

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal determination

Topotecan, pegylated liposomal doxorubicin hydrochloride, paclitaxel, trabectedin and gemcitabine for treating recurrent ovarian cancer

1 Recommendations

- 1.1 Paclitaxel in combination with platinum or as monotherapy is recommended within its marketing authorisation as an option for treating recurrent ovarian cancer.
- 1.2 Pegylated liposomal doxorubicin hydrochloride (PLDH) as monotherapy is recommended within its marketing authorisation as an option for treating recurrent ovarian cancer.
- 1.3 PLDH in combination with platinum is recommended as an option for treating recurrent ovarian cancer.^{1,2.}

¹ At the time of publication (February 2016), PLDH (Caelyx) in combination with platinum did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing medicines – guidance for doctors for further information.

² The use of PLDH (Caelyx) in combination with platinum is outside the terms of the marketing authorisation for Caelyx. Consequently the statutory funding requirement does not apply to this recommendation. NICE received a remit to appraise this combination under Regulation 5 of the [National Institute for Health and Care Excellence \(Constitution and Functions\) and the Health and Social Care Information Centre \(Functions\) Regulations 2013](#).

1.4 The following are not recommended within their marketing authorisations for treating the first recurrence of platinum-sensitive ovarian cancer:

- gemcitabine in combination with carboplatin
- trabectedin in combination with PLDH
- topotecan.

The Appraisal Committee was unable to make recommendations on the use of these technologies for treating platinum-sensitive ovarian cancer beyond the first recurrence.

1.5 Topotecan is not recommended within its marketing authorisation for treating recurrent platinum-resistant or platinum-refractory ovarian cancer.

1.6 People whose treatment with gemcitabine in combination with carboplatin, trabectedin in combination with PLDH, or topotecan 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 technologies

Gemcitabine

2.1 Gemcitabine (various companies) is a chemotherapeutic agent that inhibits DNA synthesis. It is a nucleoside analogue with antitumour activity against a number of solid tumours. Gemcitabine, in combination with carboplatin, has a UK marketing authorisation for the treatment of 'patients with locally advanced or metastatic epithelial ovarian carcinoma, in combination with carboplatin, in patients with relapsed disease following a recurrence-free interval of at least 6 months after platinum-based, first-line therapy'.

- 2.2 Gemcitabine is administered by intravenous infusion. The recommended dosage is 1000 mg/m² of body surface area administered on days 1 and 8 of each 21-day cycle. After gemcitabine, carboplatin is given on day 1 consistent with a target area under curve of 4.0 mg/ml×min. The summary of product characteristics lists the following as the most common adverse reactions associated with gemcitabine treatment: leukopenia, thrombocytopenia, anaemia, dyspnoea, vomiting, nausea, elevation of liver transaminases and alkaline phosphatase, allergic skin rash, alopecia, haematuria, mild proteinuria, influenza-like symptoms and oedema/peripheral oedema.
- 2.3 Gemcitabine is available in 200 mg, 1 gram and 1.5 gram vials at net prices of £29.80, £154.82 and £213.93 respectively (excluding VAT; 'British national formulary' [BNF] October 2015). The cost of gemcitabine 1000 mg/m² for 1 cycle (based on a body surface area of 1.7 m²) on day 1 and 8 of every 21 days is £487.46 (excluding administration costs). Costs may vary in different settings because of negotiated procurement discounts.

Paclitaxel

- 2.4 Paclitaxel (various companies) is a cytotoxic anticancer drug that belongs to the taxane group of drugs. Taxanes prevent the formation of mitotic spindles, interfering with the process of cell division and resulting in cell death. Paclitaxel has a UK marketing authorisation 'for the treatment of metastatic carcinoma of the ovary after failure of standard, platinum containing therapy'.
- 2.5 Paclitaxel is administered by intravenous infusion. The recommended dosage is 175 mg/m² of body surface area administered over a period of 3 hours, with a 3-week interval between treatment cycles. Paclitaxel has also been evaluated in randomised controlled trials with a weekly interval between

treatment cycles, and this is in line with clinical practice for the treatment of platinum-refractory or -resistant recurrent ovarian cancer. The summary of product characteristics lists the following as the most common adverse reactions associated with paclitaxel treatment: infection, myelosuppression, neutropenia, anaemia, thrombocytopenia, leukopenia, bleeding, mild hypersensitivity reactions, neurotoxicity, hypotension, diarrhoea, vomiting, nausea, mucositis, alopecia, arthralgia and myalgia.

- 2.6 Paclitaxel is available in 5 ml (30 mg), 16.7 ml (100 mg), 25 ml (150 mg) and 50 ml (300 mg) vials at net prices of £66.85, £200.35, £300.52 and £601.03 respectively (excluding VAT; BNF October 2015). At list price, the cost of a dose of paclitaxel 175 mg/m² (based on an average body surface area of 1.7 m²) is £601 per 3-weekly cycle (excluding administration costs). The cost of paclitaxel 80 mg/m² is £301 per weekly dose. However, the weekly regimen is currently unlicensed. Costs may vary in different settings because of negotiated procurement discounts.

Pegylated liposomal doxorubicin hydrochloride

- 2.7 Pegylated liposomal doxorubicin hydrochloride (Caelyx, Janssen-Cilag; PLDH) is an anthracycline – a group of cytotoxic antibiotics that inhibit DNA synthesis. They also interact with cell membranes, altering their function and generating cytotoxic chemicals. PLDH has a UK marketing authorisation for the treatment of advanced ovarian cancer in women for whom a first-line platinum-based chemotherapy regimen has failed. It has been studied in combination with carboplatin for the treatment of platinum sensitive ovarian cancer but this combination does not have a marketing authorisation.

- 2.8 PLDH is administered by intravenous infusion. The recommended dosage is 50 mg/m² of body surface area once every 4 weeks for

as long as the disease does not progress and the patient continues to tolerate treatment. Using PLDH at lower doses in combination with other chemotherapeutic agents has been studied in clinical trials. The summary of product characteristics lists the following as the most common adverse reactions associated with treatment with PLDH: anorexia, nausea, stomatitis, vomiting, palmar–plantar erythrodysesthesia, alopecia, rash, asthenia, fatigue and mucositis.

- 2.9 PLDH is available in 10 ml (20 mg) and 25 ml (50 mg) vials at net prices of £360.23 and £712.49 respectively (excluding VAT; BNF October 2015). The cost per dose of PLDH 50 mg/m² (based on an average body surface area of 1.7 m²) on day 1 of every 28-day cycle is £1425 (excluding administration costs). Costs may vary in different settings because of negotiated procurement discounts.

Topotecan

- 2.10 Topotecan (various companies) is a naturally derived chemotherapeutic agent that prevents DNA replication in cancer cells. It has a UK marketing authorisation for the treatment of women with ‘metastatic carcinoma of the ovary after failure of first-line or subsequent chemotherapy’. The recommended dosage is 1.5 mg/m² of body surface area per day, administered by intravenous infusion over 30 minutes daily for 5 consecutive days, with 3 weeks between each course. If well tolerated, treatment may continue until disease progression. The summary of product characteristics lists the following as the most common adverse reactions associated with treatment with topotecan: febrile neutropenia, neutropenia, thrombocytopenia, anaemia, leukopenia, nausea, vomiting and diarrhoea, constipation, abdominal pain, mucositis, alopecia, anorexia, infection, pyrexia, asthenia and fatigue.

- 2.11 Topotecan is available in 1 mg and 4 mg vials at net prices of £87.88 and £261.55 respectively (excluding VAT; BNF October 2015). The cost of topotecan 1.5 mg/m² (based on an average body surface area of 1.7 m²) on days 1–5 every 21-day cycle is £1308 per cycle (excluding administration costs). Costs may vary in different settings because of negotiated procurement discounts.

