Olaparib for maintenance treatment of relapsed, platinum-sensitive, BRCA mutation-positive ovarian, fallopian tube and peritoneal cancer after response to second-line or subsequent platinum-based chemotherapy

Technology appraisal guidance

Published: 27 January 2016

nice.org.uk/guidance/ta381

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 are 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.

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

1   Recommendations

1.1   Olaparib is recommended within its marketing authorisation as an option for treating adults with relapsed, platinum sensitive ovarian, fallopian tube or peritoneal cancer who have BRCA1 or BRCA2 mutations and whose disease has responded to platinum based chemotherapy only if:

- they have had 3 or more courses of platinum based chemotherapy and

- the drug cost of olaparib for people who remain on treatment after 15 months will be met by the company.

1.2   People whose treatment with olaparib is not recommended in this NICE guidance, but was started within the NHS before this guidance was published, should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.

2 The technology

2.1 Olaparib (Lynparza; AstraZeneca) is a poly-ADP-ribose polymerase (PARP) enzyme inhibitor that selectively kills tumour cells with an impaired homologous recombination DNA repair pathway while sparing normal cells. Olaparib has a marketing authorisation in the UK as 'monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed BRCA-mutated (germline and/or somatic) high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy'. It is administered orally and the recommended dose is 400 mg twice daily.

2.2 The summary of product characteristics lists the following very common adverse reactions for olaparib: decreased appetite; headache; dizziness; dysgeusia; nausea; vomiting; diarrhoea; dyspepsia; and fatigue. For full details of adverse reactions and contraindications, see the summary of product characteristics.

2.3 The list price of olaparib is £3550 per pack, with each pack containing 448 capsules of 50 mg each (equivalent to 28 days' treatment of 16 capsules per day at continuous full dose of treatment, price excludes VAT, 'British national formulary' [BNF] edition 70). The company has agreed a patient access scheme with the Department of Health, and this was updated after the second appraisal committee meeting. This scheme involves the NHS paying for a patient's treatment with olaparib up to a certain time, with the company providing olaparib free-of-charge beyond that point and for as long as each individual patient continues to have olaparib. The Department of Health considered that this patient access scheme would not constitute an excessive administrative burden on the NHS.

3   Evidence

The Appraisal Committee considered evidence submitted by AstraZeneca and a review of this submission by the Evidence Review Group (ERG). See the Committee papers for full details of the evidence.

Clinical effectiveness

3.1   The key clinical evidence came from a phase II trial (Study 19) that was an international, multicentre, double-blind, randomised, placebo-controlled trial comparing olaparib with routine surveillance (a 'watch and wait' strategy) in patients with platinum-sensitive epithelial ovarian cancer (including fallopian tube and peritoneal cancer). Study 19 included 265 patients and took place at 82 study centres in 16 countries. The patients started olaparib or matching placebo within 8 weeks of their last dose of a platinum-containing regimen. Patients were included in the trial only if their disease was platinum-sensitive, which was defined as disease progression more than 6 months after completing their penultimate platinum regimen. The mean age of the trial population was 57 years and 96% of patients were white.

3.2   The company's submission focused on a subgroup of 136 patients with BRCA gene mutations, because this is the population covered by the marketing authorisation. In Study 19, knowledge of BRCA-mutation status was not a requirement for entry into the study. BRCA-mutation status was determined for almost all patients in the trial, but this was largely done retrospectively. In the original clinical study report, the subgroup analysis by BRCA-mutation status was based on germline-BRCA status at entry to the study. In the analysis presented in the submission, and on which the licensed indication is based, patients were classified as having the BRCA mutation (referred to as BRCAm) if the mutation was identified in a sample of either their blood (germline mutation) or their tumour (somatic or tumour mutation).

3.3   The company explained that the demographic characteristics of the BRCAm subgroup were generally consistent with the whole trial population and the 2 groups were well balanced in terms of age and ethnicity. There were fewer people aged over 65 years in the BRCAm subgroup than the whole trial population, but the company explained that this is consistent with inherited

germline BRCA mutations in relapsed, high-grade serous epithelial ovarian cancer.

3.4   Olaparib was associated with a statistically significant improvement in the primary outcome of progression-free survival for the whole trial population and also for the BRCAm subgroup. For the whole population, median progression-free survival was 8.4 months in the olaparib group and 4.8 months in the placebo group (hazard ratio [HR] 0.35; 95% confidence interval [CI] 0.25 to 0.49). For the BRCAm subgroup, median progression-free survival was 11.2 months in the olaparib group and 4.3 months in the placebo group (HR 0.18; 95% CI 0.10 to 0.31).

3.5   The company explained that Study 19 was not powered to assess overall survival and that survival data were immature. An interim analysis of overall survival was done in November 2012. Crossover to olaparib was not permitted during the treatment period of the study, but after completing the study 23% of patients in the placebo arm had a poly-ADP-ribose polymerase (PARP) inhibitor (a second PARP inhibitor was not permitted in the olaparib group). The company specified that this was likely to have a confounding effect on the overall survival results, in favour of the placebo group. Therefore, the company performed an additional post-hoc analysis of overall survival to investigate the effect of crossover to olaparib from the placebo arm. A restriction method was used that excluded data from centres in which some patients had received PARP inhibitors after disease progression. This excluded 25% (67/265) of patients in the whole trial population and 29% (39/136) of patients in the BRCAm population.

3.6   For the whole trial population, overall survival analysis was done when 58% of the patients had died (November 2012). Median overall survival was 29.8 months (95% CI 27.2 to 35.7) in the olaparib arm and 27.8 months (95% CI 24.4 to 34.0) in the placebo arm. A statistically significant difference in median overall survival was not identified in the whole trial population at this point (HR 0.88; 95% CI 0.64 to 1.21; p=0.44).

3.7   For the BRCAm subgroup, overall survival analysis was done when 52% of the patients had died. A statistically significant difference in overall survival was not identified at this point (median 34.9 months in the olaparib arm and 31.9 months in the placebo arm; HR for death 0.73; 95% CI 0.45 to 1.17;

p=0.19). In the analysis that excluded patients who had a PARP inhibitor after disease progression, the median survival was also 34.9 months in the olaparib group, but fell to 26.6 months in the placebo group. This gave a statistically significant difference in overall survival between the groups of 8.3 months (HR for death 0.52; 95% CI 0.28 to 0.97; p=0.039).

3.8   For the whole population, there was a statistically significant improvement in the time from randomisation to treatment discontinuation or death for olaparib compared with placebo (HR 0.39; 95% CI 0.30 to 0.51). For the BRCAmsubgroup, median time to treatment discontinuation or death was 11.0 months in the olaparib arm and 4.6 months in the placebo arm (HR 0.36; 95% CI 0.24 to 0.53).

3.9   There was also a statistically significant improvement in time to first subsequent therapy or death with olaparib, defined as the time from randomisation to the start of the first cancer therapy after discontinuation of olaparib or placebo, or death. In the whole population, the HR was 0.41 for olaparib compared with placebo (95% CI 0.31 to 0.54). For the BRCAm subgroup, the median time to first subsequent therapy or death was 15.6 months in the olaparib group and 6.2 months in the placebo group (HR 0.33; 95% CI 0.22 to 0.50; p<0.00001). The difference in median time to first subsequent therapy or death between placebo and olaparib was 9.4 months, compared with a median progression-free survival difference of 6.9 months.

3.10   Olaparib was associated with a statistically significant improvement in time to second subsequent therapy or death, defined as the time from randomisation to the start of the second line of cancer therapy after discontinuing olaparib or placebo, or death. In the whole population, the HR for time to second subsequent therapy or death for olaparib compared with placebo was 0.54 (95% CI 0.41 to 0.72). For the BRCAm subgroup, the median time to second subsequent therapy or death was 23.8 months in the olaparib group and 15.2 months in the placebo group, a difference of 8.6 months (HR 0.44; 95% CI 0.29 to 0.67; p=0.00013).

3.11   Study 19 collected adverse event data from the time of consent to treatment to 30 days after the last dose of treatment. The most common adverse events in the whole trial population were nausea (71%), fatigue (52%), vomiting (34%), diarrhoea (27%) and abdominal pain (25%). The most common adverse events in

the BRCAm subgroup for olaparib were nausea (73%), fatigue (54%), vomiting (36%), diarrhoea (30%) and abdominal pain (23%).The most common grade 3 or higher adverse events for olaparib in the BRCAm subgroup were fatigue (7%), anaemia (5%) and neutropenia (4%). In the olaparib treatment group, 6 people (4.4%) in the whole trial population and 5 people (6.8%) in the BRCAm subgroup stopped treatment because of adverse events.

