compare rucaparib with placebo (the company used placebo data from ATHENA-MONO as a proxy for routine surveillance data). People in ATHENA-MONO were categorised into 4 randomisation stratification groups:

- BRCA mutation positive
- BRCA mutation negative and HRD positive
- BRCA mutation negative and HRD negative
- BRCA mutation negative and HRD unknown.

Among the people without a BRCA mutation, 22.1% had HRD-positive cancer, 44.2% had HRD-negative cancer and 12.3% had HRD-unknown cancer. A hierarchical step-down procedure was specified for the analysis of the endpoints from ATHENA-MONO. This meant that statistical significance could

only be assessed for the intention-to-treat (ITT) and HRD (a preplanned subgroup) populations, and the progression-free survival (PFS) and overall survival (OS) endpoints. At the 23 March 2022 data cut, there was a statistically significant benefit for rucaparib compared with placebo for PFS in the ITT population (hazard ratio [HR] 0.52, 95% confidence interval [CI] 0.40 to 0.68). The results for PFS were nominally significant at the 5% significance level in the:

- BRCA mutation-negative and HRD-negative subgroup (HR 0.65, 95% CI 0.45 to 0.95)
- BRCA mutation-negative HRD-unknown subgroup (HR 0.39, 95% CI 0.20 to 0.78)
- BRCA mutation-negative HRD-negative plus HRD-unknown subgroups combined (HR 0.59, 95% CI 0.42 to 0.81).

The PFS results favoured rucaparib over placebo in the BRCA mutation-negative and HRD-positive subgroup (HR 0.58, 95% CI 0.33 to 1.01). There were no statistically significant differences between treatment arms for OS. But the results were immature at both the 23 March 2022 (24.7% death events for the ITT population) and 9 March 2023 (35.0% death events for the ITT population) data cutoffs. The hazard ratio for OS was 0.61 (95% CI 0.29 to 1.30) in the BRCA mutation-negative HRD-positive subgroup and 0.75 (95% CI 0.48 to 1.17) in the BRCA mutation-negative HRD-negative subgroup. The company considered the hazard ratio for OS in the BRCA mutation-negative HRD-negative plus HRD-unknown subgroup to be confidential, so it cannot be reported here. The committee concluded that the ATHENA-MONO study was appropriate for decision making. It also concluded that rucaparib showed clinical benefit for PFS compared with placebo in the:

- BRCA mutation-negative HRD-positive subgroup
- BRCA mutation-negative HRD-negative subgroup
- BRCA mutation-negative HRD-unknown subgroup.

Indirect data sources

3.7 The clinical-effectiveness evidence for olaparib plus bevacizumab and for bevacizumab alone (represented by the placebo plus bevacizumab treatment arm) was from PAOLA-1, a phase 3 double-blind randomised controlled trial. PAOLA-1 included adults with newly diagnosed advanced ovarian, fallopian tube or primary peritoneal cancer that had responded to first-line chemotherapy plus bevacizumab. PAOLA-1 used a bevacizumab dose of 15 mg/kg rather than the 7.5 mg/kg dose that is used in clinical practice for bevacizumab alone (see section 3.4). The company explained that no relevant evidence for the efficacy of bevacizumab 7.5 mg/kg in the first-line maintenance treatment setting was identified. The EAG agreed that, given the lack of relevant evidence, it was not possible to include data for bevacizumab alone at a dose of 7.5 mg/kg in the indirect comparisons. Clinical advice to the EAG suggested that, although there was no direct evidence comparing the efficacy and safety of the 2 bevacizumab doses, there was likely to be little difference between them. So, the EAG thought that it was appropriate to use data for bevacizumab at a dose of 15 mg/kg as a proxy for the 7.5 mg/kg dose. But the company was concerned that the clinical equivalence of bevacizumab 7.5 mg/kg to bevacizumab 15 mg/kg had not been formally established in the first-line maintenance treatment for advanced ovarian cancer setting. So, it thought that the EAG's use of clinical efficacy for bevacizumab 15 mg/kg to inform a bevacizumab 7.5 mg/kg comparison was inappropriate. The clinical experts at the first committee meeting agreed that the assumption of clinical equivalence between the 2 doses was difficult to answer definitively. But they noted that similar median PFS values were seen in ICON 7, which investigated the 7.5 mg/kg dose, and GOG-0218, which investigated the 15 mg/kg dose. These studies evaluated bevacizumab at the respective doses in both the induction and maintenance treatment settings. The clinical experts noted that there were likely differences between the populations in the ICON 7 and GOG-0218 studies. But they thought that an assumption of clinical equivalence was broadly appropriate. The company repeated its concerns and its disagreement with the EAG's approach to assume clinical equivalence between the 7.5 mg/kg and 15 mg/kg doses in response to consultation on the draft guidance. The EAG agreed that, ideally, cost and efficacy should relate to the same dose. But it recalled that efficacy data relating to the bevacizumab 7.5 mg/kg dose in the maintenance setting was not available. It noted that it was unaware of any robust evidence that shows the similarity of, or any differences in,

the clinical efficacy of the 2 doses of bevacizumab.

At the second meeting, the EAG explained that it did not think that it was appropriate to do indirect or naive treatment comparisons of ICON 7 and GOG-0218. This was mainly because:

- there were differences in the trial populations
- people were randomised to induction treatment rather than to the maintenance treatment.

