NICE National Institute for Health and Care Excellence

NICE guidance

Niraparib 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.

Contents

This guidance replaces TA673.

1 Recommendations

1.1 Niraparib can be used as an option for the maintenance treatment of advanced epithelial (FIGO stages 3 and 4) high-grade ovarian, fallopian tube or primary peritoneal cancer after a response to first-line platinum-based chemotherapy in adults, only if:

- they did not have or could not tolerate bevacizumab as part of first-line induction chemotherapy
- the company provides niraparib according to the commercial arrangement.

1.2 This recommendation is not intended to affect maintenance treatment with niraparib for advanced (FIGO stages 3 and 4) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer after response to first-line platinum-based chemotherapy that was started in the Cancer Drugs Fund before this guidance was published and that is not covered by recommendation 1.1. For those people, niraparib will be funded by the company until they and their NHS healthcare professional consider it appropriate to stop.

What this means in practice

Niraparib must be funded in the NHS in England for the condition and population in the recommendations, if it is considered the most suitable treatment option. Niraparib must be funded in England within 90 days of final publication of this guidance.

There is enough evidence to show that niraparib provides benefits and value for money, so it can be used routinely across the NHS in this population.

NICE has produced tools and resources to support the implementation of this guidance.

Why the committee made these recommendations

This evaluation reviews the evidence for niraparib for the maintenance treatment of advanced (FIGO stages 3 and 4) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer (from here, advanced ovarian cancer) after response to first-line platinum-based chemotherapy in adults (NICE technology appraisal guidance 673). It also reviews new evidence collected during the managed access period, which includes evidence from clinical trials and from people having treatment in the NHS in England.

For this evaluation, niraparib was considered only for people who did not have or could not tolerate bevacizumab as part of first-line induction chemotherapy, in line with the evidence provided by the company. This does not include everyone who it is licensed for.

For people who would not have bevacizumab, usual treatment for advanced ovarian cancer is olaparib or rucaparib.

Clinical trial evidence shows that niraparib increases how long people have before their condition gets worse compared with placebo. Niraparib has not been directly compared in a clinical trial with olaparib or rucaparib. Results from indirect comparisons are highly uncertain but suggest that niraparib may work as well as olaparib and rucaparib.

The cost-effectiveness evidence, based on an assumption that niraparib works as well as olaparib and rucaparib, suggests that costs for niraparib are similar to or lower than costs for olaparib and rucaparib. The most likely cost-effectiveness estimates show that niraparib is a cost-effective option. So, it can be used.

2 Information about niraparib

Marketing authorisation indication

2.1 Niraparib (Zejula, GlaxoSmithKline) is indicated 'as a monotherapy for the maintenance treatment of adult patients with advanced epithelial (FIGO Stages III and IV) high-grade 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 niraparib.

Price

2.3 The list price of niraparib is £4,500 for a 56-pack of 100-mg tablets, and £6,750 for an 84-pack of 100-mg tablets (BNF online, accessed November 2025).

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

Sustainability

2.5 For information, GlaxoSmithKline did not disclose its Carbon Reduction Plan for UK carbon emissions.

3 Committee discussion

The evaluation committee considered evidence submitted by GlaxoSmithKline, 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

3.1 Ovarian cancer is a general term referring to ovarian, fallopian tube and peritoneal cancer. Ovarian cancer is often linked to breast cancer gene (BRCA) mutations and homologous recombination deficiency (HRD) status, which result in an increased risk of developing the condition. The FIGO (International Federation of Gynaecology and Obstetrics) system classifies ovarian cancer into different stages. Advanced stages are characterised by the spread of cancer into the abdominal cavity or to lymph nodes (stage 3) or the presence of distant metastases, such as in the bones, liver or lungs (stage 4). Approximately 60% of people with ovarian cancer are diagnosed at an advanced stage (FIGO stage 3 to 4). The patient experts explained that even when initial treatment is successful, people with ovarian cancer and their families face a great deal of anxiety about the risk of recurrence. They added that people may face toxicity with the available maintenance treatments (see section 3.2). So, it is important for people to have alternative treatment options. The patient and clinical experts explained that niraparib would offer people an additional option for maintenance treatment after first-line treatment. The committee concluded that people with the condition and healthcare professionals would welcome a further treatment option for maintenance treatment of advanced ovarian cancer.