3.12   Health-related quality of life was assessed in Study 19 using the Trial Outcome Index (TOI), the Functional assessment of Cancer Therapy/National Comprehensive Cancer Network Ovarian Symptom Index (FOSI), and the Functional assessment of Cancer Therapy Ovarian (FACT-O) questionnaires. There were no statistically significant differences in the average change in health-related quality of life for olaparib compared with placebo.

Cost effectiveness

3.13   The company initially submitted 2 economic analyses; 1 that excluded the cost of BRCA testing, and an additional 1 that included the cost of germline BRCA testing (blood test) and the costs and benefits of expanding testing to the relatives of people identified as having germline mutations. Following consultation, the company submitted further analyses that included the cost of tumour testing.

Company's economic model (costs of BRCA testing excluded)

3.14   The company's model compared olaparib with routine surveillance in patients withBRCA mutation-positive, platinum-sensitive relapsed ovarian cancer. There were 4 states in the model: progression-free (with or without maintenance treatment); first subsequent treatment; second subsequent treatment; and death. All patients entered the model in the progression-free health state. The model had a fixed treatment regimen lasting a maximum of 6 cycles and a time horizon of 15 years. A discount rate of 3.5% was applied to costs and health benefits and the analysis was done from an NHS and personal social services perspective.

3.15   The proportion of the hypothetical cohort in each health state in the company's model was estimated using semi-Markov-state transitions, in which time in each health state depends on the time since entry into that state. The company

stated that this approach was more flexible than the partitioned survival approach, traditionally used to evaluate fixed chemotherapy regimens. It also stated that this approach was preferable when survival data were immature, and had been used in NICE's technology appraisal guidance on bevacizumab in combination with paclitaxel and carboplatin for first-line treatment of advanced ovarian cancer. Transition probabilities for the BRCAm subgroup were estimated by fitting parametric survivor functions to time-to-event data from Study 19. The parametric models were adjusted for Ashkenazi Jewish ancestry (a risk factor for BRCA gene mutation), time to progression on penultimate platinum therapy, and full compared with partial response to the last platinum therapy before study enrolment. The company stated that a log-normal distribution had been used for estimating the time to first subsequent treatment or death because the goodness-of-fit Bayesian information criterion values showed this model to be the most appropriate. The company also stated that visual inspection of the cumulative survival plot for time to first subsequent treatment or death showed that the proportional hazards assumption had been met.

3.16   In the base-case analysis, the confounding effect from patients in the placebo group having a PARP inhibitor after disease progression was adjusted for. This was done by assuming that the probability of moving from the first subsequent treatment state to the second subsequent treatment state in the placebo group was the same as in the olaparib treatment group, in which further PARP inhibitors were not allowed after treatment with olaparib was stopped. The predicted mean and median times to first subsequent treatment and time to death were based on the results of the analysis that adjusted for use of a PARP inhibitor in the routine surveillance group (see section 3.5). The predicted median overall survival in the model was 38 months for the olaparib population and 26 months for the routine surveillance population.

3.17   Study 19 did not include a generic measure of health-related quality of life (such as the EQ-5D), which could have been used to estimate utilities. For the progression-free health states, utilities were obtained by mapping FACT-O data from Study 19 to EQ-5D by applying a published algorithm. Utility estimates for the subsequent-therapy health states were obtained from the estimates in the OVA-301 trial of trabectedin plus pegylated liposomal doxorubicin hydrochloride (PLDH) compared with PLDH alone in patients with relapsed advanced ovarian cancer in NICE's technology appraisal guidance on

trabectedin for the treatment of relapsed ovarian cancer. Health-related quality of life decrements associated with adverse events were not included in the base-case analysis because the company stated that they were not found to be associated with a statistically significant or clinically meaningful change in utility values.

3.18   The company's model included costs for post-study chemotherapy, monitoring (such as CT scans) and adverse events. The monthly cost of olaparib was based on the UK list price at the time of developing the model (that is, £3950 per pack). The list price has subsequently decreased to £3550 per pack (see section 2.3). The mean daily dose of olaparib used in the model was based on the actual mean daily dose used in Study 19. A unit cost of £127 was applied for an outpatient visit, £3 for a blood test and £90 for a CT scan. It was assumed that all patients with advanced ovarian cancer would have regular scheduled follow-up consultations as part of their ongoing care. Therefore no additional administration costs were applied for treatment with olaparib. The rates of treatment with subsequent chemotherapy after disease progression were based on data from Study 19. The acquisition costs of subsequent chemotherapy were obtained from the Electronic Marketing Information Tool (eMit) for generic drugs and from the British national formulary (BNF).

3.19   The deterministic incremental cost-effectiveness ratio (ICER) estimated by the company's model for olaparib compared with routine surveillance was £49,826 per quality-adjusted life year (QALY) gained. The probabilistic ICER was £49,146 per QALY gained.

3.20   The company's probabilistic analysis showed that at a maximum acceptable amount for an additional QALY of £30,000, olaparib had a 2% probability of being cost effective compared with routine surveillance. If the maximum acceptable amount for an additional QALY was £50,000, then olaparib would have a 52% probability of being cost effective compared with routine surveillance.

3.21   The company did a series of deterministic one-way sensitivity analyses to assess the effect of varying the costs, utility estimates and clinical data in the model. The company varied the input values for key parameters by 20% of the value used in the deterministic base case. The lowest ICER reported in the company's one-way sensitivity analysis was £38,975 per QALY gained (utility for olaparib,

progression-free [on maintenance therapy] state, 0.92). The highest ICER reported in the company's one-way sensitivity analysis was £69,051 per QALY gained (utility for olaparib, progression-free [on maintenance therapy] state, 0.61).

3.22   The company did a series of scenario analyses. A key driver of the cost-effectiveness results was the estimate of overall survival used in the model (that is, whether it was derived from the model or based on trial data) and the parametric survival curves applied to the distribution of time from first subsequent treatment or death (generalised gamma or log normal). When trial data were used, applying the generalised gamma distribution increased the base-case ICER to £80,715 per QALY gained, and applying the log-normal distribution increased the base-case ICER to £68,812 per QALY gained. When the cost of BRCA-mutation testing was included, the cost of olaparib treatment increased by approximately £2900. This resulted in an ICER of £53,089 per QALY gained for olaparib compared with routine surveillance.

Company's economic analyses (costs and benefits of BRCA testing included)

3.23   The company did additional economic analyses comparing olaparib with routine surveillance in people with BRCAm, platinum-sensitive relapsed ovarian cancer, which included the costs and benefits of extending BRCA-mutation testing to their relatives. This analysis combined the results of the company's first cost-effectiveness analysis with results from the cost–utility analysis of genetic testing for women with a family history of breast cancer, which was developed as part of NICE's guideline on familial breast cancer.

3.24   The model was a semi-Markov design with a number of health states including incidence of new cancers, survival and death. The Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA) was used to analyse the pattern of inheritance of a specific genetic trait (such as the BRCA1 or BRCA2 mutation). This identified 5 family pedigrees, with different risk-of-disease profiles. The model had a 50-year time horizon. A discount rate of 3.5% was applied to costs and health benefits and the analysis was done from an NHS perspective.

3.25   The results were obtained by adding the incremental costs and QALYs from the company's first analysis to the costs and QALYs for BRCA-mutation testing and

comparing these with no testing (from the economic model used in NICE's guideline on [familial breast cancer](...)). Across the 5 individual pedigrees, the ICER for olaparib compared with routine surveillance ranged from £33,069 per QALY gained to £41,716 per QALY gained, with an average ICER of £39,343 per QALY gained.

Evidence Review Group comments

3.26   The ERG was satisfied that all relevant clinical studies were included in the company's submission. The ERG questioned the extent to which Study 19 reflected clinical practice in England, because it used blood (for inherited germline mutations) and tumour (for acquired somatic mutations) BRCA-mutation testing to select patients. It commented that these tests may not be routinely performed in England and that it is unclear if tumour testing would be possible in England on a large scale. Therefore, the ERG considered that the population in the trial may differ from the population treated in clinical practice in England.

3.27   The ERG commented that the clinical study report for Study 19 lacked clarity as to when and under which circumstances patients had subsequent chemotherapy after disease progression. Therefore the outcomes of time to first subsequent therapy or death and time to second subsequent therapy or death may not reflect routine clinical practice in England. Clinical advisers for the ERG suggested that this would be most likely to shorten estimates and may affect comparative estimates between study groups.