The company agreed that it was difficult to establish the efficacy of the 7.5 mg/kg dose in the maintenance setting. The committee recalled that, in NICE's technology appraisal guidance on olaparib with bevacizumab for maintenance treatment of advanced high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer:

- bevacizumab maintenance treatment at a dose of 7.5 mg/kg was accepted as a relevant comparator
- the clinical evidence from PAOLA-1 for the 15 mg/kg dose was thought to be the best available evidence.

The committee understood the data limitations and challenges associated with determining the efficacy of bevacizumab maintenance treatment at a dose of 7.5 mg/kg. It also had not seen any alternative modelling of the efficacy of the 7.5 mg/kg dose, other than the clinical efficacy derived from PAOLA-1. The committee concluded that using PAOLA-1 clinical efficacy data for bevacizumab 15 mg/kg to inform the bevacizumab 7.5 mg/kg comparator was appropriate for decision making.

Indirect treatment comparisons

3.8 The company presented indirect treatment comparisons (ITC) for rucaparib compared with olaparib plus bevacizumab and bevacizumab alone. It also presented ITCs comparing rucaparib with niraparib, but they were not critiqued by the EAG. Also, the committee did not think that the results were relevant for

decision making because niraparib was not a relevant comparator (see section 3.3). The company did unadjusted naive ITCs and unanchored matching-adjusted indirect comparisons (MAICs) for PFS, OS and PFS second event (PFS2) outcomes in the BRCA mutation-negative HRD-positive subgroup and the HRD-negative plus HRD-unknown subgroup. It was not possible to present ITCs and MAICs for the BRCA mutation-negative HRD-negative subgroup. The EAG thought that the methods the company used to do the MAICs were generally appropriate. The company also did additional PFS MAICs that assumed piecewise hazard ratios. In the BRCA mutation-negative HRD-positive subgroup, both the unadjusted naive ITC and unanchored MAIC results for PFS favoured olaparib plus bevacizumab compared with rucaparib. For the comparisons of rucaparib compared with bevacizumab alone, the PFS results favoured rucaparib in both the BRCA mutation-negative HRD-positive and BRCA mutation-negative HRD-negative or HRD-unknown subgroups. All OS results showed no statistically significant difference between rucaparib and olaparib plus bevacizumab or bevacizumab alone, with all reported hazard ratios being close to 1. The company thought that the MAICs did not meaningfully affect the survival curves for any of the endpoints and that the resulting adjustment of the hazard ratios was limited. The EAG thought that the MAIC results were more valid than the unadjusted naive ITC results. But it noted that the adjustments had little effect (the MAIC and ITC results were similar). It also thought that the results of the piecewise MAICs were likely to be more valid than the results from the base-case MAICs for the comparisons in the BRCA mutation-negative HRD-positive subgroup. The committee noted that the ITCs were not used in the base-case analyses of the economic model, so they had no impact on decision making.

Evidence of long-term survivorship

3.9 The company noted that a slowing of the PFS hazards was seen at about 100 weeks in the BRCA mutation-negative HRD-positive population in PAOLA-1 for both the olaparib plus bevacizumab and bevacizumab-alone treatment arms. The company understood that a slowing of hazards was also seen in the PRIMA trial (that is, the study of niraparib maintenance treatment in newly diagnosed advanced ovarian cancer). It thought that this provided evidence of the long-term survivorship seen in advanced ovarian cancer populations that is amplified by PARP inhibitor therapy. The company noted that follow up in ATHENA-MONO

ended at the time when slowing of the hazard was seen in the PRIMA and PAOLA-1 trials. It recalled that PFS extrapolations produced from the final 2022 data cut of PAOLA-1 showed a plateau, which had been less evident in the earlier 2019 data cut. A similar observation was made for PFS in PRIMA. The company recalled that the assumption that some people could be cured was accepted by the evaluation committee for NICE's technology appraisal guidance on olaparib with bevacizumab for maintenance treatment of advanced high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer. But the company acknowledged that the clinical-effectiveness evidence from ATHENA-MONO to support the long-term survivorship assumption for people having rucaparib was immature. The EAG acknowledged that there was precedent for PARP inhibitors to produce PFS curves that plateaued. But it was concerned that the PFS data from ATHENA-MONO did not yet show a slowing of the PFS hazards that would support the assumption of long-term survivorship for rucaparib. The EAG also noted that the proportions of people who experience long-term survivorship were uncertain for olaparib plus bevacizumab and bevacizumab alone. The clinical experts noted that they expected to see some people having rucaparib who would experience long-term remission in line with other PARP inhibitors. The committee accepted that long-term survivorship is seen in some people having treatment with PARP inhibitors for advanced ovarian cancer. The committee concluded that it was likely that a proportion of people having rucaparib would experience long-term survivorship. But it did not think that this was evident in the PFS or OS data from ATHENA-MONO.

Economic model

Company's modelling approach

3.10 The company presented a partitioned survival model with 4 health states to estimate the cost effectiveness of rucaparib in people with BRCA mutation-negative HRD-positive or HRD-negative advanced ovarian cancer. The 4 health states were progression free, first disease progression, second disease progression and death. In the model, data from the ATHENA-MONO study was used to inform the clinical parameters for rucaparib compared with routine surveillance. PFS and time to treatment discontinuation were based on the

23 March 2022 data cut. OS and PFS2 were based on the 9 March 2023 data cut. The company used naive treatment comparisons of Kaplan–Meier curves, assuming that the imbalances across trials did not affect survival curves remarkably. The committee concluded that the model was appropriate for decision making.