Trabectedin

- 2.12 Trabectedin (Yondelis, PharmaMar) is an anticancer agent that binds to the minor groove of the DNA and bends the helix to the major groove, which disrupts the cell cycle. It has a UK marketing authorisation, in combination with PLDH, for the treatment of women 'with relapsed platinum-sensitive ovarian cancer'. The recommended dosage is 1.1 mg/m² of body surface area, immediately after PLDH 30 mg/m², administered every 3 weeks as a 3-hour infusion. The summary of product characteristics lists the following as the most common adverse reactions associated with treatment with trabectedin: neutropenia; thrombocytopenia; anaemia; leukopenia; anorexia; headache; vomiting; constipation; hyperbilirubinemia; fatigue; increases in alanine aminotransferase, aspartate aminotransferase, blood alkaline phosphatase, gamma-glutamyltransferase, blood creatine phosphokinase, and blood creatinine; and decrease in blood albumin.
- 2.13 Trabectedin is available in 250-microgram and 1-mg vials at net prices of £363.00 and £1366.00 respectively (excluding VAT; BNF October 2015). The cost of trabectedin 1.1 mg/m² (based on an average body surface area of 1.7 m²) is £2732 per dose (excluding administration costs).
- 2.14 The company has agreed a patient access scheme with the Department of Health. If trabectedin plus PLDH had been recommended, this scheme would apply to patients who need more

than 5 cycles of treatment, with the company authorising an appropriate rebate from cycle 6 onwards. An update to the patient access scheme was approved during the appraisal. If trabectedin had been recommended, this scheme would have provided an additional simple discount to the list price of trabectedin with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.

3 Evidence

The Appraisal Committee (section 8) considered evidence from a number of sources (section 9).

Clinical need and practice

- 3.1 Ovarian cancer is a common gynaecological cancer which represents a group of different tumours arising from diverse types of ovarian tissue. The most common type arises from epithelial cells (the outside layer of cells), and can often spread from the ovary to any surface within the abdominal cavity, including the fallopian tubes and peritoneal cavity. Symptoms of ovarian cancer tend to be non-specific and include persistent pelvic and abdominal pain, abdominal bloating, urinary frequency or urgency, loss of appetite, and abnormal or postmenopausal bleeding. Most women are diagnosed with advanced stage disease.
- 3.2 Recurrent ovarian cancer may be categorised according to the response to first-line platinum chemotherapy as follows: platinum-sensitive (disease that responds to first-line platinum-based therapy but relapses after 6 months or more,– can be further subdivided into partially platinum-sensitive disease that relapses between 6 and 12 months and fully platinum sensitive disease that relapses after 12 months or more); platinum-resistant (disease that relapses

within 6 months of completion of initial platinum-based chemotherapy); and platinum-refractory (disease that does not respond to initial platinum-based chemotherapy). However, the 'partially platinum-sensitive' and 'platinum-resistant' categories should not necessarily be defined rigidly.

- 3.3 Ovarian cancer predominantly occurs in older women, with over 80% of cases being diagnosed in women over 50 years. In 2010, around 7000 new cases of ovarian cancer were diagnosed and there were approximately 4300 deaths from ovarian cancer in the UK. The overall 5-year survival rate for ovarian cancer is approximately 43%. Although a significant percentage of women have ovarian cancer that responds to initial chemotherapy, between 55% and 75% relapse within 2 years of completing treatment with chemotherapy.
- 3.4 Fear of recurrence and subsequent treatment, particularly for women with platinum-refractory disease, has an emotional impact. Recurrence of disease is associated with poorer prognosis and treatment options are limited. Treatment for recurrent ovarian cancer is also likely to diminish people's physical and emotional wellbeing to a point where they can no longer work, or need ongoing support with day-to-day activities. In NICE technology appraisal guidance 91 (to be replaced by the recommendations in this final appraisal determination), the recommended options for the second-line (or subsequent) treatment of women with platinum-sensitive or partially platinum-sensitive advanced ovarian cancer were paclitaxel in combination with a platinum-based compound (carboplatin or cisplatin), or PLDH for partially platinum-sensitive ovarian cancer and for women allergic to platinum-based compounds. The recommended second-line (or subsequent) treatment options for women with platinum-resistant or platinum-refractory ovarian cancer, and for women allergic to platinum based

compounds, were single-agent paclitaxel, PLDH, or topotecan for women for whom PLDH and paclitaxel were considered inappropriate. NICE technology appraisal guidance 222 (also to be replaced by the recommendations in this final appraisal determination) did not recommend trabectedin in combination with PLDH for treating relapsed platinum-sensitive ovarian cancer.

Clinical effectiveness

3.5 The Assessment Group carried out a systematic review and identified 16 randomised controlled trials, evaluating 14 different pairwise comparisons that met the inclusion criteria. Eleven of these trials were open label, and the masking technique was unclear in the remaining studies. The size of the trial populations ranged from 61 to 976 patients. The interventions in the trials were paclitaxel (6 trials), pegylated liposomal doxorubicin hydrochloride (PLDH; 5 trials), topotecan (3 trials), gemcitabine (1 trial) and trabectedin (1 trial). The Assessment Group stated that 5 of these trials evaluated the interventions and comparators within their licensed indications, dosage and routes of administration. The remaining 11 trials included dosages or routes of administration different from the relevant marketing authorisations. The population in 9 of the 16 trials was restricted to women experiencing their first recurrence. This included the main trials available for gemcitabine plus carboplatin and trabectedin plus PLDH, and 3 of the 4 trials for topotecan. One trial comparing weekly topotecan with 3-weekly topotecan included women with platinum resistance who were experiencing subsequent recurrences. The Assessment Group stated that in general the trials were well designed and conducted. It expressed some concerns about the difference in baseline characteristics between trials, that masking and independent reviewer assessment in some trials was unclear, that some trials were not sufficiently powered to detect differences in overall

survival and progression-free survival, and that the results of some trials may have been confounded because patients crossed over between the intervention and control groups.

- 3.6 The Assessment Group determined that it was appropriate to analyse the results from patients with platinum-sensitive disease and patients with platinum-resistant or -refractory disease separately. Patients with platinum allergy were assumed to have the same probability of response to therapy as patients without an allergy for the same non-platinum treatments, and therefore treatments for patients with platinum allergy were not analysed separately. The Assessment Group stated that there were insufficient data for most comparisons to carry out a standard pairwise meta-analysis. Consequently, a series of network meta-analyses were conducted for platinum-sensitive disease, and platinum-resistant or -refractory disease using a Bayesian Markov Chain Monte Carlo simulation. In the absence of individual patient data for all trials, the network meta-analysis synthesised data on relative treatment effect from the whole study populations.
- 3.7 For patients with platinum-sensitive disease, it was not possible to construct a complete network based on the trials identified, and therefore it was necessary to generate 2 discrete networks. Platinum-sensitive network 1 evaluated platinum-based treatments and platinum-sensitive network 2 evaluated non-platinum-based treatments. The Assessment Group emphasised that these networks cannot be compared directly. For trials not limited to patients with platinum-sensitive, -resistant or -refractory disease, results for the full trial population were presented, but the Assessment Group stated that these results were not synthesised in a network meta-analysis because, in practice, patients with platinum-sensitive, -resistant or -refractory disease would not have

the same range of treatments and therefore the results of this analysis would not be clinically meaningful.

3.8 In general, the Assessment Group stated that treatment groups within trials were well matched. Some differences in baseline characteristics between trials were identified, in particular with respect to length of the platinum-free interval, number of previous lines of chemotherapy and the method used to diagnose recurrence. However, the Assessment Group considered that the magnitude of these differences was unlikely to affect estimates of the relative effect of treatment and the trials were sufficiently clinically homogeneous to compare the clinical effectiveness of treatments. The Assessment Group clarified that the assessment of clinical homogeneity was limited to platinum-sensitive network 1, which evaluated platinum-based therapies. For this network, the Assessment Group considered that as a result of the imbalance in Eastern Cooperative Oncology Group (ECOG) status at baseline, the treatment effect associated with platinum may have been underestimated. Baseline characteristics were not reported for subgroups, and therefore an assessment of clinical heterogeneity was not possible for platinum-sensitive network 2 evaluating non-platinum-based regimens, or for platinum-resistant or -refractory groups, because both were informed by subgroup analyses. The Assessment Group also expressed concern that the subgroup data may not have been sufficiently powered to detect differences in overall survival or progression-free survival. In addition, it was noted that statistical assessment of heterogeneity was not possible for either network, primarily because of the low number of trials identified.

3.9 The Assessment Group specified that unadjusted hazard ratios were used for progression-free survival and overall survival in the network meta-analysis. It acknowledged that adjusting for baseline

characteristics may be important because certain characteristics are considered to influence prognosis. However, in the absence of a consistent dataset for all comparisons, the Assessment Group did not consider it appropriate to analyse a blend of unadjusted and adjusted hazard ratios.