3.28   The ERG considered that the clinical effectiveness evidence from Study 19 was weak and at a high risk of bias because of a number of problems:

3.29   The ERG considered overall survival, rather than progression-free survival, to be the most clinically relevant measure to assess the effect of a treatment on survival.

3.30   The ERG commented that time to first subsequent therapy or death and time to second subsequent therapy or death could be considered more clinically relevant than progression-free survival. This is because, in England, patients with ovarian cancer often have treatment after disease progression if their symptoms cause problems. However, the ERG considered that there were issues

with time to first subsequent therapy or death and time to second subsequent therapy or death in the context of Study 19, including that the analyses were post hoc.

3.31   The ERG highlighted that it had concerns about the validity of the treatment pathway in the model. It noted that all patients who survived the first subsequent therapy event and all patients who survived the second subsequent therapy event were assumed to go on to have another course of active chemotherapy. The ERG stated that it may not be realistic to assume that all patients with advanced ovarian cancer would be well enough to have active chemotherapy. The ERG added that its clinical advisers had suggested that it was more clinically realistic to assume that some patients would opt for best supportive care. It also noted that the company's model limited the number of subsequent chemotherapy treatments to a maximum of 2, but 32% of patients in Study 19 had 3 or more subsequent chemotherapy treatments.

3.32   The ERG had concerns about the structure of the company's model and considered that it would have been more appropriate to use a partitioned survival model approach to estimate transition probabilities.

3.33   The ERG was concerned by the exclusion of progression-free survival (the primary end point in Study 19) from the model, and that overall survival data from Study 19 were not directly included. It also expressed concern that the time to first subsequent therapy or death outcome data used in the model were collected post hoc so may have been biased, and that the continued use of olaparib beyond disease progression was permitted, which may not reflect the marketing authorisation.

3.34   The ERG had concerns about the company's approach to modelling the time-to-event outcomes. It was unclear to the ERG why certain covariates such as Ashkenazi Jewish ancestry had been adjusted for, but others such as patients' age and performance status had not. It was also unclear how covariates had been included in the extrapolated Kaplan–Meier curves. The ERG was also concerned that the company's curve-fitting process did not appear to have included any external data, or expert subjective judgement on the plausibility of the extrapolated curves. It noted that curve fitting appeared to have been based only on visual inspection of how well the curves fit the observed data, and goodness of fit according to Akaike information criterion and Bayesian

information criterion statistics. The ERG also noted that the company's submission stated that the assumption of proportional hazards was met for the time-to-event outcomes of time to treatment discontinuation or death and for time to first subsequent therapy or death. However the ERG noted that the log–log survival plots for each of these outcomes showed that the curves for each treatment group crossed, indicating that the proportional hazards assumption may not be appropriate.

3.35   The ERG was concerned that the model overestimated the results that were seen in the trial, and that the degree of overestimation was consistently greater in the olaparib group. It considered that the median time to first subsequent therapy or death predicted in the model was upwardly biased by 4.4 months, the median time to second subsequent therapy or death was upwardly biased by 3.2 months and the median overall survival was upwardly biased by 3.1 months. The ERG noted that there was also a degree of overestimation in the routine surveillance group. The median time to first subsequent therapy or death predicted in the model was upwardly biased by 0.8 months and the median time to second subsequent therapy or death was upwardly biased by 0.7 months. By contrast, the median overall survival estimate in the model for the routine surveillance group was 5.9 months lower than the results from the trial. Therefore the ERG did not have confidence in the overall survival gains or QALY benefits predicted for olaparib in the company's model.

3.36   The ERG had concerns about the utility estimates used for the first subsequent therapy (0.72) and second subsequent therapy (0.65) health states, noting that these were derived from estimates for progression-free survival and progressed disease from the EVO-301 trial in NICE's technology appraisal guidance on trabectedin for the treatment of relapsed ovarian cancer. The ERG suggested that the company's model implicitly assumed that patients in the first subsequent therapy state have a health-related quality of life comparable to that of patients with stable disease, and that patients in the second subsequent therapy state have a health-related quality of life comparable to that of patients with progressive disease. The ERG also noted that the company's model assumed that adverse events do not have any additional effect on patients' health-related quality of life. It highlighted that the validity of these assumptions was not discussed in the company's submission.

3.37   The ERG did not agree with excluding the cost of BRCA-mutation testing from the company's base-case analysis. It highlighted that the NICE guide to the methods of technology appraisal 2013 states that if a diagnostic test to establish the presence or absence of a biomarker is carried out solely to support the treatment decision for the specific technology, the associated costs of the diagnostic test should be incorporated into the assessments of clinical and cost effectiveness.

3.38   The ERG amended the company's model by correcting 2 errors and including the cost of BRCA-mutation testing. This increased the probabilistic base-case ICER to £53,374 per QALY gained. However, the ERG did not believe that the company's model provided robust estimates of overall survival or QALY gains. Therefore it advised caution in interpreting any results produced using the model.

3.39   The ERG did not consider it appropriate to combine the results of the company's model with the model developed for NICE's guideline on familial breast cancer. It noted that the 2 models were different in terms of the treatment pathway assumed for ovarian cancer. The ERG pointed out that the model in NICE's guideline on familial breast cancer does not include olaparib as a treatment option for ovarian cancer. Therefore the company's analysis reflected a scenario in which BRCA-mutation testing and olaparib treatment were available for the patient but not for their relatives. The ERG suggested that the 5 family pedigrees identified may not reflect the range of possible family structures seen in the population with advanced ovarian cancer. It therefore did not consider that the ICERs from the analysis that included BRCA testing were meaningful.

3.40   The ERG did not accept that all relevant comparisons had been included in the analysis such as: no testing and no drug; testing and no drug; and testing and drug treatment for people who test positive for a BRCA mutation. The ERG commented that the analysis may therefore have led to inappropriate conclusions, because the benefit of the joint intervention was driven by the costs and benefits of BRCA testing rather than the costs and benefits of olaparib treatment.

Additional analyses submitted by the company in response to consultation

3.41   The company included the cost of somatic testing as a sensitivity analysis in its model. The results of this additional sensitivity analysis incorporating the costs of tumour testing and corrections to 2 errors in the model identified by the ERG (see section 3.38) produced a probabilistic ICER of £51,587 (incremental costs £47,032; incremental QALYs 0.91) and a deterministic ICER of £51,552 (incremental costs £45,879; incremental QALYs 0.89) for olaparib compared with routine surveillance.

3.42   To address concerns raised by the Committee in the first appraisal consultation document about the structure of the model and the plausibility of the projected survival benefits associated with olaparib, the company conducted an analysis of projected survival outcomes for the population that excluded sites where patients in the placebo group were able to crossover to a PARP inhibitor in the Study 19 BRCAm subgroup. This used an alternative modelling approach by fitting overall survival from Study 19. The company reported that the results of these analyses provided reassurance that the projected survival and QALY benefits associated with olaparib as well as the resulting ICERs compared with routine surveillance had not been overestimated when compared with the original submission. The results of the analyses, including the costs of somatic testing, produced ICERs ranging from £37,917 to £66,491 using independent fitting models and £54,618 to £57,349 using a treatment-adjusted model.

ERG's comments on the additional evidence

3.43   The ERG had serious concerns about the validity of the company's new survival analysis. In particular, it highlighted that the modelled estimates of overall survival provided by the company were very different to those produced by the ERG in their exploratory analyses. Other comments included that the company provided no details of the parameter estimation procedure, or the statistical software used, and that the methods and rationale for covariate adjustment in the survival modelling were unclear. Therefore, the ERG believed that the company's new survival analysis did not produce reliable estimates of overall survival. Full details of all the evidence are in the Committee papers.

Subgroup of patients who received 3 or more lines of platinum-based chemotherapy before randomisation

3.44   The company submitted clinical evidence for the subgroup of patients in Study 19 who received 3 or more lines of platinum-based chemotherapy before randomisation. The company reported that the demographic characteristics of this subgroup were generally consistent with the overall BRCAm population for both arms of the study and that there may be a clinically relevant imbalance in prognostic factors between the 2 treatment arms, potentially favouring placebo. Patients randomised to the placebo arm were more likely to be younger than 50 years (29.4% compared with 14.9% in the olaparib arm), have achieved a complete response to their previous chemotherapy (61.8% compared with 44.7%) and have favourable Federation of Gynaecological Oncologists (FIGO) staging (61.8% compared with 85.1% were diagnosed with FIGO stage IIIC or IV disease).The olaparib arm had a higher proportion of patients who were fully platinum-sensitive (63.8% compared with 47.1%) and who had an ECOG performance status of 0 (85.1% compared with 73.5%).