Modelling PFS

PFS in the BRCA mutation-negative HRD-positive population

3.11 The company fitted standard parametric distributions to the PFS, PFS2, OS and time to treatment discontinuation endpoints in the BRCA mutation-negative HRD-positive subgroup. But it was concerned that the standard parametric distributions for olaparib plus bevacizumab and bevacizumab alone did not provide a good visual fit to the observed data. It said that the Kaplan–Meier curves for olaparib plus bevacizumab and bevacizumab alone showed an increased hazard of progression between 12 and 24 months. This was consistent with a 'rebound effect' that has been seen in other ovarian cancer trials after bevacizumab treatment was stopped. So, the company modelled PFS using the respective PAOLA-1 Kaplan–Meier curves for olaparib plus bevacizumab or bevacizumab alone. This was followed by a parametric distribution (log-logistic for olaparib plus bevacizumab and log-normal for bevacizumab alone). The company thought that using PFS parametric distributions based on the early dataset from ATHENA-MONO would bias the results against rucaparib. This was because there was not enough follow up or events to show the expected plateau indicative of a cure in ATHENA-MONO (see section 3.9). So, for rucaparib, PFS was modelled using the ATHENA-MONO Kaplan–Meier curve, followed by the hazard pattern from the longer follow up of PAOLA-1 trial's olaparib plus bevacizumab arm to extrapolate. A standard log-normal parametric distribution was used for routine surveillance. The EAG was concerned about the lack of evidence to support an assumption of long-term survivorship for rucaparib (see section 3.9). So, it used standard parametric distributions, which do not rely on the long-term survivorship assumption, to extrapolate PFS for all treatments and subgroups in its preferred analyses. The EAG applied generalised gamma curves to model PFS for both rucaparib and olaparib plus bevacizumab in the BRCA mutation-negative HRD-positive subgroup. It applied a log-logistic curve to model

PFS for bevacizumab alone and agreed with the company to use a log-normal curve for routine surveillance. The EAG thought that its preferred PFS curves had a good visual fit to the ATHENA-MONO Kaplan–Meier curves but acknowledged its curve fits were not as good compared with the PAOLA-1 data. The committee had some concerns about the company's approach to modelling PFS (see section 3.13 and section 3.14). It preferred the EAG's modelling of PFS for the BRCA mutation-negative HRD-positive population.

PFS in the BRCA mutation-negative HRD-negative population

3.12 The company used separately fitted log-normal distributions in its base-case analyses to model PFS for both rucaparib and routine surveillance in the BRCA mutation-negative HRD-negative subgroup. The company said that it had used parametric survival curves to capture the long-term survivorship assumption instead of estimating cure fractions. The EAG agreed with the company's choice of curves to model rucaparib and routine surveillance. Similar to the BRCA mutation-negative HRD-positive population (see section 3.11), the company noted that the standard parametric curves for bevacizumab alone showed poor fit to the PAOLA-1 data. So, it used the Kaplan–Meier curve followed by a parametric distribution to extrapolate PFS. The company selected the exponential distribution to model the tail of the curve for its base-case analyses, based on long-term plausibility and validated by clinical expert input. As described in section 3.11, the EAG had concerns with the company's piecewise Kaplan–Meier plus parametric curve approach for estimating PFS. It did not think that a fully parametric distribution imposed an explicit assumption that long-term survivorship occurs. So, it applied a log-logistic curve to model PFS for bevacizumab alone.

In its response to consultation, the company was concerned that the fully parametric log-logistic curve did not reflect the rapid progression seen in people treated with placebo plus bevacizumab in PAOLA-1. The company maintained its preference to use the piecewise Kaplan–Meier plus exponential curve to model PFS for bevacizumab alone because it reflected the particular shape of the PAOLA-1 data. The EAG thought that, without evidence to support using alternative modelling approaches, the same approach should be used to extrapolate PFS for rucaparib and bevacizumab alone. But the company said that

applying the same extrapolation approach is for treatments with the same mechanism of action, whereas rucaparib and bevacizumab differ in mechanism of action. The committee thought that both the company's piecewise curve and the EAG's fully parametric curve for bevacizumab alone showed rapid progression that then levelled off. But it was concerned about the low number of events used to inform a long-term extrapolation after the Kaplan–Meier cut off in the company's piecewise approach. The committee had some additional concerns with the company's approach (see section 3.13 and section 3.14) and preferred the EAG's approach.

Relationship between PFS, PFS2 and OS

3.13 The company checked the plausibility of the long-term extrapolations in its economic model. It explained that the expected relationship between PFS, PFS2 and OS (when PFS is less than or equal to PFS2, and PFS2 is less than or equal to OS) may not hold when standard parametric curves are used. It noted that PFS2 in particular was highly affected by data immaturity. So, to overcome the issue of crossing curves and to reflect the assumption of long-term survivorship (see section 3.9), the company constrained the OS and PFS2 extrapolation curves to not be lower than the PFS curve. Both the OS and PFS2 curves were assumed to follow the trajectory of PFS from the point of crossing. The company also constrained the PFS2 curve to not be higher than the OS curve. From the point of crossing, PFS2 was assumed to follow the trajectory of OS. The EAG was concerned that these constraints were activated relatively early in the company's model and resulted in clinically implausible PFS2 and OS estimates. It noted that the issue of crossing curves was because the assumption of long-term survivorship only applied to PFS, and not PFS2 or OS. This was because of the relative immaturity of those endpoints. The company clarified that, because the OS curve followed the trajectory of PFS, OS did take on the long-term survivorship assumption implicitly. The EAG was unable to introduce a long-term survivorship assumption directly into the extrapolation of PFS2 and OS. So, it removed the long-term survivorship assumption from PFS in its preferred modelling (see section 3.11 and section 3.12). The EAG acknowledged that the issue of crossing curves still remained in its approach to modelling PFS. But it said that that point of crossing was at a later time point. The committee agreed with the concerns highlighted by the EAG, and preferred the EAG's modelling

approach.