Clinical management

Treatment pathway and comparators

3.2 First-line treatment for advanced ovarian cancer is surgery and platinum-based chemotherapy (with or without bevacizumab). Surgical options are primary

debulking surgery before first-line chemotherapy treatment, or interval debulking surgery between cycles of first-line chemotherapy. Some people may also initially have platinum-based chemotherapy without debulking surgery. People whose cancer has a complete or partial response to platinum-based chemotherapy typically then have first-line maintenance treatment. First-line maintenance treatment options are:

- bevacizumab, for people whose cancer responded to first-line platinum-based chemotherapy with bevacizumab
- olaparib with bevacizumab, for people whose cancer:
  - responded to first-line platinum-based chemotherapy with bevacizumab and
  - is HRD positive (defined as having either a BRCA1 or BRCA2 mutation, or genomic instability; see NICE's technology appraisal guidance on olaparib with bevacizumab for maintenance treatment of advanced high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer [TA946]).
- olaparib, for people whose cancer:
  - responded to first-line platinum-based chemotherapy and
  - 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 [TA962])
- rucaparib for people whose cancer responded to first-line platinum-based chemotherapy and is:
  - BRCA mutation negative and HRD positive, or
  - BRCA mutation negative, and the HRD status is negative or unknown, and bevacizumab is not an option (see NICE's technology appraisal guidance on rucaparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy [TA1055]).

    The company positioned niraparib for people who had a complete or

partial response to first-line platinum-based chemotherapy. This included people regardless of BRCA mutation or HRD status. The company stated that olaparib and rucaparib were the relevant comparators. It added that poly-ADP-ribose polymerase (PARP) inhibitor monotherapy (such as niraparib) is an option for people who did not have or could not tolerate bevacizumab during induction chemotherapy. The company noted that in TA946, olaparib with bevacizumab was recommended as an option for people whose cancer responded to first-line platinum-based chemotherapy with bevacizumab. Similarly, the commissioning criteria for bevacizumab as a maintenance treatment specify that it can only be used after first-line chemotherapy with bevacizumab. It also highlighted that systemic anti-cancer therapy (SACT) data for niraparib showed that most people did not have bevacizumab during induction treatment and have platinum-based chemotherapy alone. So, the company did not think olaparib with bevacizumab or bevacizumab monotherapy were relevant comparators.

Based on the company's positioning of niraparib, the EAG agreed with the company's rationale for excluding olaparib with bevacizumab, and bevacizumab monotherapy, as comparators. It noted that in TA1055 for rucaparib (also a PARP inhibitor), for the BRCA mutation-negative HRD-negative or HRD-unknown population, the guidance recommends rucaparib maintenance treatment only for people for whom bevacizumab maintenance treatment is not suitable. So, it suggested that any recommendation for niraparib should be consistent and apply if bevacizumab is not a treatment option. A clinical expert stated that people who would usually be offered bevacizumab are those who have residual disease after surgery, particularly people with ascites and pleural effusions. People with complete clearance of disease would usually be offered maintenance treatment without bevacizumab.

The committee noted the difference between the populations that would and would not usually be offered maintenance treatment with bevacizumab (that is, bevacizumab monotherapy or bevacizumab with olaparib). It also noted that for people for whom maintenance treatment with bevacizumab is suitable, niraparib may also be suitable. But, it had not seen comparisons of niraparib against bevacizumab monotherapy or

bevacizumab with olaparib. The committee concluded that, for people for whom bevacizumab is not suitable, olaparib and rucaparib are the appropriate comparators. It further concluded that, in the absence of comparisons against bevacizumab monotherapy and olaparib with bevacizumab, niraparib could only be recommended for people for whom bevacizumab is not suitable.