Progression-free survival

- 3.10 For platinum-sensitive network 1 evaluating platinum-based regimens, the Assessment Group included 5 trials evaluating progression-free survival in the network meta-analysis. Results from the network meta-analysis found that paclitaxel plus carboplatin, gemcitabine plus carboplatin, and PLDH plus carboplatin statistically significantly improved progression-free survival compared with platinum alone with hazard ratios of 0.73 (95% confidence interval [CI] 0.64 to 0.84), 0.71 (95% CI 0.57 to 0.90) and 0.59 (95% 0.50 to 0.71) respectively. PLDH plus carboplatin was found to be statistically significantly more effective at prolonging progression-free survival than paclitaxel plus carboplatin (HR=0.81, 95% CI 0.71 to 0.92). No other statistically significant differences were identified between platinum-combination regimens.
- 3.11 For the platinum-sensitive network 2 evaluating non-platinum-based regimens, the Assessment Group included 3 trials evaluating progression-free survival in the network meta-analysis. Results found that trabectedin plus PLDH statistically significantly improved progression-free survival compared with PLDH alone, paclitaxel alone and topotecan alone, with hazard ratios of 0.73 (95% CI 0.56 to 0.94), 0.44 (95% CI 0.26 to 0.82) and 0.55 (95% CI 0.38 to 0.82) respectively. No statistically significant differences were identified among the monotherapies evaluated (that is, PLDH, topotecan, and paclitaxel).

- 3.12 For the platinum-resistant or platinum-refractory ovarian cancer group, the Assessment Group included 3 trials evaluating progression-free survival for inclusion in the network meta-analysis. The Assessment Group also highlighted that trabectedin plus PLDH is outside of the scope for this subgroup, and although the data were included in the network to capture all the available evidence, they were not included in the economic analysis. Results from the network meta-analysis found no statistically significant differences in progression-free survival between PLDH, paclitaxel and topotecan alone, and these results were in line with results from the individual trials.
- 3.13 For the fully platinum-sensitive ovarian cancer subgroup, the Assessment Group stated that although 3 trials (OVA-301, ICON4/AGO-OVAR, and a study by Pfisterer et al.) included subgroups with fully platinum-sensitive ovarian cancer, only the OVA-301 trial reported data, so it was not possible to perform an indirect comparison. In addition, 4 trials (OVA-301, CALYPSO, ICON4/AGO-OVAR and the study by Pfisterer et al.) included subgroups with partially platinum-sensitive recurrent ovarian cancer, but only the OVA-301 and CALYPSO trials reported data, and as they did not contain a common comparator it was not possible to make an indirect comparison. The OVA-301 trial reported a statistically significant improvement in progression-free survival with trabectedin plus PLDH compared with PLDH alone (HR=0.65, 95% CI 0.45 to 0.92; p=0.015). The CALYPSO trial reported a statistically significant improvement in progression-free survival with PLDH plus carboplatin compared with paclitaxel plus carboplatin (HR=0.73, 95% CI 0.58 to 0.90; p=0.004).

Overall survival

- 3.14 For platinum-sensitive network 1 evaluating platinum-based regimens, the Assessment Group included 6 trials evaluating

overall survival in the network meta-analysis. Results indicated that PLDH plus carboplatin statistically significantly improved overall survival compared with platinum therapy alone (HR=0.79, 95% CI 0.64 to 0.97). Paclitaxel plus carboplatin was also found to statistically significantly improve overall survival compared with platinum alone (HR=0.77, 95% CI 0.66 to 0.91). No other statistically significant differences in overall survival were identified between platinum-combination regimens.

3.15 For platinum-sensitive network 2 evaluating non-platinum-based regimens, the Assessment Group included 4 trials evaluating overall survival in the network meta-analysis. Results indicated that PLDH alone statistically significantly improved overall survival compared with topotecan alone (HR=0.73, 95% CI 0.56 to 0.97). Trabectedin plus PLDH was also found to statistically significantly improve overall survival compared with topotecan alone (HR=0.60, 95% CI 0.43 to 0.86). No other statistically significant differences were identified between platinum-combination regimens.

3.16 For the platinum-resistant or platinum-refractory ovarian cancer group, the Assessment Group included 4 trials evaluating overall survival in the network meta-analysis. The Assessment Group stated that trabectedin plus PLDH is outside of the scope for this subgroup and although the data were included in the network to capture all the available evidence, the data were not included in the economic analysis. Results from the network meta-analysis found no statistically significant differences in overall survival among the treatments evaluated. This was in line with results from the individual trials.

3.17 For the fully platinum-sensitive ovarian cancer group, the Assessment Group identified 4 trials evaluating overall survival. The Assessment Group stated that it was not possible to perform a network meta-analysis because only 2 of the trials reported the

necessary data for analysis and these trials did not have a common comparator.

- 3.18 For the partially platinum-sensitive ovarian cancer group, the Assessment Group identified the same 4 trials evaluating overall survival. As before, the Assessment Group constructed 2 networks. Network 1, evaluating platinum-based regimens, included only 1 trial (CALYPSO). No statistically significant difference in overall survival was identified for PLDH plus carboplatin compared with paclitaxel plus carboplatin in this trial. For network 2, evaluating non-platinum-based regimens, results indicated that trabectedin plus PLDH statistically significantly improved overall survival compared with PLDH alone (HR=0.84, 95% CI 0.667 to 1.032). Trabectedin plus PLDH was also found to statistically significantly improve overall survival compared with topotecan alone (HR=0.60, 95% CI 0.43 to 0.86).

Quality of life

- 3.19 Of the 16 trials identified, 10 reported data on quality of life. The most commonly used scale in the trials was the EORTC QLQ-C30 questionnaire. However, the Assessment Group reported that there were considerable differences in the level of reporting of results, the questionnaires used to evaluate quality of life, and the time points for evaluation. Broadly, improvements in quality of life were identified for PLDH plus platinum compared with paclitaxel plus platinum; paclitaxel compared with oxaliplatin; and trabectedin plus PLDH compared with PLDH alone, in a subgroup of patients with partially platinum-sensitive ovarian cancer.

Adverse reactions

- 3.20 The Assessment Group stated that the most frequently reported adverse reactions in the trials reflected those listed in the individual

summaries of product characteristics. Consequently, based on advice from clinical experts, the Assessment Group limited its network meta-analyses to the following severe grade 3–4 adverse events, which it considered to be the most problematic: allergic reaction, alopecia, anaemia, fatigue, febrile neutropenia, nausea/vomiting and neuropathy. In many cases a network meta-analysis was not possible due to lack of available data. The majority of results, supplemented by the individual trial results when a network meta-analysis was not possible, indicated that the likelihoods of adverse events were not statistically significantly different across treatment regimens. However, in some instances, chemotherapies were estimated as having statistically significantly lower risks of 1 or more adverse events but significantly higher risks of other adverse events. For example, when compared with paclitaxel plus platinum, PLDH plus platinum was associated with statistically significantly lower risks of allergic reaction and alopecia but statistically significantly higher risks of anaemia and nausea/vomiting. Overall, no chemotherapy was consistently associated with either a lower risk or a higher risk of the adverse events assessed.

Cost effectiveness

Company's model – trabectedin

3.21 The company for trabectedin submitted cost-effectiveness evidence as part of its submission. The company developed a decision analytical model comparing trabectedin plus PLDH with PLDH alone in patients with recurrent platinum-sensitive ovarian cancer for whom platinum-based chemotherapy was not suitable because of allergy or intolerance or because they have partially platinum-sensitive disease. The cohort only had 1 previous platinum-based chemotherapy regimen, and experienced recurrence or progression.