Committee preferences for modelling PFS

3.14 The committee thought it likely that a proportion of people having rucaparib would experience long-term survivorship. But it recalled that this was not yet evident in the PFS or OS data from ATHENA-MONO (see section 3.9). It also accepted the EAG's concerns about the company's extrapolations and the resulting crossing of curves relatively early in the model (see section 3.13). For the reasons set out in sections 3.11 to 3.13, the committee preferred to use the EAG's approach to modelling PFS with standard parametric curves for all treatments and subgroups in its decision making.

Mortality hazards

3.15 The company used a log-normal distribution to model OS for rucaparib in the BRCA mutation-negative HRD-positive subgroup. The EAG thought that the company's modelling approach produced implausible long-term OS hazards for rucaparib compared with olaparib plus bevacizumab that were not supported by clinical evidence. It noted that, when using the log-normal curve, the mortality hazards for people having rucaparib were higher than the mortality hazards for people having olaparib plus bevacizumab until 3 years. From 3 years onwards, the mortality hazards for people having rucaparib were lower than for people having olaparib plus bevacizumab. The EAG explained that the ATHENA-MONO Kaplan–Meier data for rucaparib OS showed that OS hazards from 3 years were possibly unreliable. This was because of substantial right censoring and low numbers at risk because of the timing of the data cut off. So, the EAG set rucaparib mortality hazards that were never lower than the mortality hazards for olaparib plus bevacizumab. The company acknowledged that there was uncertainty around the long-term hazard for survival in people having rucaparib. But it was concerned that the EAG's assumption was arbitrary and not supported by clinical evidence. In response to the factual accuracy check on the EAG's report, the company submitted observed OS data from ATHENA-MONO and PAOLA-1. This data showed that the mortality hazard for rucaparib fell below that of olaparib plus bevacizumab from week 100. It also recalled that the PAOLA-1

data showed acceleration of progression hazard and an increase in the OS hazard for olaparib plus bevacizumab after 96 weeks. The EAG thought that there was no statistical basis for concluding a difference in hazards between rucaparib and olaparib plus bevacizumab in the 98- to 148-week interval. It recalled the substantial right censoring in the 148- to 198-week interval. It also noted that there were no events from 198 weeks to trial data cut off that could be used to estimate a hazard. The clinical experts explained that the observed differences in mortality hazards may have been because of the differing toxicity between rucaparib and olaparib plus bevacizumab. They also noted that ATHENA-MONO included more people with a high risk for progression than PAOLA-1. This could have influenced the higher mortality hazard seen for rucaparib earlier in the trial. The clinical experts thought that, all else being equal, there was no reason why the mortality hazards for rucaparib would be lower than for olaparib plus bevacizumab. The committee noted the EAG's concerns with the OS hazards for rucaparib and olaparib plus bevacizumab seen in the data from week 98. It thought that the evidence showing rucaparib mortality hazards falling below the mortality hazards of olaparib plus bevacizumab was not robust, so was uncertain. So, the committee concluded that the EAG's approach of setting rucaparib mortality hazards so that they were never lower than the mortality hazards for olaparib plus bevacizumab was appropriate.

Source of utility values

3.16 Health-related quality-of-life data was collected from ATHENA-MONO using the EQ-5D-5L questionnaire. The data was mapped to EQ-5D-3L data using the algorithm reported by Hernández Alava et al. (2023) to give health-state utility values. The company considered the health-state utility values from ATHENA-MONO to be confidential, so they cannot be reported here. The utility values applied in the company's base-case analysis differed between the BRCA mutation-negative HRD-positive and the BRCA mutation-negative HRD-negative subgroups. Clinical advice given to the EAG stated that it was unlikely that health-related quality of life would differ by subgroup. So, the EAG thought that it was more appropriate to populate the model using utility values derived from the ATHENA-MONO ITT population. The clinical experts at the committee meeting said that the length of time on treatment and response rates varied across the 2 subgroups, which may affect overall quality of life. But the experts explained

that there was no reason to expect a difference in the health-state utility values assigned to people in the 2 subgroups. The committee concluded that it had not been presented with substantial evidence that utility values would differ across the 2 subgroups. So, it concluded that it preferred to use the ATHENA-MONO ITT data to inform the utility values for both subgroups.