Clinical effectiveness

PRIMA

3.3 PRIMA was a double-blind, randomised controlled trial comparing niraparib (n=487) with placebo (n=246) as maintenance treatment of advanced ovarian cancer. It included people with or without a BRCA gene mutation, who had advanced (FIGO stages 3 or 4) high-grade ovarian, fallopian tube or primary peritoneal cancer that was in response (complete or partial) to first-line platinum-based chemotherapy. The primary endpoint was progression-free survival (PFS) based on blinded independent central review (BICR). PRIMA excluded people with stage 3 cancer who had no visible residual disease after primary debulking surgery. The company therefore referred to the trial population as a high-risk population. Its rationale for excluding people without visible residual disease was that their prognosis was thought to be better than that of other groups with advanced ovarian cancer. At the start of the trial, everyone in the niraparib arm had a 300-mg daily starting dose. But in November 2017, the trial was changed to incorporate an individualised starting dose, which depended on body weight and platelet count. People had treatment until disease progression or up to a maximum of 36 months, but people who were benefitting from treatment according to investigator assessment could continue having treatment beyond 36 months.

The median follow up was 73.9 months in the niraparib arm and 73.8 months in the placebo arm. At the final data cut (8 April 2024), results were reported for investigator-assessed PFS (among other outcomes), which was used in the company's economic modelling (see section 3.8). Median investigator-assessed PFS was 13.8 months in the niraparib arm and 8.2 months in the placebo arm in

the intention-to-treat (ITT) population (hazard ratio [HR] 0.66; 95% confidence interval [CI] 0.55 to 0.78). Median overall survival (OS) was 46.6 months in the niraparib arm and 48.8 months in the placebo arm in the ITT population (HR 1.01; 95% CI 0.84 to 1.23).

At the committee meeting, a clinical expert highlighted that OS rates have improved since PARP inhibitors were introduced in UK clinical practice. They stated that an OS benefit was likely not shown in the PRIMA trial because it was not powered to detect differences in OS. Additionally, some people in the placebo arm crossed over to have a PARP inhibitor after progression, which diluted the OS benefit for niraparib. The committee concluded that niraparib improves PFS compared with placebo for people with advanced ovarian cancer that has completely or partially responded to first-line platinum-based chemotherapy.

PRIME

3.4 PRIME was a double-blind, randomised controlled trial comparing niraparib (n=255) with placebo (n=129) as maintenance treatment of advanced ovarian cancer. It included people with or without a BRCA gene mutation, who had advanced (FIGO stages 3 and 4) high-grade ovarian, fallopian tube or primary peritoneal cancer that was in response (complete or partial) to first-line platinum-based chemotherapy. The primary endpoint was PFS based on BICR. In contrast to the PRIMA trial, the PRIME trial included people with stage 3 cancer who had no visible residual disease after primary debulking surgery. The company therefore referred to the trial population as a mixed-risk population. People who were randomised to the niraparib arm of the trial had an individualised dose that depended on body weight and platelet count. People had treatment until disease progression or unacceptable toxicity, up to a maximum of 36 months.

The median follow up in the niraparib population was 27.5 months, and 27.6 months in the placebo population. At the primary analysis clinical cut off (30 September 2021), median PFS as assessed by BICR was 24.8 months in the niraparib arm and 8.3 months in the placebo arm in the ITT population (HR 0.45; 95% CI 0.34 to 0.60). There was also a statistically significant improvement in investigator-assessed PFS for niraparib (HR 0.47; 95% CI 0.36 to 0.62). Median OS was not reached in either treatment arm, but the data showed a numerical

benefit in favour of niraparib (HR 0.63; 95% CI 0.38 to 1.03). The company stated that the results from PRIME complement findings from PRIMA by providing data on the efficacy of niraparib regardless of risk of relapse (that is, in a mixed-risk population). The committee concluded that the results from PRIME supported the findings from PRIMA that niraparib improves PFS compared with placebo.

Indirect treatment comparisons

Company's indirect treatment comparisons

3.5 Because there was no direct evidence comparing niraparib with olaparib or rucaparib, the company did Bucher indirect treatment comparisons (ITCs). The primary objectives of the ITCs were to estimate the relative treatment effect for:

- niraparib compared with olaparib in the BRCA-mutation-positive population
- niraparib compared with rucaparib in the BRCA-mutation-negative population.