3.45   The clinical evidence showed statistically significant benefits for olaparib compared with placebo for progression-free survival, time to first subsequent treatment or death, and time to secondary subsequent treatment or death. Median progression-free survival was 11.2 months in the olaparib group and 4.3 months in the placebo group (HR adjusted for stratification factors 0.11; 95% CI 0.05 to 0.23). Median time to first subsequent treatment or death was 13.6 months in the olaparib group and 5.6 months in the placebo group (HR adjusted for stratification factors 0.28; 95% CI 0.16 to 0.49). Median time to secondary subsequent treatment or death was 20.3 months in the olaparib group and 14.3 months in the placebo group (HR adjusted for stratification factors 0.41; 95% CI 0.24 to 0.70). No statistically significant improvement in overall survival was reported. Median time to death was 31.3 months in the olaparib arm and 26.5 months in the placebo arm without adjustment for crossover (HR adjusted for stratification factors 0.69; 95% CI 0.38 to 1.27) and 32.9 months for olaparib and 20.6 months for placebo with adjustment for crossover (HR adjusted for stratification factors 0.56; 95% CI 0.26 to 1.20).

3.46   The company submitted 2 economic models that assessed the cost effectiveness of olaparib in the subgroup of patients who received 3 or more previous lines of platinum-based chemotherapy before randomisation: its semi-Markov model

based on 4 health states (see section 3.14) adapted for this subgroup, and a more standard partitioned survival model with 3 health states (using extrapolated overall survival estimates for the population of Study 19 from sites where crossover was not permitted) to support the robustness of the model. Both models included the costs of somatic testing. They also incorporated a reduced list price of £3550 per pack, and a revised patient access scheme that the company had agreed with the Department of Health (see section 2.3).

3.47   In the company's 4 health-state model, the base case analysis used the best fitting curves (based on AIC/BIC statistics and visual inspection) for the independently fitted parametric curves for time to first subsequent therapy or death (log normal); time to treatment discontinuation or death (log logistic); first subsequent treatment to second subsequent treatment (log normal) and second subsequent treatment to death (Weibull). The base case deterministic ICER for olaparib compared with routine surveillance was £37,583 per QALY gained and the probabilistic ICER was £37,864 per QALY gained. The company did a series of scenario analyses to assess the impact on model outcomes of using alternative parametric distributions for the time to first subsequent therapy or death. The results of the analyses, excluding the generalised gamma distribution which the company reported was unstable, produced ICERs ranging from £37,583 to £42,876 using independent fitting models and £39,036 to £49,244 using a treatment-adjusted model.

3.48   In the company's 3 health-state model, the base case analysis used the best fitting parametric survival curves from the independently fitted models for overall survival (log normal); progression-free survival/time to first subsequent treatment (log normal) and time to treatment discontinuation (log logistic). The base case deterministic ICER for olaparib compared with routine surveillance was £46,806 per QALY gained and the probabilistic ICER was £45,343 per QALY gained. Scenario analyses to assess the impact of using alternative parametric distributions on model outcomes produced ICERs ranging from £40,000 to £59,664 using independent fitting models and £49,290 to £70,826 using a treatment-adjusted model (excluding the generalised gamma distribution).

ERG's comments on the evidence for the subgroup of patients who received 3 or more lines of platinum-based chemotherapy before randomisation

3.49   The ERG considered that the clinical evidence for the subgroup of patients who received 3 or more previous lines of platinum-based chemotherapy before randomisation should be interpreted with caution because of the small sample size and a potential imbalance between the 2 treatment groups, caused by known and unknown confounders.

3.50   The ERG reiterated its concerns about the appropriateness of the company's 4 health-state model structure which the ERG considered may skew the available evidence, producing estimates of incremental survival for olaparib that are exaggerated.

3.51   The ERG considered the fit of the company's modelled overall survival predictions against the empirical Kaplan–Meier curves. It was concerned that the company's 4 health-state model overestimated the probability of survival for patients receiving olaparib beyond 2 years, and underestimated the probability of survival for patients on routine surveillance beyond 2.5 years. In addition, the survival curves indicated no survival benefit for olaparib compared with placebo beyond 3.2 years whereas the model suggested that the greatest difference in survival happened beyond this time. The ERG also found that the company's 4 health-state model produced a higher estimate of incremental health gain (1.43 life years) than the highest estimates from the 3 health-state model (1.10 life years) and Study 19 (0.347 years without adjustment for treatment crossover, and 0.507 years with adjustment for treatment crossover).

4   Committee discussion

The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of olaparib, having considered evidence on the nature of recurrent ovarian cancer and the value placed on the benefits of olaparib by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

4.1   The Committee considered the need for treatment in people with relapsed platinum-sensitive ovarian cancer. It heard from the patient experts that a diagnosis of ovarian cancer has a devastating effect on patients and their families, and affects all aspects of their lives. People with advanced or recurrent ovarian cancer are aware that the disease has a poor prognosis and it is of great importance to them and their families that treatments are available that maximise length and quality of life. In addition, knowledge that they are carriers of the mutated BRCA gene is an additional burden because of the implications for relatives. The Committee also heard from the patient experts that after a first recurrence, people consider further disease recurrence inevitable, with an increasing likelihood of treatment resistance with each relapse. This has a major emotional effect. The Committee heard from the clinical expert that the only active treatment available for disease recurrence is chemotherapy, which has multiple side effects. Any treatment that extends the period between courses of chemotherapy means longer periods in which people can lead a normal life. The Committee noted written comments that stated that ovarian cancer outcomes in the UK lag behind those in some other countries. The clinical expert stated that outcome data in the UK were more complete than those from many other countries, where it may be collected in only a few specialist centres. International comparisons were therefore not necessarily reliable. However, in some countries outside the UK, there was a tendency for more radical surgical techniques to be used, which may contribute to better outcomes. The expert also confirmed that people with BRCA mutation-positive ovarian cancer generally had better outcomes for duration of response to platinum therapy than those with the non-mutated (wild type) BRCA gene. The Committee noted that this had been demonstrated in the placebo arms of Study 19, although it noted consultee comments that this did not necessarily apply at all stages of disease. The Committee recognised that ovarian cancer is a devastating condition for patients, and that relapse after initial chemotherapy is common. It concluded that a drug treatment that improves quality of life and extends

periods of remission for patients with BRCA mutation-positive ovarian cancer would be highly valued by patients and their families.

Clinical effectiveness

4.2　The Committee noted that the key clinical-effectiveness evidence in the company's submission came from a phase II randomised controlled trial (Study 19) that compared olaparib with placebo in patients with relapsed platinum-sensitive ovarian cancer. It also noted that the evidence presented from Study 19 focused on a subgroup analysis of patients with BRCA1 or BRCA2 gene mutations (BRCAm). It heard from the company that most of the Study 19 trial population had been tested for BRCAm retrospectively rather than before enrolment into the study, because it had not been their intention to pursue a marketing authorisation specifically for the BRCAm population. The Committee also noted that the company had specified in its submission that the demographic characteristics of the BRCAm subgroup were generally consistent with the whole trial population. The Committee noted comments from the Evidence Review Group (ERG) that interaction tests between the BRCAm subgroup and the whole population in the trial were inconclusive, so it was not possible to be certain that the treatment effect was different in the BRCAm subgroup. It heard from the clinical expert that there is a biologically plausible reason why people with BRCA mutation-positive disease would benefit more from olaparib than the whole trial population. This could be explained by the relationship between malfunctioning BRCA genes and the development of homologous recombination deficiency, and the subsequent effect on DNA repair. The Committee concluded that olaparib was clinically effective in the treatment of recurrent, platinum-sensitive ovarian cancer. It accepted the clinical expert's view that there is a biologically plausible reason for olaparib being particularly effective in the BRCAm subgroup.