Induction treatment costs

3.17 The company noted that the cost of bevacizumab induction treatment was an unavoidable additional cost to the NHS associated with the treatment pathway of olaparib plus bevacizumab and bevacizumab-alone maintenance treatment. It also recalled that the appraisal committee for NICE's technology appraisal guidance on olaparib plus bevacizumab for maintenance treatment of advanced ovarian, fallopian tube or primary peritoneal cancer initially preferred to include the treatment cost of bevacizumab induction to the olaparib plus bevacizumab and bevacizumab-alone treatment arms. The company recognised that the cost of bevacizumab induction was eventually removed from NICE's technology appraisal guidance on olaparib with bevacizumab for maintenance treatment of advanced high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer during the review of the new evidence collected as part of the managed access agreement. But it thought that this was likely to be because of the induction costs cancelling out across the treatment arms. So, the company included the cost of bevacizumab induction treatment as a one-off cost at the start of the economic model in both the olaparib plus bevacizumab and bevacizumab-alone treatment arms. It assumed that 100% of people in these treatment arms incurred the cost of 6 cycles of bevacizumab. The committee recalled that, when NICE's technology appraisal on olaparib with bevacizumab started, first-line treatment with bevacizumab was not available in routine commissioning. But the marketing authorisation for olaparib plus bevacizumab was only for people whose cancer had responded to first-line treatment with bevacizumab. So, to implement olaparib plus bevacizumab as a maintenance treatment option, a change to the routine first-line treatment pathway was needed. So, an extended treatment pathway was considered in NICE's initial technology appraisal guidance on olaparib plus bevacizumab. The committee noted that, if rucaparib maintenance treatment becomes available, it would not change the treatment pathway before maintenance treatment is offered. The EAG

thought that it was inappropriate to include induction treatment costs in the economic model because the focus of this evaluation was maintenance treatment. It noted that, in the model, the point from which costs and outcomes are estimated was after response to first-line platinum chemotherapy. Clinical advice to the EAG noted that people having rucaparib maintenance, if recommended, may also have bevacizumab as part of their induction treatment. The clinical experts at the first committee meeting agreed with the EAG's clinical advisers. They explained that the decision about whether to use bevacizumab induction treatment in clinical practice is based on an assessment of need. It is not determined by the PARP inhibitor to be used. The committee noted that this was consistent with the evidence from the ATHENA-MONO trial in which 17.8% of people had bevacizumab induction treatment (see section 3.5).

At the second meeting, a representative from NHS England confirmed that induction treatment with bevacizumab could be used before rucaparib maintenance treatment if rucaparib becomes available. The committee also recalled that about a third of people who have olaparib plus bevacizumab in the NHS do not have bevacizumab induction chemotherapy. The committee understood that a condition of people having maintenance treatment with bevacizumab at a dose of 7.5 mg/kg is that it follows the completion of induction chemotherapy with bevacizumab 7.5 mg/kg. So, it could be considered that the decision point for maintenance treatment is earlier in the treatment pathway. But it noted that a decision point from the choice of induction treatment had not been modelled by the company. It also recalled the advice from the clinical experts that the choice of having bevacizumab induction treatment was not influenced by the availability of later treatment options. The committee thought that it was inconsistent to include induction costs only for the olaparib plus bevacizumab and bevacizumab-alone treatment arms in the model. It noted that it had not been presented with a strong justification for why the decision point for rucaparib as a maintenance treatment should be considered from the start of induction treatment. So, it preferred to remove the costs of bevacizumab induction treatment from the model.

Relative dose intensity

3.18 Constant relative dose intensity values were included by the company in the

calculation of costs for rucaparib, olaparib plus bevacizumab, and bevacizumab alone. In the model, the company multiplied relative dose intensity for each treatment by the respective cost per administration. The company considered the relative dose intensity values for rucaparib from ATHENA-MONO to be confidential, so they cannot be reported here. The EAG noted that the rucaparib relative dose intensity in ATHENA-MONO varied over time. So, it thought that it was more appropriate to apply relative dose intensity on a cycle-by-cycle basis. But cycle-by-cycle data for relative dose intensity was not available from PAOLA-1 for olaparib plus bevacizumab and bevacizumab alone. So, the EAG removed all relative dose intensity multipliers from its preferred analyses. The Cancer Drugs Fund lead recalled that rucaparib had the same cost per pack regardless of the strength per tablet (see section 2.3). So, dose reductions are not expected to be associated with substantial cost savings if applied in practice. But the company's application of relative dose intensity multipliers in the model reduced the cost per administration of each treatment, including rucaparib. So, removing relative dose intensity multipliers from the model increased treatment costs, and reduced the cost effectiveness of rucaparib against all comparators. So, the committee preferred the EAG's approach to remove all relative dose intensity multipliers from the treatment-cost calculations. It noted that this was also consistent with its preferred approach to assume no dose reductions in 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. At the second committee meeting, an NHS England representative said that it was not unusual for people to need dose reductions for rucaparib. They also confirmed that it did not reduce the cost of rucaparib to the NHS. The committee maintained its preference to remove all relative dose intensity multipliers from the treatment-cost calculations at the second meeting.

BRCA mutation-negative HRD-unknown population

3.19 In its comments on the draft guidance, the company stated that, in clinical practice, 16% to 24% of people with BRCA mutation-negative ovarian cancer have unknown HRD status. It stated that these people would not be eligible for routine access to rucaparib in the draft guidance. The committee noted that the company had not presented any cost-effectiveness evidence for either the

HRD-unknown or the HRD-negative plus HRD-unknown subgroups. The company explained that it excluded the HRD-unknown subgroup from its analyses to present NICE with a clean and conservative analysis, and the most reliable evidence available. The company was concerned that the committee did not consider the PFS and OS estimates presented as the lower bound of the benefit of rucaparib. This was because a benefit has been shown with PARP inhibitors in HRD-positive and HRD-negative subgroups. The company also said that, because HRD status does not affect the efficacy of bevacizumab or routine surveillance, its efficacy results were conservative. The committee considered these comments. It noted that that the PFS and OS results for the HRD-negative plus HRD-unknown subgroup were broadly similar to those of the HRD-negative alone subgroup (see section 3.6). So, the committee concluded that it would not expect the cost-effectiveness estimates for the HRD-negative plus HRD-unknown subgroup to differ substantially from those for the HRD-negative group alone.