- 3.22 The structure was identical to the model developed for NICE technology appraisal guidance 91. Disease was classified into 3 distinct periods: stable disease, progressive disease, and death.
- 3.23 The company stated that because the OVA-301 trial was not powered for subgroup analysis within the platinum-sensitive group, data for the entire platinum-sensitive population were considered appropriate for the cost-effectiveness analyses. The company fitted 5 parametric survival distributions, adjusting for potential covariates. Based on the Weibull distributions, the mean progression-free survival for trabectedin plus PLDH and PLDH alone was 11.26 and 8.25 months respectively. Based on the log-logistic distributions, the mean overall survival for trabectedin plus PLDH and PLDH alone was 44.69 and 34.97 months respectively.
- 3.24 The company's base-case deterministic results, incorporating the patient access scheme for trabectedin, indicated incremental costs of £13,397 and incremental quality-adjusted life years (QALYs) of 0.49 for trabectedin plus PLDH compared with PLDH alone, resulting in an incremental cost-effectiveness ratio (ICER) of £27,573 per QALY gained. The corresponding probabilistic results indicated an ICER of £27,761 per QALY gained, and the ICER was most sensitive to the estimate of overall survival. Scenario analyses indicated that the results were also sensitive to the adjustment of the platinum-free interval as an explanatory variable and alternative survival distributions for progression-free survival and overall survival.
- 3.25 The company argued that trabectedin was eligible for consideration under the end-of-life criteria. It stated that trabectedin plus PLDH was indicated for women with a life expectancy of less than 2 years without treatment: for patients treated with PLDH alone, median overall survival in the platinum-sensitive and partially platinum-sensitive populations was 24.1 months and 16.4 months

respectively. Accounting for the imbalance in platinum-free interval and other prognostic factors in the platinum-sensitive population reduced the median to 19.4 months. For women with platinum-sensitive and partially platinum-sensitive recurrent ovarian cancer, trabectedin treatment increased median survival (after correction of prognostic factors including progression-free interval) by 4 months, and the estimated mean survival suggested this extension of life could be in excess of 9 months. The company also estimated that trabectedin would be indicated for approximately 500 women with relapsed platinum-sensitive ovarian cancer in 2014.

Assessment Group's model

3.26 The Assessment Group conducted a systematic review and stated that no cost-effectiveness analyses including the full range of interventions and comparators were available in the literature. It noted that the majority of analyses available were based on the model developed for NICE technology appraisal guidance 91. The Assessment Group considered that this model structure, also adopted by the company for trabectedin, was the most appropriate for the decision problem, and therefore used it to develop a de novo model. The model had a lifetime time horizon, which was set as 15 years because at this point over 99.9% of patients in the model would have died. In NICE technology appraisal guidance 91, and other models based on it, the time spent in each health state was based on the estimated mean time to progression (time spent in the stable disease health state) and mean time to death (time spent in the progressed disease health state, after subtracting time spent in the stable disease health state). The Assessment Group incorporated a similar methodology to estimate the proportion of patients in each health state, but full survival curves rather than mean estimates were derived from the clinical data for each therapy. The Assessment Group stated that this would

appropriately capture time in the economic model, and facilitate the assignment of costs, utilities and discounting.

3.27 The NICE scope for this appraisal specified that the interventions of interest for women with platinum-sensitive ovarian cancer were paclitaxel alone or paclitaxel plus platinum chemotherapy, PLDH alone or PLDH plus platinum chemotherapy, gemcitabine plus carboplatin, trabectedin plus PLDH, and topotecan. The Assessment Group explained that although all interventions specified in the scope were considered, 2 independent networks were constructed evaluating platinum and non-platinum-based regimens, and therefore interventions were not simultaneously compared with each other.

3.28 The populations with platinum-sensitive disease and platinum-resistant or -refractory disease were modelled separately and there was no explicit analysis of the full population. The Assessment Group explained that this was because separation of the results by platinum sensitivity is more clinically relevant because the platinum-free interval was a key prognostic factor, as confirmed by experts, and this approach was also in line with the data available to inform the analysis. The Assessment Group stated that data for women with fully or partially platinum-sensitive disease was insufficient, so these groups were considered in sensitivity rather than base-case analyses. The Assessment Group considered that response to non-platinum-based therapies would be expected to be consistent between patients with or without an allergy or intolerance to platinum-based therapy. Therefore, the platinum-allergic subgroup was included in platinum-sensitive network 2 and platinum-resistant and platinum-refractory subgroups.

3.29 The Assessment Group noted 3 main concerns with the use of data from the network meta-analyses in the model. First, due to lack of individual patient data, the network meta-analyses synthesised

data from the whole trial population. Individual patient data would have allowed for differences in baseline characteristics within and between trials to be incorporated. In addition, as discussed in section 3.9, unadjusted hazard ratios were incorporated, which could include potential bias. Second, using hazard ratios based on the literature assumes proportional hazards; that is, the relative treatment effects captured by the hazard ratios hold true across all time points. However, log-cumulative hazard plots indicated that this assumption may not be appropriate. The Assessment Group highlighted that when the relative hazard decreases over time for both progression-free survival and overall survival, the model was likely to overestimate the relative benefit of treatment and vice versa. Third, it was noted that several of the included trials allowed for crossover, which could have confounded overall survival data. The Assessment Group was unable to assess the degree of crossover bias because of a lack of individual patient data and because none of the trials described the crossover treatment.

- 3.30 The Assessment Group included grade 3 and 4 adverse events associated with significant costs in the base-case analysis – allergic reaction, anaemia, febrile neutropenia, nausea and vomiting. The relative likelihood of an adverse event associated with each therapy was estimated from the network meta-analysis. Adverse events were not analysed by population because of a lack of data; instead, adverse event data from any population (platinum sensitive or platinum resistant/refractory) were included in the analysis, therefore assuming that the likelihood of an adverse reaction is independent of the platinum-free interval. Inconsistent reporting between trials led to differences in the networks of treatments available to assess the relative effect of treatment on each adverse event. Consequently, estimates of the impact of treatment on the rates of adverse events were not available for all treatments for all adverse events. Although it was possible to

estimate the possibility of each adverse event for the baseline treatment in each network, odds ratios and expert opinion were used to estimate probabilities for the remainder.

3.31 The Assessment Group conducted a systematic review and identified 22 studies measuring health-related quality of life. It was noted that the utility values based on the OVA-301 trial were most relevant, because EQ-5D utility values in the recurrent ovarian cancer population for the health states needed for the economic model were reported, and were based on a large sample of patients (n=600). The company clarified that these utilities were derived from the platinum-sensitive population (n=400). The mean estimates of utility in the stable and progressive disease health states were estimated to be 0.718 and 0.649 respectively. These estimates were used in NICE technology appraisal guidance 222, and were identical to the EQ-5D data identified by the Assessment Group from the systematic review of the literature. Disutilities associated with adverse events were not included in the base-case analysis because the estimates identified were based on small samples. This was also to avoid double counting, because the effect of adverse events on quality of life associated with trabectedin plus PLDH and PLDH alone were already included in health state EQ-5D estimates from NICE technology appraisal guidance 222. This was explored in sensitivity analyses.

3.32 The Assessment Group model included costs associated with the technologies, administration costs, health state-related costs and adverse event costs. Chemotherapy costs per cycle were estimated using drug costs in the 'British national formulary' (BNF). The regimens used were as per the summaries of product characteristics (see section 2), except for PLDH, which was assumed to be started at a dose of 40 mg/m² of body surface area in the base case (the licensed dose was considered in a scenario

analysis) and paclitaxel, which was assumed to be used in a weekly regimen (80 mg/m²/week) in the platinum-resistant or refractory subgroup only. These modifications were based on the advice of clinical experts and were intended to reflect the regimens used in clinical practice in the NHS.

- 3.33 The model assumed that treatments would be administered as infusions in a hospital, and associated administration costs were included in the model. For the base-case analyses, it was assumed that no vial sharing would happen.

Results of network 1 – platinum-based regimens in platinum-sensitive disease

- 3.34 Both deterministic and probabilistic results indicated that PLDH plus platinum was strictly dominated by (that is, it was more costly and less effective than) paclitaxel plus platinum. Similarly, gemcitabine plus carboplatin was extendedly dominated by paclitaxel plus platinum (that is, its ICER was higher than that of the next, more effective, option when compared with platinum). Therefore, PLDH plus platinum and gemcitabine plus carboplatin were excluded, leaving paclitaxel plus platinum compared with platinum alone as the only relevant comparison for this network. For this comparison, the deterministic ICER was estimated as £24,361 per QALY gained; paclitaxel plus platinum was associated with an estimated incremental cost of £5694 and an additional 0.23 quality-adjusted life years (QALYs) when compared with platinum alone. The probabilistic ICER for paclitaxel plus platinum compared with platinum alone was £24,539 per QALY gained. The Assessment Group also estimated an ICER of £114,410 per QALY gained for gemcitabine plus carboplatin compared with platinum alone and an ICER of £30,188 per QALY gained for PLDH plus platinum compared with platinum alone.