4.3　The Committee noted that olaparib was associated with a statistically significant improvement in median progression-free survival compared with placebo in the BRCAm subgroup and in the whole trial population. It also noted that olaparib was associated with statistically significant gains in time to first subsequent therapy or death and time to second subsequent therapy or death in the BRCAm subgroup and in the whole trial population. The Committee considered the most appropriate outcomes for assessing clinical effectiveness in the trial. It noted that the primary outcome in Study 19 was progression-free

survival, assessed by measuring tumour growth on scans using standardised Response Evaluation Criteria in Solid Tumors (RECIST) criteria. Overall survival was a secondary outcome in the trial. Time to treatment discontinuation, time to first subsequent therapy and time to second subsequent therapy were considered to be key outcomes by the company, but had been identified post hoc in the trial. The Committee discussed how disease progression was defined in Study 19 compared with clinical practice in England. It noted that the ERG had questioned whether a rise in CA125 protein or results from scans would be used in clinical practice to define disease progression. The Committee heard from the clinical expert that most clinicians would decide when to treat disease progression based on recurrence of disease symptoms, but this would be informed by other information that showed the disease was progressing. The Committee questioned whether the main therapeutic benefit of olaparib is in delaying disease progression or in delaying the time to further chemotherapy, and also discussed the advantages and disadvantages of the outcomes used in Study 19. It heard that the primary trial outcome of progression-free survival was assessed using an objective measure of tumour growth, but that scans were performed at 3-monthly intervals in the trial, and therefore it was not possible to determine the exact time when disease progression occurred. It also heard from the patient expert that the way in which progression was defined was not of great relevance to patients; their main concern was extending the period in which they enjoyed good quality of life and freedom from the adverse effects of chemotherapy. The Committee noted that the need for further treatment would depend on whether patients presented with disease symptoms, and decisions on starting chemotherapy could be affected by multiple factors such as patient preference, local protocols, and variation in clinical practice. The clinical expert indicated that time to first subsequent therapy and time to second subsequent therapy were considered to be good indicators of whether treatment had a clinical effect that carried on beyond progression and into subsequent courses of therapy, however it was not accepted by regulators as a primary measure of efficacy to support licensing. Regarding the prediction of overall survival, there was no evidence that time to subsequent therapy provided a better indication of likely overall survival benefit than progression-free survival, and progression-free survival itself did not have a predictable relation to overall survival, partly because of the increasing use of sequential therapies. The Committee heard from the company that the data for time to first subsequent therapy and time to second subsequent therapy had the advantage of being more complete than both the progression-free and the overall survival data. The Committee

concluded that all the measures of disease progression in the trial were relevant to patients, but that time to treatment discontinuation, time to first subsequent therapy and time to second subsequent therapy had been identified post hoc. Therefore they should be viewed with caution because the defined primary objective outcome of the trial was progression-free survival.

4.4   The Committee discussed the estimates of overall survival in Study 19. It noted that the data presented for overall survival were from an interim analysis and that the final analysis is not yet available. The Committee accepted that the overall survival data presented by the company were immature, but it noted that no statistically significant difference in median overall survival between olaparib and placebo was identified in the whole trial population, or in the BRCAm subgroup. The Committee acknowledged that the estimates of overall survival may have been confounded because 23% of patients in the placebo group had a poly-ADP-ribose polymerase (PARP) inhibitor in subsequent rounds of treatment. It noted that the company had attempted to adjust for this in a post-hoc analysis by excluding sites where patients in the placebo group were able to crossover to a PARP inhibitor. The Committee noted that without adjustment, the difference between treatment groups in median overall survival in the BRCAm subgroup was 3 months (not statistically significant) but if sites where subsequent PARP inhibitor treatment was allowed were excluded, this resulted in a statistically significant difference in median overall survival of 8.3 months for olaparib compared with placebo. However, it also noted that sample size for this analysis was small: only 97 patients. The Committee also heard from the clinical expert that in clinical practice there were some patients, possibly 10% to 15%, who did exceptionally well on olaparib and who did not have a relapse for several years. It is not currently possible to identify these exceptional survivors, although research is being done on why olaparib appears to be particularly effective in some patients. The Committee heard from the company that this is supported by evidence from Study 19 showing that 11% of patients in the olaparib group remain on treatment after 70 months. The Committee concluded that in Study 19, olaparib increased progression-free survival and time to subsequent therapy compared with placebo, in the whole trial population and in the BRCAm subgroup. It also concluded that because of the immaturity of the data and subsequent use of a PARP inhibitor in some patients, there remained uncertainty about the extent to which olaparib increases overall survival compared with placebo in patients with BRCA mutation-positive ovarian cancer.

4.5   The Committee considered further clinical evidence supplied by the company relating to BRCA mutation-positive patients in Study 19 who had received 3 or more lines of platinum-containing therapy. The Committee noted that this subgroup contained fewer patients than the total BRCA mutation-positive population in the trial, and that there were imbalances in baseline characteristics, some of which potentially favoured placebo and others that potentially favoured olaparib. Nevertheless, the progression-free survival benefit in this subgroup was 6.9 months (hazard ratio [HR] 0.11). In addition, the median overall survival benefit was 12.3 months (HR 0.56) when sites which allowed crossover were excluded. The Committee noted the clinical expert's comments that a difference of this magnitude had never previously been seen in ovarian cancer treatment. The Committee concluded that there was evidence of benefit for olaparib in those patients who had received three or more lines of platinum-based chemotherapy.

Cost effectiveness

4.6   The Committee considered the company's model that compared olaparib with routine surveillance in patients with BRCA mutation-positive, platinum-sensitive relapsed ovarian cancer, excluding the cost of BRCA testing. It noted that the model was a semi-Markov-state transition design rather than a more standard partitioned survival model. It considered that the model structure was unconventional and very different to those used in previous appraisals (see section 3.15). The Committee expressed concern that progression-free survival data from Study 19 had not been included in the model, even though this was the pre-specified primary outcome that had been used to assess clinical benefit in the trial. In addition, overall survival data from Study 19 had not been directly incorporated into the model. The Committee noted comments from the company that the time to first and second subsequent therapy from Study 19 had been used in the model, because these data were more complete compared with the immature overall survival data from the trial. However, the Committee was concerned that intermediate outcomes had been used to make assumptions about longer-term overall survival, and considered that it would have been more conventional to fit a curve directly to the overall survival data, with adjustment for crossover to a PARP inhibitor in the placebo arm. The Committee concluded that the company's model was a novel design that lacked external validity, and that the

use of sequential intermediate outcomes to model overall survival relied on a large number of assumptions that may not all be reasonable.

4.7 The Committee discussed the estimates of overall survival for the whole BRCA mutation-positive population derived from the company's 4 state model. It noted that graphical plots of survival probability derived from the model showed that the difference between the curves for olaparib and placebo increased at later time points, implying that the overall survival benefit from olaparib increases over time. The Committee noted that no data to support this had been provided. The Committee also acknowledged the clinical expert's view that greater separation of the curves over time would not be expected during treatment for cancer. The Committee compared the median values of the various time-to-event outcomes for olaparib estimated from the company's model with the results from the trial. It was concerned that the modelled estimates for olaparib were consistently higher than the observed results in the trial, noting that the median overall survival estimate for olaparib was 3.1 months longer in the model than in the trial, time to first subsequent therapy or death was 4.4 months longer in the model and time to second subsequent therapy or death was 3.2 months longer (see section 3.35). Conversely, in the routine surveillance arm of the model, the modelled median overall survival was 5.9 months lower than the median in the trial. The Committee did however acknowledge that this discrepancy in the routine surveillance data was smaller when compared with the analysis of trial data that excluded sites where patients in the placebo group were able to crossover to a PARP inhibitor. The Committee also noted the ERG's concerns about the company's approach to modelling the time-to-event outcomes, and about the curve fitting process used in the model (see section 3.34). It accepted that the choice of appropriate parametric functions to extrapolate observed data for a small number of patients is a challenging and not a totally objective process; however the substantial disagreement between the results from Study 19 and the model predictions undermined confidence in the modelling used by the company. The Committee concluded that the company's modelling of benefit for the whole BRCA mutation-positive population overestimated the benefit of olaparib and therefore underestimated the incremental cost-effectiveness ratio (ICER) for olaparib compared with routine surveillance.

4.8 The Committee discussed the company's use of time to subsequent treatment to represent the benefit of olaparib on disease progression in the 4-state model.

It noted that the difference between treatment groups in median time to first subsequent therapy or death was longer (9.4 months) than for the primary efficacy end point in the trial, progression-free survival, for which the difference between the medians was 6.9 months. The Committee concluded that although the data may be more complete, there was no evidence that the use of time to first and second subsequent treatment was a more accurate method for calculating overall survival than the more conventional use of planned trial outcomes such as progression-free and overall survival.