Cost-effectiveness estimates

Acceptable incremental cost-effectiveness ratio

3.20 NICE's manual on health technology evaluations notes that, above a most plausible incremental cost-effectiveness ratio (ICER) of £20,000 per quality-adjusted life year (QALY) gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. But it will also take into account other aspects including uncaptured health benefits. The committee noted the following uncertainties:

- OS data for rucaparib is immature (see section 3.6)
- direct treatment comparisons were not available for rucaparib compared with olaparib plus bevacizumab or bevacizumab alone (see section 3.7)
- appropriate clinical-effectiveness data was not available for bevacizumab at the relevant monotherapy maintenance dose of 7.5 mg/kg (see section 3.7)
- evidence of long-term survivorship had not been seen in the ATHENA-MONO

data for rucaparib (see section 3.9).

The committee thought that the clinical effectiveness of rucaparib was likely to be similar to the clinical effectiveness of other PARP inhibitors used in the maintenance treatment of advanced ovarian cancer. It also thought that it had sufficient certainty in the likely long-term benefit of rucaparib as another PARP inhibitor in the treatment pathway. In addition, the committee thought that the uncertainty in the modelling of PFS was reflected in its preference for the EAG's more conservative approach (see section 3.14). So, the committee concluded that an acceptable ICER for the BRCA mutation-negative HRD-positive and BRCA mutation-negative HRD-negative subgroups would be around £30,000 per QALY. For people in the BRCA mutation-negative HRD-negative subgroup who cannot have bevacizumab, see section 3.26 for the acceptable ICER.

Committee preferred assumptions

3.21 The committee's preferred assumptions were:

- modelling the bevacizumab-alone comparator at a dose of 7.5 mg/kg (see section 3.4)
- modelling PFS using the EAG's preferred standard parametric curves (see sections 3.11 to 3.14)
- setting the mortality hazards for rucaparib so that they are never lower than the mortality hazards for olaparib plus bevacizumab (see section 3.15)
- using health-state utility values based on the ITT population from ATHENA-MONO (see section 3.16)
- excluding the cost of bevacizumab induction treatment (see section 3.17)
- excluding relative dose intensity from treatment-cost calculations (see section 3.18).

The most likely ICERs cannot be reported here because of confidential commercial arrangements for rucaparib, olaparib, bevacizumab and

subsequent treatments in the pathway. With the committee's preferred assumptions, most of the cost-effectiveness estimates for the BRCA mutation-negative HRD-positive subgroup were within the range considered an acceptable use of NHS resources. The results for this subgroup also showed that rucaparib is less costly but less effective than olaparib plus bevacizumab.

When the committee's preferred assumptions were incorporated for the BRCA mutation-negative HRD-negative subgroup, the cost-effectiveness estimates were above the range normally considered a cost-effective use of NHS resources. The cost-effectiveness estimates compared with bevacizumab alone were considerably higher. The committee recalled its preferred assumptions for the modelling of treatment costs, that is, removing relative dose intensity and the cost of bevacizumab induction treatment, and costing bevacizumab at the 7.5 mg/kg dose. It noted that these were key drivers of the cost-effectiveness estimates in this subgroup. It meant that the estimates for this subgroup remained above the range normally considered a cost-effective use of NHS resources even when PFS for bevacizumab was modelled using the company's preferred piecewise curve. So, the committee did not recommend rucaparib for routine use in the NHS in the BRCA mutation-negative HRD-negative population.

Managed access

Recommendation with managed access

3.22 Having concluded that rucaparib could not be recommended for routine use for the BRCA mutation-negative HRD-negative subgroup, the committee then considered whether it could be recommended with managed access. The committee considered whether a recommendation with managed access could be made:

- The company's managed access proposal noted that the OS data from ATHENA-MONO was immature. It also noted that data cuts from the trial were event driven but it anticipated ATHENA-MONO to reach data maturity

within 3 years. So NICE's managed access feasibility assessment concluded that clinical-effectiveness data could be collected within a reasonable timeframe and without undue burden on people having treatment or the NHS system.

- The committee considered the uncertainties in the evidence (see section 3.20) and the key issues raised by the EAG. It noted that NICE's managed access feasibility assessment stated that key modelling uncertainties would not be resolved by further data collection, including:
  - the clinical similarity of the 7.5 mg/kg and 15 mg/kg doses of bevacizumab maintenance treatment (see section 3.7)
  - the source of utility values (see section 3.16)
  - the inclusion of bevacizumab induction treatment costs (see section 3.17
  - using relative dose intensity multipliers (see section 3.18).