The company identified 4 trials that were potentially suitable for the ITCs: PRIMA, PRIME, SOLO-1 and ATHENA-MONO. SOLO-1 was a double-blind, randomised controlled trial comparing olaparib with placebo as a maintenance treatment of advanced ovarian cancer. ATHENA-MONO was a double-blind, randomised controlled trial comparing rucaparib with placebo as a maintenance treatment of advanced ovarian cancer. Both trials included people with stage 3 cancer who had no visible residual disease after primary debulking surgery. After the feasibility assessment, the company concluded that any ITCs involving these trials were likely inappropriate and fundamentally flawed because of differences in the timing and type of HRD tests used and inclusion criteria about visible residual disease status. So, it clarified that the ITCs were exploratory.

For the ITCs comparing niraparib with olaparib for investigator-assessed PFS and PFS based on BICR, the company used subgroup data from SOLO-1. The subgroup comprised people with a BRCA mutation who were considered high risk (that is, they had either stage 3 cancer with visible residual disease after

primary debulking surgery, or stage 4 cancer). It chose this approach to allow a fairer comparison with the PRIMA population with respect to residual disease status. For both PFS outcomes, the results were not statistically significant and had wide confidence intervals. The exact results are considered confidential and cannot be reported here. The company did not do an ITC for OS because SOLO-1 did not report OS data for the same high-risk subgroup.

For comparisons of niraparib with rucaparib, the company stated that it was more suitable to use data from PRIME than from PRIMA. This was because subgroup analyses from ATHENA-MONO have not been published in a population comparable to that of PRIMA (that is, excluded people with stage 3 cancer without visual residual disease). So, it compared niraparib with rucaparib in a broader, mixed-risk population. For investigator-assessed PFS, the company only did comparisons in the ITT population because of data limitations. For PFS based on BICR, it did ITCs in the ITT population, the BRCA-mutation-negative HRD-positive subgroup, and the BRCA-mutation-negative HRD-negative subgroup. For all analyses, the results were not statistically significant. For OS, it did an ITC in the ITT population. As for PFS, the results were not statistically significant. The company did not do ITCs for the overall BRCA-mutation-negative subgroup.

Reliability of indirect treatment comparisons

3.6 The EAG highlighted that there were considerable differences in the baseline characteristics between the ITT populations of the PRIME and ATHENA-MONO trials. For example, differences in the median age, the proportion of people with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 and the proportion of people with an ovarian primary tumour location. It was also concerned about the relevance of the PRIME trial to UK clinical practice. For example, PRIME solely comprised a Chinese population, and HRD status was assessed using an unvalidated assay. The clinical experts at the committee meeting stated that the guidelines in China are similar to those in Europe, so this was not a concern for generalisability to UK clinical practice. But, the HRD assay that was used in PRIME was different from that used in UK clinical practice, so this may have affected generalisability. The company stated that the HRD assay

used, the BGI Genomics HRD assay, has been validated in a recent study.

The EAG believed that using PRIMA trial data (rather than PRIME trial data) for the ITCs between niraparib and rucaparib would better reflect clinical practice and it used this data to update the ITCs. It stated that the most robust use of the data from both the ATHENA-MONO and PRIMA trials would be to do separate comparisons for the BRCA-mutation-negative HRD-negative subgroup and BRCA-mutation-negative HRD-positive subgroup. So, for these subgroups, it did ITCs for investigator-assessed PFS and OS. The results are considered confidential and cannot be reported here. The EAG acknowledged that there were also differences in the baseline characteristics of the ITT populations of the PRIMA and ATHENA-MONO trials and noted there were limitations in both its and the company's ITCs. The company stated that comparisons of the high-risk population from PRIMA (see section 3.5) to mixed-risk populations from other trials were inappropriate. This was because restricting ITCs based on PRIMA to a high-risk population was essential for valid statistical inference. But the company stated that the split of high-risk and low-risk populations in the PRIME and ATHENA-MONO trials was unknown. So, the EAG noted that the company's concerns about the statistical validity of ITCs involving PRIMA may also apply to the ITCs using PRIME. The EAG's clinical experts indicated that a high-risk population is likely to experience a greater relative treatment benefit from PARP inhibitors than a low-risk population. The EAG added that this was also supported by data from both ATHENA-MONO and SOLO-1. So, it thought that the ITCs done using the PRIMA trial were unlikely to be biased in favour of rucaparib.