4.9 The Committee considered the modelled estimates of overall survival for the whole BRCA mutation-positive population in the company's model. It noted that the mean overall surival benefit was 16.3 months in the model. This contrasted with the difference in medians for overall survival of 3 months in the trial (8.3 months when crossover sites were excluded). The Committee appreciated that the mean benefit may exceed the difference in the medians reported in the trial since a normal distribution cannot be assumed, and some people may derive a prolonged benefit which was not captured in the trial. However it questioned whether an average overall survival benefit of 16.3 months was plausible, and noted that the modelling method did not use any of the overall survival data directly from the trial.

4.10 The Committee considered further analyses submitted by the company, in its response to consultation, that attempted to address some of the concerns raised by the Committee about the structure of the 4-state model and the plausibility of the projected survival benefits associated with olaparib. It noted that the further analyses used an alternative modelling approach that involved fitting parametric curves to overall survival data from Study 19, and that the company intended the analyses to provide reassurance that its model produced a reliable estimate of the overall survival gain of olaparib. The Committee also considered the ERG's critique of these analyses and was aware that the modelled estimates of overall survival produced by the company were very different to those produced by the ERG in their exploratory analyses, despite apparently being based on similar data. In one relevant example the overall survival estimated by the company was almost double that estimated by the ERG. The Committee heard from the company that the differences could be explained by the fact that the company had adjusted the overall survival data in the trial for a range of baseline prognostic factors, in particular response to platinum-based therapy. It also heard that the company considered this to be

necessary and justified because the treatment groups in the subgroup of patients with BRCA mutation-positive disease were not well balanced for all these factors. The Committee considered that the new modelling was not clearly explained in the company's response to consultation and was concerned about its validity. It was therefore not persuaded that the results of the alternative modelling approach provided the appropriate reassurance that the company's 4-state model produced a robust estimate of the overall survival gain of olaparib.

4.11   The Committee discussed the utility estimates in the company's model. It was disappointed that no preference-based measures of quality of life were collected in Study 19. It noted that the company had estimated utility values for the progression-free health states by mapping FACT-O data from Study 19 to EQ-5D, whereas estimates for the subsequent therapy health states were derived from estimates used in the appraisal of trabectedin and pegylated liposomal doxorubicin hydrochloride (PLDH) in NICE's technology appraisal guidance on trabectedin for the treatment of relapsed ovarian cancer. The Committee noted that there was an increase in utility from 0.71 in the progression-free (discontinued maintenance therapy) health state to 0.72 in the first subsequent-therapy health state and it questioned the improvement in utility between the 2 states because chemotherapy is known to have an adverse effect on a patient's quality of life. The Committee heard from the company that this increase in utility was a discrepancy in the model but not a clinically important difference in utilities, and did not affect the ICERs. The Committee also considered that it was unclear why the utility in the routine surveillance health state decreased from 0.77 for the progression-free (on maintenance therapy) health state to 0.71 in the progression-free (discontinued maintenance therapy) state, because no difference in utility would be expected for patients who were taking, or who had stopped taking, placebo. The Committee heard from the company that this decrease in utility could be explained by the fact that the same utilities for both treatment arms were used in the model for reasons of consistency, but this factor did not have a significant effect on the ICERs. The Committee concluded that some of the utility estimates lacked face validity, but accepted that utility values were not key drivers of the cost-effectiveness results.

4.12   The Committee considered the appropriateness of the company's exclusion of the costs of BRCA testing from its cost-effectiveness analysis for the whole

BRCA mutation-positive population. The Committee heard from one of the patient experts that blood testing for germline mutations in people with ovarian cancer is becoming available as part of routine NHS services in England. This follows recommendations in NICE's guideline on familial breast cancer. Knowledge of blood BRCA-mutation status allows consideration of olaparib treatment for the patient, and also the screening of asymptomatic relatives for the genetic mutation. The Committee accepted the company's view that it was appropriate to exclude the costs of germline BRCA blood testing in the model. However, it heard from the clinical and patient experts that olaparib is also indicated for patients who do not have the inherited form of the mutation, but who do have a tumour that is positive for a BRCA mutation. Both inherited and non-inherited forms can be detected by testing a sample from the tumour (although it will not distinguish between them). However, tumour testing is not widely available through the NHS. The Committee noted that, in its response to consultation, the company had provided an analysis that included the cost of somatic testing, which the Committee agreed was appropriate.

4.13   The Committee considered the company's cost-effectiveness results from its analysis that excluded the costs of germline testing for a BRCA mutation. It noted that the company's analysis, submitted in response to consultation, that incorporated the costs of tumour testing in line with the Committee's preference (and corrections to 2 minor errors in the model identified by the ERG; see section 3.41) produced a probabilistic ICER of £51,600 for olaparib compared with routine surveillance. However, the Committee considered that this was likely to be an underestimate of the true ICER because it overestimated the overall survival gain associated with olaparib (see section 4.5). It also noted that the ICER increased in all the company's scenario analyses. The Committee was aware that using an alternative modelling approach fitting overall survival from Study 19, and including the costs of somatic testing, produced ICERs ranging from £37,900 to £66,500 using independent fitting models and £54,600 to £57,300 using a treatment-adjusted model. However, it was unsure of the validity of these results (see section 4.5). The Committee concluded that the ICERs presented by the company for olaparib compared with routine surveillance for the overall population of patients with relapsed BRCA mutation-positive, platinum-sensitive ovarian cancer were considerably above the range normally considered to be a cost-effective use of NHS resources (that is, £20,000 to £30,000 per QALY gained).

4.14 The Committee considered supplementary advice from NICE that should be taken into account when appraising treatments that may extend the life of patients with short life expectancy and that are licensed for indications that affect small numbers of people with incurable illnesses. For this advice to be applied, all the following criteria must be met.

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months.

- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment.

- The treatment is licensed or otherwise indicated for small patient populations normally not exceeding a cumulative total of 7000 for all licensed indications in England.

  In addition, when taking these criteria into account, the Committee must be persuaded that the estimates of extension to life are robust, and the assumptions used in the reference case of the economic modelling are plausible, objective and robust.

4.15 The Committee discussed whether the whole population of patients with relapsed BRCA mutation positive, platinum sensitive ovarian cancer who had previously been treated with platinum based chemotherapy would be expected to have a mean life expectancy of less than 24 months. It was aware that median overall survival for the BRCAm subgroup in the placebo arm of Study 19 was 31.9 months and that this fell to a median of 26.6 months only in a smaller subgroup of patients when the sites that allowed crossover to a PARP inhibitor were excluded. In addition, it noted that the overall survival associated with routine surveillance estimated by the company in its economic model was a median of 26 months and a mean of 29.8 months. The Committee noted views expressed by the clinical expert, and consultees in their response to consultation, that the overall survival estimates seen in the trial may be higher than those in clinical practice in England because of differences in surgical and other treatments in England compared with some other countries that participated in the trial. The Committee gave further consideration to the range and relevance of the evidence available on the expected survival of people with BRCA mutation positive ovarian cancer after 2 or more courses of chemotherapy. It noted that Study 19 had included 8 UK participating sites and no evidence had been presented to suggest that the results of the trial would

not be generalisable to the UK population. The Committee also took note of the results from the control arm of a randomised controlled trial of a different drug for platinum-sensitive, relapsed ovarian cancer (the ICON 6 trial), which indicated that the median life expectancy could be as low as 20 months. However, it noted that this was not a trial for people with BRCA mutation positive disease and did not correspond to the population for whom olaparb is licensed. It also considered a retrospective subgroup analysis of an Australian observational study of patients with ovarian cancer, which included 41 patients with BRCA mutation positive ovarian cancer. It noted that this showed a median survival of 21.9 months in the BRCA mutation positive group (mean not supplied) compared with 27.6 months for the BRCA mutation negative population and that these results were contrary to testimonies received from the clinical experts that people with BRCA mutation positive disease generally have better responses to platinum treatment. It also noted that the trial was conducted entirely outside the UK. The Committee acknowledged that there was uncertainty about the life expectancy of people with relapsed BRCA mutation positive platinum sensitive ovarian cancer, but taking all the available evidence into account, it agreed that the control arm of Study 19 provided the best available evidence on life expectancy without olaparib because it included a population corresponding directly with those eligible for olaparib treatment and had included UK sites. Furthermore, because it had accepted the efficacy estimates for olaparib on the basis of the results from Study 19 and considered them to be generalisable to patients in England it considered it appropriate also to derive estimates of life expectancy without olaparib treatment from the trial. All the trial and modelled estimates of life expectancy exceeded 24 months. The Committee was therefore not persuaded that the life expectancy for the whole population of people with relapsed, BRCA mutation positive, platinum sensitive ovarian cancer had been shown to be less than 24 months without olaparib treatment. Because the 24 month life expectancy criterion had not been met, the Committee concluded that the end of life criteria did not apply to olaparib when considering the overall population of patients with relapsed BRCA mutation positive, platinum sensitive ovarian cancer.