  It also noted that incorporating its preferred assumptions for these key issues led to a large increase in the estimates of cost effectiveness.
- The committee accepted that further data collection was likely to reduce the uncertainty in the assumption of long-term survivorship (see section 3.9) and modelling of PFS (see sections 3.11 to 3.14). It noted the company's comment that long-term OS extrapolations for rucaparib had improved with 1 additional year of data from ATHENA-MONO, between the 2022 and 2023 data cuts. But the committee recalled that:
  - the company and EAG used the same log-normal parametric curves to model PFS for rucaparib and routine surveillance in the BRCA mutation-negative HRD-negative population, and only differed in their approaches to modelling bevacizumab (see section 3.12)
  - the choice of PFS curve for bevacizumab alone had a small impact on the cost-effectiveness estimates compared with the combined impact of the other key modelling uncertainties, which would not be resolved by further data collection.

  So, the committee was not persuaded that the new evidence to be

collected in the company's managed access proposal would sufficiently support the case for recommendation. The committee thought that rucaparib did not have plausible potential to be cost effective at the agreed price in the BRCA mutation-negative HRD-negative subgroup (see section 3.21). The committee concluded that rucaparib did not meet the criteria to be considered for a recommendation with managed access for the BRCA mutation-negative HRD-negative subgroup. So, it could not recommend rucaparib for use with managed access as an option for people with BRCA mutation-negative HRD-negative advanced ovarian cancer after complete or partial response to first-line platinum-based chemotherapy.

Consideration of people who cannot have bevacizumab

Unmet need for people who cannot have bevacizumab

3.23 The committee recognised the unmet need for people in the BRCA mutation-negative HRD-negative population (see section 3.1). It also understood that, for people in this subgroup who cannot have bevacizumab, there are no other treatments in routine commissioning and routine surveillance is the only option. It noted that the cost-effectiveness estimates for rucaparib compared with routine surveillance were closer to the range considered an acceptable use of NHS resources than the cost-effectiveness estimates compared with bevacizumab. It thought that the BEV3 and BEV10 commissioning approval criteria may allow people with BRCA mutation-negative HRD-negative ovarian cancer who cannot have bevacizumab to be identified as a distinct population in clinical practice. So, the committee invited the company to submit clinical and cost-effectiveness evidence for this subgroup.

Clinical evidence for people who cannot have bevacizumab

3.24 At the third appraisal committee meeting, the committee considered evidence

presented by the company for a subgroup of people in ATHENA-MONO. This included people with BRCA mutation-negative HRD-negative or HRD-unknown advanced ovarian cancer who would not be eligible for treatment with bevacizumab because they did not meet the commissioning approval criteria. The subgroup included people with FIGO stage 3 disease at diagnosis and complete resection or microscopic residual disease (less than 1 cm). The EAG said that the subgroup was appropriately defined and that the placebo arm of ATHENA-MONO was an appropriate proxy for routine NHS surveillance. But it noted that there were considerably fewer people in the placebo arm than the rucaparib arm. It also noted that a higher proportion of people in the placebo arm had stage 3 disease, which could have biased the results in favour of rucaparib. The committee agreed with these points. The company presented PFS and PFS2 results from a May 2024 ad-hoc analysis. The results for OS were from the earlier 9 March 2023 data cut. The company considered the exact results confidential so they cannot be reported here. The committee noted that the PFS, PFS2 and OS results favoured bevacizumab compared with placebo. But, it recalled that the OS result was immature (see section 3.6). The committee concluded that rucaparib showed clinical benefit for PFS compared with placebo in people who would not be eligible to have bevacizumab in clinical practice.

Updated survival extrapolations for people who cannot have bevacizumab

3.25 The company updated its model to include the committee's preferred assumptions relevant to the bevacizumab ineligible subgroup. For the source of utility values, see section 3.16 and, for the relative dose intensity of rucaparib, see section 3.18. It also updated the parametric distributions for PFS, PFS2, OS and time to treatment discontinuation in its model. The EAG said that the company's distributions resulted in logically impossible relationships between PFS, PFS2 and OS. This was because the PFS curve crossed the PFS2 curve and the PFS2 curve crossed the OS curve. The company rectified this by using a capping rule to maintain the logical relationship between the 3 outcomes (so that, at all time points, PFS was less than or equal to PFS2 and PFS2 was less than or equal to OS). The EAG acknowledged that the available trial data made it difficult to fit logically complimentary PFS, PFS2 and OS curves. This was because the OS data was immature and from an earlier data cut than the PFS and PFS2 data. But

the EAG said that the need for the capping rule forced steep and clinically implausible rises and falls in the hazard ratios. It added that this was triggered relatively early in the model. The EAG thought that it was necessary to vary either the OS, or the PFS and PFS2 curves, to present a logically coherent set. It explained that using alternative OS curves did not resolve the early PFS and PFS2 capping for routine surveillance. So, the EAG retained the company's log-normal OS curves but used different PFS and PFS2 curves:

- For PFS, the EAG used a log-normal instead of odds spline with 1 knot for rucaparib and a log-normal instead of generalised gamma for routine surveillance.
- For PFS2, the EAG used a log-logistic instead of generalised gamma for rucaparib and a generalised gamma instead of log-normal for routine surveillance.