The committee noted the EAG's concerns about the use of PRIME data. It also noted the differences in the baseline characteristics between PRIME and ATHENA-MONO. It added that the company had listed a number of baseline characteristics that differed between the trials but had not specified whether these factors were prognostic factors or treatment effect modifiers. It stated that this added uncertainty about the impact that these may have on the results. The committee acknowledged that the potential treatment effect modifiers could not be adjusted for using more complex statistical methods like a multi-level network meta-regression because of the lack of patient-level data for either trial. So, overall, it thought the results of any ITCs using the PRIME trial would be unlikely to generate reliable estimates of relative effectiveness. The committee then considered whether the PRIMA trial would be more suitable, for which patient-

level data was available. It considered whether a multi-level network meta-regression could have been done to attempt to adjust for the treatment effect modifiers. The company stated that even if a multi-level network meta-regression were done, this would be limited by any analyses that included PRIMA, because of the lack of subgroup data for ATHENA-MONO and SOLO-1 for the high-risk population (with the exception of PFS data for SOLO-1). The company highlighted that there were differences in the maturity of the OS data between the ITT populations in PRIMA and ATHENA-MONO: OS data was approximately 60% mature in PRIMA and only about 35% mature in ATHENA-MONO. The company had not attempted to adjust for crossover within the clinical trials (see section 3.3), which the committee noted added further uncertainty to the OS results. The committee stated that multi-level network meta-regression using PRIMA versus the comparator trials would likely have produced more reliable results than both the company's and EAG's ITCs. But it acknowledged that the differences in the visible residual disease status between PRIMA and the comparator trials, as well as further differences in the eligibility criteria noted in the company submission, would likely limit the reliability of a multi-level network meta-regression. The committee concluded that the company's and EAG's ITC results produced highly uncertain estimates of the effectiveness of niraparib compared with the comparators. It further concluded that it was highly uncertain whether any further indirect comparisons using data from PRIME or PRIMA would produce robust results.

Assumption of clinical equivalence

3.7 The company assumed clinical equivalence between niraparib and the comparators, olaparib and rucaparib. For the comparison against olaparib, the company assumed equivalence based on the results of the ITCs of PRIMA versus SOLO-1 in the high-risk population that showed no statistically significant difference in PFS. It did not do an ITC for OS (see section 3.5), but it noted that clinical equivalence in OS was supported by real-world evidence. It provided SACT data for niraparib and olaparib that showed overlapping OS Kaplan–Meier curves up to 27 months before divergence. The company stated that the divergence was caused by small patient numbers in the tail of the Kaplan–Meier curve. It also stated that clinical equivalence between niraparib and olaparib was supported by a South Korean real-world evidence study in a BRCA-mutation-

positive population, in which there was no statistically significant difference in PFS or OS. Additionally, the company's clinical experts stated that the UK SACT data and the South Korean real-world evidence study provided evidence of a class effect across PARP inhibitors.

For the comparison against rucaparib, the company justified the assumption of clinical equivalence with the results of the ITC for PFS and OS (see section 3.5) showing no statistically significant differences. It added that the class effect across PARP inhibitors also applied to this comparison. The company also provided a 'fixed margin analysis' (described in Kaul and Diamond 2007) to support its claims of clinical equivalence. It thought that non-inferiority was demonstrated for 2 of the 6 ITCs for which the fixed margin analysis was done.

The EAG had several concerns with the company's fixed margin analysis. It noted that fixed margin analyses were not possible for OS results because data from ATHENA-MONO did not show superiority of rucaparib over placebo in either of the populations for which the company did ITCs. For PFS, based on BICR, it noted a range of non-inferiority margins depending on the subgroup. It was concerned that this disparity may have indicated that the margins were not clinically meaningful. Also, it was concerned that the 'dual use' of data from ATHENA-MONO and SOLO-1 may bias the assessment for non-inferiority. For example, ATHENA-MONO was used to derive the non-inferiority margin, which was then also subsequently used to assess non-inferiority for the ITC of niraparib to rucaparib.