3.35 One-way sensitivity analyses on various model parameters indicated that the comparisons of paclitaxel plus platinum, and PLDH plus platinum, when compared with platinum alone, were most sensitive to the relative effect of treatment on overall survival. For example:

- When the lower bounds of the hazard ratio for survival for gemcitabine plus carboplatin compared with paclitaxel plus platinum was used, the ICER for gemcitabine plus carboplatin compared with platinum alone was £23,578 per QALY gained. However when the upper bound was used, gemcitabine plus carboplatin was dominated.
- When the hazard ratio for survival for platinum alone compared with paclitaxel plus platinum was used, gemcitabine plus carboplatin was dominated by platinum alone. When the lower bound of the hazard ratio for survival for gemcitabine plus carboplatin compared with paclitaxel plus platinum was used, paclitaxel plus platinum was less costly and less effective than gemcitabine plus carboplatin. When the upper bound was used, the ICER was £8719 per QALY gained.
- When the lower bound of the hazard ratio for survival for PLDH plus platinum compared with paclitaxel plus platinum was used, the ICER for PLDH plus platinum compared with paclitaxel plus platinum was £20,672 per QALY gained. When the upper bound was used, PLDH plus platinum was less costly and less effective than paclitaxel plus platinum.

The Assessment Group stated that the impact of other parameters, such as the relative effect of treatment on progression-free survival and the utility value associated with each health state, were relatively minimal.

3.36 Probabilistic sensitivity analyses indicated that at a maximum acceptable ICER of £20,000 per QALY gained, the probabilities of paclitaxel plus platinum or PLDH plus platinum being considered cost effective compared with platinum alone were 13% and 3% respectively. Furthermore, PLDH plus platinum was estimated to be almost as likely to result in greater costs and QALYs as to be dominated by paclitaxel plus platinum. The Assessment Group highlighted that the costs and QALYs accumulated by the addition of paclitaxel or PLDH to platinum therapy were similar, producing cost-effectiveness estimates that were sensitive to minor changes in parameter estimates.

Results of network 2 – non-platinum-based regimens in platinum-sensitive disease

3.37 Base-case results (deterministic and probabilistic) indicated that topotecan was dominated by PLDH. Topotecan was therefore removed from the analysis and the relevant fully incremental comparisons of PLDH compared with paclitaxel and trabectedin plus PLDH compared with PLDH alone were presented. When compared with paclitaxel, PLDH was associated with an incremental cost of approximately £3900 and approximately 0.16 additional QALYs. This resulted in ICERs of £23,733 and £25,931 per QALY gained in the deterministic and probabilistic analyses, respectively. When compared with PLDH alone, trabectedin plus PLDH was associated with an incremental cost of approximately £13,000 and 0.16 additional QALYs. The resulting ICERs for trabectedin plus PLDH compared with PLDH alone were £85,212 and £81,353 per QALY gained in the deterministic and probabilistic analyses respectively.

3.38 The Assessment Group did a series of one-way sensitivity analyses on various model parameters. In network 2, the cost-effectiveness estimates for all 3 comparisons (PLDH compared with paclitaxel,

trabectedin plus PLDH compared with paclitaxel, and trabectedin plus PLDH compared with PLDH alone) were most sensitive to the relative effect of treatment on overall survival:

- When the lower bound of the hazard ratio for overall survival for paclitaxel compared with PLDH was used, PLDH dominated paclitaxel, but when the upper bound was used the ICER for PLDH compared with paclitaxel was £15,900 per QALY gained.
- When the lower bound of the hazard ratio for survival for trabectedin plus PLDH compared with PLDH alone was used, the ICER for trabectedin plus PLDH compared with PLDH alone was £44,266 per QALY gained. When the upper bound was used, PLDH alone dominated trabectedin plus PLDH.
- When the lower bound of the hazard ratio for overall survival for trabectedin plus PLDH compared with PLDH alone was used, the ICER for trabectedin plus PLDH compared with topotecan was £18,437 per QALY gained. When the upper bound was used, the ICER was £30,754 per QALY gained.
- When the lower bound of the hazard ratio for survival for topotecan compared with PLDH was used, the ICER for trabectedin plus PLDH compared with topotecan was £35,482 per QALY gained. When the upper bound was used, the ICER was £18,478 per QALY gained.

3.39 The Assessment Group did a series of scenario analyses and noted that the base-case results were robust in the majority of the scenarios modelled, with the exception of the scenario in which PLDH monotherapy was assumed to be used at its full licensed dose (50 mg/m² of body surface area). In this scenario topotecan remained dominated, the deterministic ICER for PLDH compared with paclitaxel increased from £23,733 to £31,222 per QALY gained and the deterministic ICER for trabectedin plus PLDH compared with PLDH alone fell from £85,212 to £77,290 per QALY

gained. The Assessment Group stated that apart from this scenario, the ICER for PLDH compared with paclitaxel remained below £30,000 per QALY gained and highlighted that topotecan was dominated by trabectedin plus PLDH in every scenario. The Assessment Group also carried out an exploratory scenario analysis, using covariate-adjusted clinical-effectiveness data from the company for trabectedin's submission, for a head-to-head comparison of trabectedin plus PLDH compared with PLDH alone. This resulted in an ICER of £35,646 per QALY gained, compared with ICERs of £85,212 and £27,573 estimated by the Assessment Group's and the company's base-case analyses respectively. The Assessment Group stated that this difference was predominantly a consequence of using adjusted clinical-effectiveness data.

Results of network 3 – platinum-resistant and platinum-refractory group

- 3.40 The Assessment Group explained that data for paclitaxel plus platinum were not available from the literature for women with platinum-resistant or -refractory ovarian cancer, so this intervention was not included in the base-case analysis. Base-case results showed that paclitaxel was dominated by PLDH alone. In the probabilistic analysis, paclitaxel was associated with an incremental cost of £901 and 0.022 fewer QALYs. Therefore, topotecan compared with PLDH was the only comparison considered in the final cost-effectiveness analysis. Topotecan was associated with an incremental cost of approximately £7000 and 0.02 additional QALYs relative to PLDH. The resulting ICERs for topotecan compared with PLDH were £449,553 and £324,188 per QALY gained in the deterministic and probabilistic analyses respectively.
- 3.41 As with platinum-sensitive networks 1 and 2, the cost-effectiveness results were most sensitive to the relative effect of treatment on overall survival:

- When the lower bound of the hazard ratio for overall survival for paclitaxel compared with PLDH was used, the ICER for paclitaxel compared with PLDH was £17,904 per QALY gained. When the upper bound was used, paclitaxel was less costly and less effective.
- For the incremental comparison of topotecan with paclitaxel, when the lower bound of the hazard ratio for overall survival for topotecan compared with PLDH was used, the ICER was £39,903 per QALY gained. When the upper bound was used, topotecan dominated paclitaxel.
- When the lower bound of the hazard ratio for overall survival for paclitaxel compared with PLDH was used, topotecan dominated paclitaxel. When the upper bound was used, the ICER for topotecan compared with paclitaxel was £39,485 per QALY gained.

3.42 The Assessment Group did a series of scenario analyses and noted that the base-case results were robust in the majority of the scenarios modelled. It highlighted that the ICER for topotecan compared with PLDH ranged from £374,963 to £503,885 per QALY gained across the scenarios. Paclitaxel was dominated in all scenarios except when the cost associated with a 50 mg/m² dose of PLDH was used and paclitaxel became the least costly treatment, resulting in an ICER of £10,480 per QALY gained for PLDH compared with paclitaxel. In an additional analysis, done after the appraisal had been referred back to the Committee after appeal, the Assessment Group modelled paclitaxel used at its licensed dose of 175 mg/m² of body surface area every 3 weeks (instead of the weekly regimen used in the base case for the network 3 analysis). In this scenario, the costs associated with paclitaxel were lower and it was no longer dominated. The ICERs for PLDH, relative to paclitaxel, were £69,935 per QALY gained at

a dose of 40 mg/m² of body surface area and £103,810 per QALY gained at a dose of 50 mg/m² of body surface area.

Additional analyses submitted by the company for trabectedin in response to consultation

- 3.43 Following consultation on the post-appeal appraisal consultation document the company submitted an analysis that retrospectively adjusted survival outcomes, treating the platinum-free interval as a categorical rather than a continuous variable. The analysis categorised patients with platinum-sensitive disease into a partially platinum-sensitive disease subgroup (platinum-free interval 6–12 months) and a fully platinum-sensitive disease subgroup (platinum-free interval more than 12 months). The company reported that the mean platinum-free interval was balanced between the two arms of the trial in the partially platinum-sensitive subgroup but that there was a 3.8 month (17%) difference favouring PLDH in the fully platinum-sensitive group, which warranted adjusting progression-free survival and overall survival by categorical platinum-free interval strata.
- 3.44 In a Cox regression analysis comparing trabectedin plus PLDH with PLDH alone, adjusting for the platinum-free interval as a categorical variable and covariates (age, race, ECOG performance score, the antigen CA-125, prior taxane use, and liver or lung involvement), the hazard ratio for progression-free survival was 0.68, 95% CI 0.52 to 0.90. Mean progression-free survival was 11.19 months with trabectedin plus PLDH and 8.28 months with PLDH alone, an incremental improvement of 2.92 months. For overall survival, the hazard ratio was 0.78, 95% CI 0.62 to 0.99, and mean overall survival was 45.03 months with trabectedin plus PLDH and 36.68 months with PLDH alone, an incremental improvement of 8.36 months.