The EAG cautioned that both the company's and the EAG's approaches could be biased because of the immature OS data. It acknowledged that the alternative PFS curves that it had used may have underestimated the end of the ATHENA-MONO PFS Kaplan–Meier data for both rucaparib and routine surveillance. The company argued that the EAG's PFS curve substantially underestimated PFS for rucaparib. It emphasised that the PFS data from ATHENA-MONO was mature. It added that its chosen distribution was a much better fit to the data and captured the anticipated plateau that had been seen with other PARP inhibitors (see section 3.9). The company thought that, because of the maturity of the PFS data, it would be more reasonable to make changes to the OS curve. The committee shared the EAG's concerns about the incoherent modelled relationship between PFS, PFS2 and OS. It appreciated that the EAG had been unable to fit an alternative OS curve that resolved the early PFS and PFS2 capping instead of varying the PFS and PFS2 curves. But it noted that the OS data was much more uncertain. It thought that the most mature dataset should be used to inform the choice of parametric curves. It also thought that the company's PFS curve provided a better fit to the data than the EAG's, and preferred to use this in the modelling.

Acceptable ICER and cost-effectiveness results for people who

cannot have bevacizumab

3.26 The committee thought that the disconnect between the PFS, PFS2 and OS curves in the company's modelling (see section 3.25) led to a high level of uncertainty in the results. It also noted the additional uncertainty from using data from a non-randomised subgroup with small numbers in the placebo arm. Because of the high level of uncertainty, the committee concluded that an acceptable ICER for this subgroup would be around the middle of the range NICE considers a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained). Using the committee's preferred survival distributions (see section 3.25), the cost-effectiveness estimates were below the level considered an acceptable use of NHS resources. So, the committee recommended rucaparib for routine use in the NHS for people with BRCA mutation-negative HRD-negative or HRD-unknown advanced ovarian cancer who cannot have bevacizumab.

Equality

3.27 The committee considered whether NICE's duties under the equality legislation required it to alter or to add to its recommendations. It noted that rucaparib is less effective than olaparib plus bevacizumab. It thought that people with BRCA mutation-negative HRD-positive advanced ovarian cancer would need to be informed of this when considering treatment options. A patient organisation explained in its submission to NICE that some people with ovarian cancer (such as people with a learning disability or communication difficulties) may struggle to access treatments if they do not fully understand the treatment options and choices. The committee understood that this may include people who lack the capacity to:

- understand the information provided by the healthcare professional
- make an informed choice.

The committee thought that people would not be disadvantaged by the recommendations, providing that healthcare professionals:

- act in the interests of the people having treatment, in line with their usual responsibilities

- tailor their explanation to each person's level of understanding
- discuss the risks and benefits with the person's carers when applicable.

The committee concluded that there was no need to alter or add to its recommendations.

Uncaptured benefits

3.28 The committee considered whether rucaparib was innovative. It did not identify additional benefits of rucaparib not captured in the economic modelling. So, the committee concluded that rucaparib was not innovative for treating advanced ovarian cancer after response to first-line platinum-based chemotherapy.

Conclusion

Overall clinical effectiveness

3.29 The clinical-effectiveness evidence showed that rucaparib improved PFS compared with placebo in both the BRCA mutation-negative HRD-positive and BRCA mutation-negative HRD-negative populations. Rucaparib is also likely to work as well as bevacizumab alone. But the results of the ITCs suggest that is not as effective as olaparib plus bevacizumab.

Recommendation for BRCA mutation-negative HRD-positive advanced ovarian cancer

3.30 The committee concluded that most of the cost-effectiveness estimates for the BRCA mutation-negative HRD-positive subgroup incorporating its preferred assumptions were within what NICE considers a cost-effective use of NHS resources. So, it recommended rucaparib for routine use for maintenance treatment of BRCA mutation-negative HRD-positive advanced ovarian cancer after response to first-line platinum-based chemotherapy. But it noted that

people should be made aware that the results for this subgroup showed that rucaparib is less costly but less effective than olaparib plus bevacizumab.

Recommendations for BRCA mutation-negative HRD-negative advanced ovarian cancer

3.31 The committee recognised the high clinical need in the BRCA mutation-negative HRD-negative subgroup. But the cost-effectiveness estimates compared with bevacizumab and routine surveillance that incorporated the committee's preferred assumptions were not within the range that NICE considers a cost-effective use of NHS resources. So, the committee did not recommend rucaparib for routine use in the NHS for this population overall. It also did not consider that rucaparib met the criteria to be considered for a recommendation with managed access in this population. But rucaparib was shown to be cost effective compared with routine surveillance for the subgroup of people with BRCA mutation-negative HRD-negative or HRD-unknown advanced ovarian cancer who would not be eligible for treatment with bevacizumab. Bevacizumab ineligibility would be because either they are not eligible under the commissioning approval criteria, or because bevacizumab is contraindicated or not tolerated. So, the committee recommended rucaparib for routine use in the NHS for this group.

4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication.

4.2 Chapter 2 Appraisal and funding of cancer drugs from July 2016 (including the new Cancer Drugs Fund) – A new deal for patients, taxpayers and industry states that for those drugs with a draft recommendation for routine commissioning, interim funding will be available (from the overall Cancer Drugs Fund budget) from the point of marketing authorisation, or from release of positive draft guidance, whichever is later. Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or cost comparison evaluation), at which point funding will switch to routine commissioning budgets. The NHS England Cancer Drugs Fund list provides up-to-date information on all cancer treatments recommended by NICE since 2016. This includes whether they have received a marketing authorisation and been launched in the UK.

4.3 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final draft guidance.

4.4 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy and the healthcare professional responsible for their care thinks that rucaparib 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.

Chairs

Radha Todd and James Fotheringham
Chairs, 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.

Rachel Williams and Emma Douch
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Zoe Charles
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Project managers

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