The company also did a Monte-Carlo simulation to estimate the probability that the hazard ratio for niraparib compared with placebo was lower than the hazard ratio for the comparator compared with placebo. Based on the population and outcome, the non-inferiority probabilities from this simulation ranged from 16.9% to 81.2%. The EAG noted that the company's categorisation of the Monte-Carlo simulation results may be open to interpretation. For example, one of the categorisations was 'close to 50%', which the EAG thought did not provide a definitive assessment of non-inferiority. The EAG also noted limitations with using normal distributions parameterised to the reported ratios. It stated that the hazard ratios were not normally distributed and that normal distributions should instead have been applied to the logarithm of the hazard ratios. It stated that it would have preferred standard non-inferiority analyses using widely implemented

approaches. It added that it would have preferred clinically validated non-inferiority margins derived from data sources that did not form a core component of the analyses. Overall, the EAG thought that equivalence, or non-inferiority, between niraparib and the comparator treatments had not been demonstrated in a statistically robust, or clinically meaningful, manner.

The committee recalled that the company's and EAG's ITC estimates of the relative effectiveness of niraparib versus the comparators were highly uncertain (see section 3.6). It noted that a recent meta-analysis of PARP inhibitors for maintenance treatment after response to first-line platinum-based chemotherapy (Petousis et al. 2025) showed comparable efficacy between niraparib, olaparib and rucaparib. This was for the combined outcome of death or recurrence. But the meta-analysis also showed that niraparib had a higher incidence of high-grade adverse events. A clinical expert stated that, based on their experience using PARP inhibitors, they would be unable to say if there are differences in effectiveness between different PARP inhibitors. Another clinical expert agreed and stated that, based on their experience, there is very little difference in effectiveness between the PARP inhibitors. The clinical experts also stated that the incidence of adverse events in the niraparib clinical trials was higher than is seen in clinical practice. They explained that, in PRIME and PRIMA, some people had a 300-mg daily starting dose based on their weight and platelet count. But in clinical practice, most people would start on a 200-mg daily dose, regardless of weight or platelet count, which is more tolerable. They added that although the different PARP inhibitors have different toxicity profiles, a choice of PARP inhibitors is valuable to patients. This is because some people may tolerate 1 PARP inhibitor better than another. A clinical expert also stated that olaparib has more drug interactions than niraparib and reiterated that having different options is important to healthcare professionals and people with the condition. The committee thought it highly uncertain that any further indirect comparisons would produce robust estimates of the relative effectiveness of niraparib against the comparators, given the differences between trials (see section 3.6). It acknowledged that healthcare professionals had experience using niraparib through the Cancer Drugs Fund and noted that healthcare professionals believed there was very little difference in the effectiveness between PARP inhibitors. On balance, it concluded that it preferred to assume clinical equivalence between niraparib and olaparib in the BRCA-mutation-positive population, and between niraparib and rucaparib in the BRCA-mutation-negative population. But it thought

that this was associated with substantial uncertainty.

Economic model

Company's modelling approach

3.8 The company presented a 3-state partitioned survival model to estimate the cost effectiveness of niraparib compared with olaparib in the BRCA-mutation-positive population and compared with rucaparib in the BRCA-mutation-negative population. The 3 health states were progression free, progressed disease and death. The company stated that a 3-state model was used, rather than a 4-state model, because of the lack of relevant PFS on the second line of treatment (PFS2) data in the high-risk population of the relevant trials. This would be needed to do appropriate ITC analyses. It added that including PFS2 data was not expected to have a substantial impact on the model results. This was because the treatment pathway after disease progression with PARP inhibitor monotherapy is the same irrespective of the first-line PARP inhibitor used. The EAG noted that all recent appraisals in advanced ovarian cancer used a 4-state model and incorporated PFS2. It stated that a 4-state model using PFS2 data would have been more appropriate and noted this as a limitation in the company's analysis. The committee recalled that it preferred to assume clinical equivalence between niraparib and the comparators (see section 3.7). So, including PFS2 was not likely to have a substantial impact on the model results. The committee accepted the company's model for decision making.

Data to inform comparisons in the economic model

3.9 In line with the assumption of clinical equivalence (see section 3.7), the company applied a hazard ratio of 1 to the baseline niraparib curves for PFS and OS to generate the olaparib and rucaparib survival curves. The EAG stated that it did not think that the evidence to support the company's assumption of clinical equivalence between niraparib and the comparators was sufficiently robust (see section 3.7). It added that despite the limitations, the ITCs were the only available measures of the relative efficacy of niraparib and the comparators. So, it

preferred to use ITC estimates in the model.