3.45 The company updated its economic model to adjust for the platinum-free interval as a categorical variable, ECOG performance score and the antigen CA125. Its analyses also incorporated the updated patient access scheme (see section 2.14). This changed the ICER for trabectedin plus PLDH compared with PLDH alone from £27,572 per QALY gained to £28,573 per QALY gained.

Assessment Group's comments on the additional evidence submitted by the company for trabectedin

3.46 The Assessment Group considered that the imbalance between the treatment groups in the platinum-free interval observed in OVA-301 did not warrant analysing the data by categorical variable. It also considered that the company's new analysis was another post-hoc analysis and therefore subject to the same concerns as the analysis of the platinum-free interval as a continuous variable. The Assessment Group commented that results from a second, independent study would be needed to demonstrate an association between duration of the platinum-free interval and response to non-platinum based treatments. It maintained that unadjusted hazard ratios should be used for survival outcomes because a consistent dataset of adjusted hazard ratios was not available to inform the network meta-analysis.

3.47 The Assessment Group incorporated the updated patient access scheme (see section 2.14) into its model. The ICER for trabectedin plus PLDH compared with PLDH alone remained above £70,000 per QALY gained. When the Assessment Group also incorporated the company's hazard ratios that were adjusted for the platinum-free interval as a categorical variable and covariates (see section 3.44), the ICER fell to £59,772 per QALY gained. Changing the dose of PLDH monotherapy from 40 mg/m² to 50 mg/m² further reduced the ICER to £54,059 per QALY gained.

4 Committee Discussion

The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of topotecan, PLDH, paclitaxel, trabectedin and gemcitabine, having considered evidence on the nature of recurrent ovarian cancer and the value placed on the benefits of these technologies by women 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 heard from clinical experts that women with recurrent ovarian cancer can experience several relapses after initial treatment with platinum-based chemotherapy, and it was very important to have a range of treatment options available at each relapse. The clinical experts stated that treatment is tailored to individuals, taking into account factors such as previous treatment, and the potential for developing platinum resistance. The patient experts stated that there is no screening programme for ovarian cancer and disease is usually identified at an advanced stage. They highlighted the emotional impact of developing recurrent ovarian cancer, particularly emphasising the fear of further recurrence and the great importance of progression-free survival to patients' wellbeing. They also highlighted the psychological benefit of having a range of treatment options available. The clinical experts stated that ovarian cancer is increasingly seen as a group of diseases, that histological subtype plays an important role in how the disease responds to particular treatments, and that many treatments are not very effective in the rarer histological subtypes. Therefore, a range of chemotherapy agents is needed until more targeted therapies become available. The Committee heard that approximately 70% of people with ovarian cancer have serous adenocarcinoma, and this was not expected to vary significantly across the trials included in the review. The Committee concluded

that progression-free survival was an important outcome measure and noted that availability of a range of treatment options is valuable for treating recurrent ovarian cancer.

4.2 The Committee discussed current clinical practice for treating recurrent ovarian cancer. The Committee heard from the clinical experts that the Assessment Group's approach of presenting results separately for women with platinum-sensitive disease and platinum-resistant or platinum-refractory disease was appropriate. The Committee heard that the majority of patients in clinical practice have platinum-sensitive disease at first recurrence, but this proportion would decline at each subsequent recurrence. The clinical experts stated that standard treatment for women with platinum-sensitive disease, including those with partially platinum-sensitive disease, is platinum-combination chemotherapy. The clinical experts pointed out that the platinum-resistant and platinum-refractory group is heterogeneous because it includes women whose disease may never have responded to platinum as well as women whose disease developed resistance over time. The Committee noted that no trials had taken this into account. The Committee heard from the clinical experts that only a small proportion of women are allergic to a particular platinum agent such as carboplatin, and that these women are offered either an alternative platinum agent (cisplatin) or non-platinum regimens. Desensitisation could also be carried out. The Committee considered the Assessment Group's assumption that women with a platinum allergy would have the same probability of response to non-platinum regimens as women without an allergy to be appropriate. The Committee concluded that the Assessment Group's approach to the decision problem was appropriate.

4.3 The clinical experts stated that in clinical practice, the licensed dose may not be adhered to. For example, the licensed 3-weekly

paclitaxel regimen is used for platinum-sensitive disease, but it is established clinical practice to use weekly paclitaxel for treating platinum-refractory or platinum-resistant disease. The Committee was aware that the trials in platinum sensitive disease used 3-weekly paclitaxel. One of the trials identified by the Assessment Group in platinum refractory/resistant disease (Lorthoraly et al.) used a weekly paclitaxel regimen. Although this trial had not been included in network 3, the experts consulted by the Assessment Group and the clinical experts at the appraisal committee meeting all confirmed that this was now standard practice in platinum-refractory or resistant disease. The Committee also heard that in practice, PLDH monotherapy is usually used at a lower dose than specified in the licence, and that the 40 mg/m² dose had become standard practice. For platinum-sensitive disease in people who could not take platinum, the Committee noted that one of the trials in network 2 used a dose of 45 mg/m² (Bafaloukos et al.). The Committee concluded that in clinical practice the licensed dose is frequently adjusted to balance efficacy against toxicity, and that there was strong clinical opinion that using 40 mg/m² PLDH as monotherapy in platinum sensitive or resistant disease, or a weekly regimen of paclitaxel in platinum-resistant or refractory disease does not reduce the clinical effectiveness of the treatments.

4.4 The Committee discussed the clinical-effectiveness evidence available, focusing on results from the Assessment Group's network meta-analyses. The Committee noted the following:

- For women with platinum-sensitive disease who had platinum-based treatment, paclitaxel, PLDH and gemcitabine (all plus carboplatin) statistically significantly improved progression-free survival compared with platinum alone. For overall survival, PLDH and paclitaxel (both plus carboplatin) gave statistically significant improvements compared with platinum alone, but

there was no statistically significant overall survival benefit from gemcitabine plus carboplatin compared with platinum alone. The Committee questioned the possible reasons why the progression-free survival benefit seen with gemcitabine plus carboplatin did not translate into an overall survival benefit in the trial or network meta-analyses as it did for PLDH and paclitaxel. The clinical experts cautioned that it is difficult to show overall survival benefits because multiple lines of treatment have a confounding effect. However, they also stated that because of the lack of overall survival benefit in the trial, in some centres gemcitabine is given only when paclitaxel plus platinum and PLDH plus platinum are unsuitable.

- For women with platinum-sensitive disease who could not have platinum-based treatment, trabectedin plus PLDH statistically significantly improved progression-free survival compared with PLDH alone, paclitaxel alone and topotecan alone. In addition, for overall survival, both PLDH monotherapy and trabectedin plus PLDH were associated with statistically significant improvements compared with topotecan.
- For women with platinum-resistant or -refractory disease, no statistically significant differences between PLDH, paclitaxel and topotecan were identified for progression-free survival or overall survival.

4.5 The Committee discussed the limitations of the analysis, particularly the differences in baseline characteristics between trials, uncertainty about whether trials were adequately powered to detect differences in overall survival and progression-free survival, and concerns about confounding because of crossover. However, the Committee also heard from the clinical experts that the results of the network meta-analyses were broadly in line with those expected from both the trial data and experience in clinical practice.

The Committee acknowledged that the analyses had

methodological limitations and that some assumptions had to be accepted. However, it noted that they had been constructed using hazard ratios from peer reviewed publications, and represented a distillation and systematic analysis of the same body of evidence that is used by clinicians and patients when deciding between the various treatments. The Committee expressed disappointment with the quality and breadth of the trial evidence, and also with some of the trial design and reporting, but on balance agreed that the Assessment Group's approach was reasonable given the data available, and accepted the clinical-effectiveness results from the network meta-analyses. It concluded that for women with platinum-sensitive disease, paclitaxel, gemcitabine and PLDH (all plus carboplatin) improved progression-free survival compared with platinum alone and that PLDH and paclitaxel (both plus carboplatin) also improved overall survival. It also concluded that trabectedin plus PLDH improved progression-free survival compared with PLDH, paclitaxel and topotecan (all given alone), and that there was evidence that PLDH alone and trabectedin plus PLDH increased overall survival compared with topotecan. Finally, it accepted that for women with platinum-resistant or platinum-refractory disease, there were no statistically significant differences in progression-free and overall survival between PLDH, paclitaxel and topotecan.