4.16   The Committee considered the additional cost-effectiveness analyses supplied by the company, relating only to the subgroup of BRCA mutation-positive patients who had received 3 or more lines of platinum-based chemotherapy. The Committee discussed the relative merits of the company's 2 models – the semi-Markov model based on 4 health states adapted for this subgroup (see

section 4.6), and a more standard partitioned survival model with 3 health states. It noted the company's view that the 4 health-state model better reflected the management of relapsed ovarian cancer because it used time to first and second subsequent treatment to model overall survival. It also heard from the patient expert that people with ovarian cancer particularly value extended time between courses of chemotherapy because this has a major impact on their quality of life. The Committee accepted that the 4 health-state model had some merit in terms of relevance to clinical practice. But it considered that the 3 health-state model provided a more conventional and objective assessment of the biological activity of the tumour because it incorporated objective measurements of tumour size to define progression of disease, and also used overall survival data from Study 19. The Committee reiterated its concerns that there was no supportive evidence that time to first and second subsequent treatment in the 4 health-state model was a more accurate method for calculating overall survival than a more conventional approach using progression-free and overall survival data from the trial (see section 4.7). It also expressed concern that the 4 health-state model overestimated the probability of survival for patients receiving olaparib and underestimated the probability of survival for patients on routine surveillance. The Commitee also agreed that a 3 health-state model had the advantage of adhering to accepted standards and provided consistency with models used in other NICE appraisals of treatments for cancer. The Committee therefore concluded that the company's 3 health-state model provided a better basis for decision making than the 4 health-state model.

4.17   The Committee considered the cost-effectiveness results from the company's 3 health-state model for the subgroup of patients who had received 3 or more previous lines of platinum-based chemotherapy. It noted that the ICERs varied according to the parametric curve used to model overall survival and, although it considered that on visual inspection the Gompertz curve might be an option, it heard from the company that the log normal and log logistic curves provided the best fit to the data. The Committee accepted that this was not unreasonable and concluded that the most plausible ICERs using independent fitting models were £46,600 to £46,800 per QALY gained (based on the log-normal and log-logistic survival plots).

4.18   The Committee considered whether the end-of-life criteria would apply to the subgroup of patients with BRCA mutation-positive disease who had received

3 or more previous lines of platinum-based chemotherapy. It noted the significant clinical need and the poorer prognosis for this group of patients. It understood that median overall survival for this subgroup in the control arm of Study 19 was 20.6 months when sites that allowed crossover to a PARP inhibitor were excluded. The Committee was aware that some of the modelled mean survival estimates for the control arm were above 2 years, but it was concerned that these were highly uncertain and it agreed that the control arm of Study 19 provided the best available evidence on life expectancy (see section 4.16). Therefore, the Committee was persuaded that the life expectancy of people who had received 3 or more lines of platinum-based chemotherapy was likely to be less than 24 months.

4.19   The Committee discussed whether olaparib met the other end-of-life criteria in patients with BRCA mutation-positive disease who had received 3 or more previous lines of platinum-based chemotherapy: small patient population and extension to life of more than an average of 3 months. It accepted the estimates in the company's submission that no more than 450 patients per year would be eligible for treatment with olaparib for BRCA mutation-positive platinum sensitive relapsed ovarian cancer. The Committee concluded that the eligible population for England did not exceed 7000 and that olaparib therefore met the end-of-life criterion for a small patient population.

4.20   The Committee referred to its previous conclusion (see section 4.4) that there is uncertainty about the survival benefit with olaparib. It noted that the trial data for the overall population of patients with relapsed BRCA mutation-positive, platinum-sensitive ovarian cancer showed a survival gain of 3 months, although this was not statistically significant. It also noted that the company's analysis, which excluded sites where patients in the placebo arm had a PARP inhibitor after disease progression, resulted in a statistically significant increase in median overall survival with olaparib of 8.3 months. It was also aware that this estimate was based on a retrospective subgroup analysis that included fewer than 100 patients. The Committee agreed that the direct trial evidence for the overall population of patients with relapsed BRCA mutation-positive, platinum-sensitive ovarian cancer was borderline for an overall survival gain of 3 months, although it was likely to be higher. It acknowledged that data from Study 19 suggested a potentially greater survival benefit with olaparib compared with placebo for the subgroup of patients with BRCA mutation-positive disease in Study 19 who had received 3 or more previous

lines of platinum-based chemotherapy, noting that the survival gain was 12.3 months when sites that allowed crossover to a PARP inhibitor were excluded. The Committee recognised the uncertainties associated with the survival estimates from the trial but it concluded that there was sufficient evidence to suggest that olaparib met the end-of-life criteria for the subgroup of patients with relapsed BRCA mutation-positive, platinum-sensitive ovarian cancer who have received 3 or more previous lines of platinum-based chemotherapy. It further concluded that the most plausible ICERs for olaparib compared with routine surveillance of £46,600 to £46,800 per QALY gained (see section 4.17) were acceptable given the greater weight given to QALYs at the end of life.

4.21 The Committee considered whether olaparib could be considered an innovative technology. It noted that olaparib has a different mechanism of action to other drug treatments for platinum-sensitive ovarian cancer, is a targeted therapy, and was developed in line with a greater emphasis on personalised medicine. It could therefore be considered a significant change in the management of relapsed BRCA mutation-positive, platinum-sensitive ovarian cancer. The Committee agreed that olaparib is innovative in this respect, but it could not identify any substantial health benefits that had not been captured in the QALY estimates. The Committee concluded that olaparib had been shown to be cost effective only for the subgroup of people who have had 3 or more previous lines of platinum-based chemotherapy, and that it could be recommended for use in the NHS for this group of patients.

4.22 The Committee considered whether it should take into account the consequences of the Pharmaceutical Price Regulation Scheme (PPRS) 2014, and in particular the PPRS Payment Mechanism, when appraising olaparib. The Committee noted NICE's position statement in this regard, and accepted the conclusion 'that the 2014 PPRS Payment Mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines'. The Committee heard nothing to suggest that there is any basis for taking a different view with regard to the relevance of the PPRS to this appraisal of olaparib. It therefore concluded that the PPRS Payment Mechanism was irrelevant for the consideration of the cost effectiveness of olaparib.

Summary of Appraisal Committee's key conclusions

TA381	Olaparib for maintenance treatment of relapsed, platinum-sensitive, BRCA mutation-positive ovarian, fallopian tube and peritoneal cancer after response to second-line or subsequent platinum-based chemotherapy	Section
Key conclusion		

Olaparib is recommended within its marketing authorisation as an option for treating adults with relapsed, platinum-sensitive ovarian, fallopian tube or peritoneal cancer who have BRCA1 or BRCA2 mutations and whose disease has responded to platinum-based chemotherapy only if: • they have had 3 or more courses of platinum-based chemotherapy and • the drug cost of olaparib for people who remain on treatment after 15 months will be met by the company. The Committee concluded that in Study 19, olaparib increased progression-free survival and time to subsequent therapy compared with placebo, in the whole trial population and in the BRCA mutation-positive (BRCAm) subgroup. It also concluded that because of the immaturity of the data and subsequent use of a poly-ADP-ribose polymerase (PARP) inhibitor in some patients, there was uncertainty about whether, and to what extent, olaparib increases overall survival compared with placebo. The Committee concluded that the incremental cost-effectiveness ratios (ICERs) presented by the company for olaparib compared with routine surveillance for the overall population of patients with relapsed BRCA mutation-positive, platinum-sensitive ovarian cancer were considerably above the range normally considered to be a cost-effective use of NHS resources (that is, £20,000 to £30,000 per quality-of-life year [QALY] gained). The Committee concluded that the end-of-life criteria did not apply to olaparib when considering the overall population of patients with relapsed BRCA mutation-positive, platinum-sensitive ovarian cancer. For the subgroup of patients with relapsed BRCA mutation-positive, platinum-sensitive ovarian cancer who have received 3 or more previous lines of platinum-based chemotherapy, the Committee accepted that the most plausible ICERs were £46,600 to £46,800 per QALY gained. The Committee concluded that there was sufficient evidence to suggest that olaparib met the end-of-life criteria for the subgroup of patients with relapsed BRCA mutation-positive, platinum-sensitive ovarian cancer who have received 3 or more previous lines of platinum-based chemotherapy.	1.1, 4.4, 4.13, 4.15, 4.17, 4.20
Current practice	