For the comparison against olaparib, data from a high-risk population from SOLO-1 were only available for PFS. So, the EAG did ITCs for PFS and OS using data from the overall BRCA-mutation-positive subgroups from the PRIMA and SOLO-1 trials. It then applied the resulting hazard ratios to the baseline niraparib curves to generate PFS (generalised gamma) and OS (1-knot normal spline) curves for olaparib.

For the comparison against rucaparib, the EAG generated a pooled BRCA-mutation-negative population from ATHENA-MONO PFS data. It then used this data to do an ITC in the BRCA-mutation-negative subgroup for PFS. In its base case, it applied the resulting hazard ratio to the baseline niraparib curve (generalised gamma) to generate a PFS curve for rucaparib. The EAG did not have access to the same ATHENA-MONO data for OS, so was unable to create a pooled population. So instead, it did 2 separate analyses for the BRCA-mutation-negative HRD-negative and BRCA-mutation-negative HRD-positive subgroups. This involved applying the hazard ratios from the EAG's ITCs for each subgroup (see section 3.6) to the baseline niraparib OS curve for the BRCA-mutation-negative population. The EAG used the resulting survival curves to produce a range of cost-effectiveness estimates for the BRCA-mutation-negative subgroup. The committee recalled that it thought the company's and EAG's ITC results produced highly uncertain estimates of the relative effectiveness of niraparib compared with the comparators (see section 3.6). It also noted that the EAG's base-case analyses (see section 3.11) resulted in quality-adjusted life year (QALY) losses for niraparib compared with olaparib and rucaparib that were clinically implausible. So, it did not believe these estimates suitable for use in the model to generate survival curves for olaparib and rucaparib. Because the committee preferred to assume clinical equivalence (see section 3.7), it thought that the company's approach should be used in its preferred analysis (that is, applying a hazard ratio of 1 to the baseline PFS and OS niraparib curves to generate the olaparib and rucaparib curves for PFS and OS).

Time to treatment discontinuation

3.10 To inform the proportion of people in the progression-free health state having

treatment in the niraparib arm, the company used time to treatment discontinuation (TTD) data from PRIMA. It used BRCA-mutation-positive or BRCA-mutation-negative subgroup Kaplan–Meier data directly for each respective comparison, for the first 77 months of the model. After this, the proportion remaining on treatment was based on the survival curve with the best statistical fit. Additionally, the company applied a stopping rule in which 90% of people stopped treatment at 36 months. This was based on clinical expert opinion that estimated the proportion of people remaining on niraparib after 36 months would range from 5% to 10%. The company also noted that PRIMA had a 36-month stopping rule. For olaparib and rucaparib, the company did not have access to the TTD Kaplan–Meier curves from SOLO-1 and ATHENA-MONO. So, it adjusted the PFS curves using adverse event discontinuation probabilities from the respective trials to estimate TTD. The company then applied the same approach as it did for niraparib, that 90% of people stop treatment at a set time point. For olaparib it used a 24-month stopping rule in line with SOLO-1, and for rucaparib it used a 24-month stopping rule in line with its summary of product characteristics.

The EAG noted that the company's approach resulted in only 10% of people who were having niraparib at 36 months continuing treatment beyond this timepoint, rather than 10% of the starting population. But it acknowledged that the company's expert meeting minutes stated that treatment continuation for someone who is progression free beyond 36 months would be extremely rare. The EAG also noted that SACT data for the BRCA-mutation-positive subgroup showed a higher proportion of people on treatment with niraparib or olaparib at 36 months than was assumed in the company's model. For niraparib, 27.5% of people remained on treatment at 36 months, decreasing to 17% at 42 months. For olaparib, SACT data showed that 13% of people remained on treatment at 36 months. So, it noted that there was uncertainty about the proportion of people remaining on treatment beyond the respective stopping rules. It also noted that in TA1055, there was a 24-month stopping rule, in which all people stopped treatment with rucaparib at 24 months. The EAG thought that it was more appropriate to use the direct trial data when available. But because of the lack of publicly available TTD discontinuation data for the comparators, the EAG also estimated treatment discontinuation based on PFS and adverse events to estimate treatment discontinuation in its base case. To maintain consistency with the accepted approach in TA1055, it assumed that all people stopped treatment