- 4.6 The Committee discussed the cost-effectiveness analyses conducted by the Assessment Group. It considered the cost-effectiveness results based on network 1 for women with platinum-sensitive recurrent ovarian cancer receiving platinum-based chemotherapy, and noted that the fully incremental deterministic results indicated that paclitaxel plus platinum was the most cost-effective treatment, with an ICER of £24,400 per QALY gained compared with platinum alone. The Committee also noted that although PLDH plus platinum was dominated by paclitaxel plus

platinum and was therefore excluded from the fully incremental analysis, the costs and QALYs were very similar to those of paclitaxel plus platinum, and the ICER for PLDH plus platinum compared with platinum alone was approximately £30,200 per QALY gained. The Committee concluded that paclitaxel plus platinum was the most cost-effective option for women with recurrent platinum-sensitive ovarian cancer but that PLDH plus platinum could also be considered a cost-effective alternative.

- 4.7 After an appeal against its provisional guidance, the Committee revisited its recommendation for using PLDH in combination with carboplatin. It was aware that use of this combination, based on the CALYPSO trial, requires giving PLDH at a dose lower than that specified in the marketing authorisation for PLDH (Caelyx), but at a dose equivalent to its licence for use in combination with trabectedin. During the appraisal, NICE had requested an exceptional direction from the Department of Health to make a recommendation for a drug outside the terms of its marketing authorisation. The Committee had expressed concern that without such a direction, it would only be able to recommend a combination of paclitaxel and platinum for people with platinum-sensitive disease, and that paclitaxel would not be suitable for some people because of toxicity or intolerance. In addition, the combination of PLDH with platinum is both clinically and cost effective, and is currently in clinical use. After NICE's request, the Department of Health obtained Ministerial agreement to direct NICE to make a recommendation under regulation 5 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013. The Committee understood that this exceptional direction was given in the light of the Committee's appraisal of the evidence, and took into account the need for a range of options for treating platinum-sensitive recurrent disease. The Committee was aware

that under regulation 5, its recommendation would not be associated with mandatory funding and this was stated in the final appraisal determination issued to consultees for appeal. However, prolonged negotiations had delayed release of the document, and the wording in the final appraisal determination differed from that in the provisional recommendations in the appraisal consultation document. The Appeal panel found that it was unfair not to have communicated transparently and provided an opportunity for consultees and commentators to respond to the proposed recommendation for the use of PLDH with platinum. On hearing the appeal panel's findings, the Committee agreed that its recommendations were appropriate, and should stand, but that in line with the Appeal panel's decision, consultees and commentators should have a further opportunity to comment on the document. Following consultation, in which no comments were received on the provisional recommendation for PLDH in combination with carboplatin, the Committee concluded that the recommendation was appropriate.

- 4.8 The Committee discussed the cost-effectiveness results for gemcitabine plus carboplatin based on network 1. It noted that gemcitabine plus carboplatin was extendedly dominated and was therefore excluded from the incremental analysis including all the treatment options. It also noted that the cost-effectiveness estimates based on the network 1 meta-analysis showed that gemcitabine plus carboplatin resulted in an ICER compared with platinum alone of £114,000 per QALY gained. The Committee noted that the results of the economic model based on the network 1 meta-analysis showed that gemcitabine plus carboplatin produced fewer QALY gains, representing less clinical benefit than paclitaxel plus platinum and PLDH plus platinum. The Committee considered that this was primarily because of the lack of overall survival benefit demonstrated with gemcitabine plus carboplatin in

the study by Pfisterer et al. The Committee noted that this trial was powered to detect a statistically significant difference in progression-free survival between treatments but not to detect a statistically significant difference in overall survival. It also noted statements from one of the clinical experts that the trial took place at a time when few post-progression therapies were available, and that overall survival has since improved because patients are now offered multiple lines of therapy. The Committee noted that extended follow-up data from Pfisterer et al. were not available. However if multiple lines of follow-on therapies had been given, although this could have increased the overall survival in both arms, confounding from subsequent lines of therapy might make the comparison between gemcitabine plus platinum and platinum alone even less reliable. Following consultation, the Committee also considered a suggestion that an overall survival advantage might not have been found because patients in the trial had received a prior taxane and might therefore have had more resistant disease than patients in other studies. The Committee acknowledged that there were uncertainties but concluded that Pfisterer et al. was the only relevant randomised controlled trial of gemcitabine plus platinum compared with platinum alone on which it could base its recommendations. It was of reasonable size, properly conducted, and was therefore appropriate for decision-making as part of the network 1 meta-analysis. The trial had not shown a statistically significant improvement in overall survival for gemcitabine plus platinum compared with platinum alone, unlike the combinations of paclitaxel and PLDH with platinum. The Committee agreed that any gain in progression-free survival was important to patients, but was satisfied that the benefits of treatment with gemcitabine on progression-free survival had been adequately captured in the model.

- 4.9 Although the Committee was satisfied that the network meta-analysis was suitable for decision-making, it noted that the clinical evidence for gemcitabine plus platinum that informed the cost-effectiveness analysis only included women with a first recurrence of ovarian cancer, at which stage paclitaxel plus platinum or PLDH plus platinum would be alternative treatment options. The Committee acknowledged that the sensitivity analysis around overall survival estimates indicated a high degree of uncertainty, and it concluded that gemcitabine could not be considered a cost-effective use of NHS resources for treating a first recurrence of platinum-sensitive ovarian cancer.
- 4.10 The Committee heard from the clinical experts that patients with ovarian cancer often had multiple lines of treatment, and that it was important to have a wide range of treatments available for use in future recurrences. The Committee noted that there was no evidence included in the assessment report on the clinical effectiveness of gemcitabine for recurrences after the first. It noted that the marketing authorisation for gemcitabine did not explicitly limit it to first recurrence. Although the Committee accepted the results of the network meta-analysis, it considered that it could not assume that identical results for relative clinical effectiveness would be found in women who had a second or subsequent recurrence. The Committee concluded that it could not make any recommendation about the clinical or cost effectiveness of gemcitabine beyond the first recurrence of platinum-sensitive ovarian cancer, and that clinicians should take this into account when considering gemcitabine plus carboplatin as a treatment option.
- 4.11 The Committee discussed the cost-effectiveness results based on network 2 in women with platinum-sensitive disease receiving non-platinum-based treatments. The Committee noted that the ICER for

PLDH monotherapy compared with paclitaxel monotherapy was approximately £23,700 per QALY gained. It also noted the Assessment Group's comments that the costs and QALYs associated with paclitaxel were similar to those of PLDH. The Committee noted that in the base case analysis the cost of PLDH monotherapy was based on the assumption that it was given at a dose lower than the dose specified in the summary of product characteristics. The Committee recalled that the clinical experts had confirmed that dose-reduction was usual in clinical practice (see section 3.46), and that the clinical effectiveness at this dose was considered to be comparable with the trial evidence. However, it was also aware that the appeal panel required the Appraisal Committee to clarify and justify the reasoning for its choice of appropriate dose regimens for different treatments and the costs used in the cost-effectiveness analyses. The Committee therefore gave further consideration to its choice of the most appropriate costing for all treatments in the modelling of cost effectiveness. The Committee discussed the 3 possibilities for estimating drug costs: the dose used in clinical practice in the NHS, where this was well established; the licensed dose; and the average doses used in the trials that informed the networks. The Committee noted paragraph 5.5.1 from the NICE [Guide to the methods of technology appraisal](#) 2013 which states that 'For the reference case, costs should relate to resources that are under the control of the NHS. These resources should be valued using the prices relevant to the NHS'. The Committee noted that the Assessment Group had used the doses in clinical practice as the most relevant. The Committee was minded to agree that for a complex appraisal of several different treatments in 3 different clinical scenarios, the dose used in clinical practice, where this was well established, was the most relevant for estimating the cost of treatment in the NHS. However, it reconsidered the other options. With regard to using the licensed