Clinical need of patients, including the availability of alternative treatments	The Committee recognised that ovarian cancer is a devastating condition for patients, and that relapse after initial chemotherapy is common. It concluded that a drug treatment that improves quality of life and extends periods of remission for patients with BRCA mutation-positive ovarian cancer would be highly valued by patients and their families.	4.1
The technology		
Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	The Committee noted that olaparib has a different mechanism of action to other drug treatments for platinum-sensitive ovarian cancer, and therefore could be considered a significant change in the management of relapsed BRCA mutation-positive, platinum-sensitive ovarian cancer. The Committee agreed that olaparib was innovative in this respect.	4.21
What is the position of the treatment in the pathway of care for the condition?	The Committee understood that olaparib is the only specific maintenance treatment for germline (inherited) and somatic (acquired) BRCA mutation-positive ovarian cancer that has a marketing authorisation for use after platinum-based chemotherapy treatments in metastatic disease.	4.1
Adverse reactions	The most common adverse events for olaparib include nausea, fatigue, vomiting, diarrhoea and abdominal pain.	2.2, 3.11
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	The Committee noted that the key clinical effectiveness evidence in the company's submission came from a phase II randomised controlled trial (Study 19) that compared olaparib with placebo in patients with relapsed platinum-sensitive ovarian cancer. It also noted that the evidence presented from Study 19 focused on a subgroup analysis of patients with BRCA1 or BRCA2 mutations (BRCAm).	4.2

Relevance to general clinical practice in the NHS	The Committee noted that Study 19 had included 8 UK participating sites and no evidence had been presented to suggest that the results of the trial would not be generalisable to the UK population.	4.15
Uncertainties generated by the evidence	The Committee concluded that all the measures of disease progression in the trial were relevant to assess the clinical effectiveness of olaparib, but that time to treatment discontinuation, time to first subsequent therapy and time to second subsequent therapy had been identified post hoc. Therefore they should be viewed with caution because the defined primary objective outcome of the trial was progression-free survival.	4.3
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	The Committee accepted the clinical expert's view that there is a biologically plausible reason for olaparib being more clinically effective in the BRCAm subgroup than in the whole trial population. The Committee acknowledged that the data suggested a potentially greater survival benefit with olaparib for the subgroup of patients with relapsed BRCA mutation-positive platinum-sensitive ovarian cancer who have received 3 or more previous lines of platinum-based chemotherapy.	4.2, 4.20
Estimate of the size of the clinical effectiveness including strength of supporting evidence	The Committee concluded that in Study 19, olaparib increased progression-free survival and time to subsequent therapy compared with placebo, in the whole trial population, in the BRCAm subgroup and in the subgroup of people who received 3 or more lines of platinum-based chemotherapy before randomisation. It also concluded that because of the immaturity of the data and subsequent use of a PARP inhibitor in some patients, there remained uncertainty about whether, and to what extent, olaparib increases overall survival compared with placebo.	4.4
Evidence for cost effectiveness		

Availability and nature of evidence	The Committee noted that the company's model was a semi-Markov-state transition design rather than a more standard partitioned survival model. It concluded that the model was a novel design that lacked external validity, and that the use of sequential intermediate outcomes to model overall survival relied on a large number of assumptions that may not all be reasonable.	4.6
Uncertainties around and plausibility of assumptions and inputs in the economic model	The Committee accepted that the choice of appropriate parametric functions to extrapolate observed data for a small number of patients is a challenging and not totally objective process; however, the substantial disagreement between the results from Study 19 and the model predictions undermined confidence in the modelling used by the company. The Committee concluded that the company's model overestimated the benefit of olaparib and therefore underestimated the ICER for olaparib compared with routine surveillance.	4.7, 4.8, 4.9, 4.10
	The Committee concluded that although the data may be more complete, there was no evidence that the use of time to first and second subsequent treatment was a more accurate method for calculating overall survival than the more conventional use of planned trial outcomes such as progression-free and overall survival.	
	The Committee questioned whether an average overall survival benefit of 16.3 months was plausible, and noted that the modelling method did not utilise any of the overall survival data directly from the trial.	
	The Committee considered that the new modelling submitted by the company in its response to consultation, that used an alternative modelling approach fitting overall survival from Study 19, was not clearly explained and it was concerned about its validity. It was therefore not persuaded that the results of the alternative modelling approach provided the appropriate reassurance that the company's model produced a robust estimate of the overall survival gain of olaparib.	

Incorporation of health-related quality-of-life benefits and utility values Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?	The Committee concluded that some of the utility estimates lacked face validity, but accepted that utility values were not key drivers of the cost-effectiveness results. The Committee could not identify any substantial health benefits that had not been captured in the QALY estimates.	4.11, 4.21
Are there specific groups of people for whom the technology is particularly cost effective?	None were identified.	–
What are the key drivers of cost effectiveness?	A key driver of the cost-effectiveness results was the estimate of overall survival used in the model (that is, whether it was derived from the model or based on trial data) and the parametric survival curves applied to the distribution of time from first subsequent treatment or death.	4.8, 4.9

Most likely cost-effectiveness estimate (given as an ICER)	The company's further analysis, submitted in response to consultation, that incorporated the costs of tumour testing in line with the Committee's preference (and corrections to 2 minor errors in the model identified by the ERG) produced a probabilistic ICER of £51,600 for olaparib compared with routine surveillance. However, the Committee considered that this was likely to be an underestimate of the true ICER because it overestimated the overall survival gain associated with olaparib.	4.12, 4.13, 4.20
	The Committee was aware that using an alternative modelling approach fitting overall survival from Study 19, and including the costs of somatic testing, produced ICERs ranging from £37,900 to £66,500 using independent fitting models and £54,600 to £57,300 using a treatment-adjusted model. However, it was unsure of the validity of these results.	
	For the subgroup of people who received 3 or more lines of platinum-based chemotherapy before randomisation, the Committee concluded that the most plausible ICERs using independent fitting models were £46,600 to £46,800 per QALY gained (based on the log normal and log-logistic survival plots).	
Additional factors taken into account		
Patient access schemes (PPRS)	The company has agreed a patient access scheme with the Department of Health. This involves the NHS paying for a patient's treatment with olaparib up to a certain time, with the company providing olaparib free-of-charge beyond that point and for as long as each individual patient continues to have olaparib.	2.3

End-of-life considerations	The Committee was not persuaded that the life expectancy for the overall population of people with relapsed BRCA mutation-positive, platinum-sensitive ovarian cancer had been shown to be less than a median of 24 months without olaparib treatment. Because the 24-month life expectancy criterion had not been met, the Committee concluded that the end-of-life criteria did not apply to olaparib when considering the overall population of patients with relapsed BRCA mutation-positive, platinum-sensitive ovarian cancer. For the subgroup of patients with relapsed BRCA mutation-positive, platinum-sensitive ovarian cancer who have received 3 or more previous lines of platinum-based chemotherapy, the Committee concluded that there was sufficient evidence to suggest that olaparib met the end-of-life criteria.	4.15, 4.18 to 4.20
Equalities considerations and social value judgements	No equalities issues were identified.	–

5   Implementation

5.1   Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

5.2   The Welsh Assembly Minister for Health and Social Services has issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 3 months of the guidance being published.

5.3   When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that if a patient has relapsed, platinum-sensitive ovarian, fallopian tube or peritoneal cancer with BRCA1 or BRCA2 mutations that has responded to platinum-based chemotherapy, and the doctor responsible for their care thinks that olaparib is the right treatment, it should be available for use, in line with NICE's recommendations.

5.4   The Department of Health and AstraZeneca have agreed that olaparib will be available to the NHS with a patient access scheme. The drug cost of olaparib for people who remain on treatment after 15 months will be met by the company. It is the responsibility of the company to communicate details of the discount to the relevant NHS organisations. Any enquiries from NHS organisations about the patient access scheme should be directed to Matthew.Dyer@astrazeneca.com or Jane.Robertson@astrazeneca.com.

6   Review of guidance

6.1   NICE proposes that the guidance on this technology is considered for review by the Guidance Executive when data from the phase III SOLO-2 study becomes available or after 2 years, whichever is sooner.

Andrew Dillon
Chief Executive
January 2016

Changes after publication

February 2016: Section 5.4 about the patient access scheme added.

ISBN: 978-1-4731-1648-1

Accreditation