with rucaparib at 24 months in its base case (rather than 90%). It also preferred to use the same stopping rule for olaparib. For niraparib, the EAG explored applying standard parametric curves to the observed Kaplan–Meier TTD curve. But it noted that none of these curves provided a good fit to the observed data. So, it preferred to use the observed Kaplan–Meier data until 36 months, after which all people were assumed to stop treatment. The clinical experts stated that the proportion of people remaining on niraparib and olaparib at 36 months onwards in the SACT data was a lot higher than they would expect. A clinical expert added that the people who would continue treatment are those who have visible disease that has not progressed, but this proportion would be very small at 36 months. The committee noted that clinical expert opinion and SACT data supported that a proportion of people may continue treatment beyond the respective stopping rule time points. So, it thought that the EAG's base case may underestimate costs because it assumed that all people stop treatment at 24 months for olaparib and rucaparib, and at 36 months for niraparib. It thought that the company's base case was more in line with the clinical expert view that a small proportion of people would remain on treatment beyond these time points. So, it concluded that it preferred to assume 90% of people stop treatment at 24 months with olaparib and rucaparib, and at 36 months with niraparib.

Cost-effectiveness estimates

Company and EAG cost-effectiveness estimates

3.11 Because of the confidential commercial arrangements for the prices of niraparib, the comparators and the other treatments in the model, the exact cost-effectiveness estimates are confidential and cannot be reported here. For the company base case, for both the BRCA-mutation-positive and BRCA-mutation-negative subgroups, the QALY difference between niraparib and the comparators was negligible and niraparib was cost saving. Cost effectiveness was assessed by calculating net health benefit. For both subgroups, the net health benefit values at threshold values of £20,000 per QALY gained and at £30,000 per QALY gained were positive.

In the EAG's base case, for both the BRCA-mutation-positive and BRCA-

mutation-negative subgroups, niraparib was associated with fewer QALYs and was cost saving. This resulted in south-west quadrant incremental cost-effectiveness ratios (ICERs) for niraparib.

The committee's preferences

3.12 For the cost-effectiveness analysis, the committee's preferred assumptions were in line with the company base case. It preferred to assume:

- clinical equivalence between niraparib and olaparib in the BRCA-mutation-positive population, with a hazard ratio of 1 applied to the baseline niraparib PFS and OS curves to generate the olaparib PFS and OS curves (see section 3.7 and section 3.9)
- clinical equivalence between niraparib and rucaparib in the BRCA-mutation-negative population, with a hazard ratio of 1 applied to the baseline niraparib PFS and OS curves to generate the rucaparib PFS and OS curves (see section 3.7 and section 3.9)
- 90% of people stop treatment with niraparib at 36 months (see section 3.10)
- 90% of people stop treatment with olaparib and rucaparib at 24 months (see section 3.10).

Other factors

Equality

3.13 NICE's guideline on identifying and managing familial and genetic risk for ovarian cancer notes that the rate of familial ovarian cancer is higher in people of Ashkenazi Jewish ethnicity. Race is a protected characteristic under the Equality Act 2010. But because its recommendation does not restrict access to treatment for some people over others, the committee agreed this was not a potential equality issue. A patient organisation noted 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 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 change or add to its recommendations.

Conclusion

3.14 The committee had seen comparisons of niraparib against olaparib for the BRCA-mutation-positive subgroup and against rucaparib for the BRCA-mutation-negative subgroup. For these subgroups, the committee concluded that the most plausible ICERs were within what NICE considers a cost-effective use of NHS resources. So, it recommended niraparib for routine use for the maintenance treatment of advanced epithelial high-grade ovarian, fallopian tube or primary peritoneal cancer after a response to first-line platinum-based chemotherapy in adults who did not have or could not tolerate bevacizumab as part of first-line induction chemotherapy.

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 90 days of its date of publication.

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

4.3 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 60 days 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 or peritoneal cancer that responded to first-line platinum-based chemotherapy and the healthcare professional responsible for their care thinks that niraparib is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Evaluation committee members and NICE project team

Evaluation committee members

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

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

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

Chair

Radha Todd
Chair, technology appraisal committee A

NICE project team

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

Dilan Savani
Technical lead

Caron Jones
Technical adviser

Jennifer Upton

Project manager

Ian Watson
Associate director

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