doses for all treatments, and assuming adherence to the full licensed starting dose for the whole course of treatment, the Committee noted that there was clear evidence that for some treatments this did not happen in clinical practice, and indeed the marketing authorisation allowed dose reduction in the case of toxicity. The Committee concluded that calculating costs on the assumption of adherence to the full starting dose was less relevant to the NHS than the doses used in clinical practice. Regarding the use of average trial doses, several trials had been used in the networks to assess clinical effectiveness. The Committee anticipated that the average dose received by patients in the trials would be lower than the licensed dose, because of toxicity, but estimates of the average dose were not uniformly available. Although the Committee appreciated that the doses used in clinical practice, even when these are well established, may not be identical to the average doses in the trials, it was reassured that there was no clinical expectation that the effectiveness achieved by the treatments as currently administered in the NHS would be significantly different to the effectiveness demonstrated in the trials. The Committee concluded that the doses used in clinical practice were generally agreed and consistent, and most relevant to the NHS. It therefore agreed with the Assessment Group, and its own previous conclusion, that cost estimates based on doses used in clinical practice were the most appropriate to use in the cost effectiveness analyses. Specifically for PLDH, the Committee considered that the estimate of treatment cost based on the licensed dose was higher than would be achieved in clinical practice and consequently the ICER of £31,200 per QALY gained for PLDH compared with paclitaxel (see section 3.39) was too high and the base case estimate of the ICER (£23,700 per QALY gained, see section 3.37) was reasonable. The Committee concluded that both paclitaxel and PLDH could be recommended

for use in the NHS for women with platinum-sensitive disease for whom platinum-based treatment was unsuitable.

- 4.12 In network 2, topotecan produced the fewest QALYs compared with PLDH monotherapy, trabectedin plus PLDH, and paclitaxel. However, it was associated with higher costs than both PLDH and paclitaxel monotherapy and was therefore dominated and excluded from the fully incremental analysis. The Committee agreed that in the network meta-analysis topotecan had not been demonstrated to be cost effective for the treatment of platinum-sensitive ovarian cancer in women unable to take platinum and that this remained the case in the sensitivity analyses. It understood that having a range of treatment options was desirable, although topotecan was not widely used in clinical practice. However, the Committee also acknowledged that the bulk of the evidence for topotecan in the context of platinum-sensitive disease was for women with a first recurrence. The Committee concluded that topotecan is not a cost-effective use of NHS resources for a first recurrence, but was unable to make a recommendation for the use of topotecan in platinum-sensitive disease beyond the first recurrence.
- 4.13 The Committee carefully considered the cost-effectiveness results for trabectedin plus PLDH compared with PLDH alone, and the comments received from the company for trabectedin during consultation. It noted the company's comment that the Assessment Group had overestimated the cost of a course of trabectedin and PLDH, and underestimated the cost of a course of PLDH alone, because it had based its calculations on a dose that was lower than the one specified in the marketing authorisation and lower than the average dose received by patients in the OVA-301 trial. The Committee noted that it had accepted using the costs for a 40 mg/m² of body surface area dose for PLDH monotherapy (as used in clinical practice) as reasonable, but that if the licensed dose

of PLDH monotherapy had been used, this would have reduced the ICER for trabectedin plus PLDH compared with PLDH alone by approximately £8000 per QALY gained (see section 3.39), calculated using the network meta-analysis for network 2. The Committee concluded that, even with this adjustment, the ICER remained too high for it to recommend the combination of trabectedin plus PLDH as a cost-effective use of NHS resources.

- 4.14 The Committee understood that the company's economic evaluation, which used clinical-effectiveness data obtained from the OVA-301 trial, had been retrospectively adjusted for the following potential covariates: imbalances between arms in the platinum-free interval, Eastern Cooperative Oncology Group (ECOG) status, and the antigen CA125. It noted that the resulting ICER using the company's model, based on the original patient access scheme, was £27,600 per QALY gained, and that this was substantially lower than the ICERs calculated by the Assessment Group based on network 2. The new base-case ICER was also substantially lower than the ICER previously estimated by the company (over £94,800 per QALY gained [without the patient access scheme], using OVA-301 data) in NICE technology appraisal guidance 222. The Committee heard from the company that the substantial reduction in the ICER since NICE technology appraisal guidance 222 was predominantly because of the post-hoc adjustment for imbalances in the platinum-free interval that were subsequently discovered, and that pre-specified adjustments to ECOG status and CA125 had less of an effect. The Committee heard from the company that the results were also partly influenced by the choice of modelling distributions, which had changed from exponential distributions in NICE technology appraisal guidance 222 to Weibull and log logistic distributions in the current appraisal because more mature overall survival data were available. The Committee accepted the views of the Assessment

Group that the company had used the best-fitting distributions in its model. However, the Committee was concerned that the log logistic extrapolation resulted in 2% of women in the treatment arm being alive after 15 years, which it considered was likely to be optimistic for women with recurrent advanced ovarian cancer.

4.15 The Committee carefully considered the company's adjustment of the treatment effects, noting that this increased the difference in median overall survival between the treatment groups from a non-statistically significant 2.9 months to a statistically significant 4.3 months. The Committee considered the company's consultation comment that the NICE Decision Support Unit [guidance for survival analyses](#) recommends 'adjusting for the characteristics of the patients included in the clinical trial of interest – thus correcting for any patient population differences which may be present between different clinical trials'. However, it understood from the Assessment Group that the focus of the Decision Support Unit guidance is on head-to-head comparisons in which patient-level data are available and where evidence synthesis between trials is not required. Guidance on adjustment of dissimilar trial level data to create a homogeneous network for which there is only a single trial informing each head-to-head comparison is not available. The Committee concluded that it was not required to accept the suggested post hoc adjustments of the trial data.

4.16 The Committee also considered the company's concerns that the conclusions around retrospective adjustment of treatment effects in the appraisal consultation document were inconsistent with those made in NICE technology appraisal guidance 222. The Committee was aware that the Evidence Review Group for NICE technology appraisal guidance 222 had accepted an adjustment for CA125, and so the Committee asked what the ICER would have been if the company had adjusted for CA125 alone in the current appraisal.

The company indicated that this analysis was not available, but that CA125 adjustment did not have a major effect on the ICER. The Committee also noted that the Appraisal Committee for NICE technology appraisal guidance 222 had not made an explicit judgement about the validity of the retrospective adjustment of CA125, but had favoured the Evidence Review Group's analysis because it used data from the fully platinum-sensitive population rather than from a post hoc partially sensitive subgroup as in the company's submission. The Committee concluded that it would have given consideration to a retrospective adjustment for CA125 for consistency with NICE technology appraisal guidance 222, had it been supplied by the company, but that this did not oblige the Committee to accept additional retrospective adjustments.

4.17 The Committee examined the assumption underpinning the adjustment for platinum-free interval, that is that response to all future therapy would be better the longer the platinum-free interval. The Committee questioned whether this applied only to further platinum therapy. One of the clinical experts indicated that the platinum-free interval was important, subject to ongoing research, and that a longer platinum-free interval may be associated with a better response to non-platinum therapies as well. The clinical expert stated that no trials have yet provided evidence to support this hypothesis for PLDH, however the Committee noted that the company considered that the post-hoc analyses from OVA-301 supported this hypothesis.

4.18 The Committee also considered the company's approach to carrying out the retrospective analysis. It was concerned that the platinum-free interval had been treated as a continuous rather than a categorical variable. It expressed concerns that this had not been done for any other trials, and questioned the accuracy with which the platinum-free interval could be assessed as a continuous

variable, because assessments are made at set intervals, and a precise date of progression would not be known. The Committee also questioned why the platinum-free interval had not been a stratification factor at randomisation (except for with the platinum-sensitive and platinum-resistant groups) if it was critical to the interpretation of the trial results. The company responded that the platinum-free interval was not considered as important a prognostic indicator at the time of the trial. It acknowledged that it had not included adjustments for the platinum-free interval in its submission for the whole platinum-sensitive population for NICE technology appraisal guidance 222 because the imbalance was not known until the final analysis of overall survival was available, which was after the final guidance from technology appraisal guidance 222. However, it was now of the opinion that it should now be retrospectively adjusted for. The Committee agreed that the platinum-free interval, recognised as an important prognostic factor, at least for further platinum therapy, should be considered carefully in the design and pre-specified analyses of future ovarian cancer trials. However, the Committee was concerned that retrospective adjustment for the platinum-free interval in non-platinum treatments, and as a continuous variable, is currently an unvalidated post-hoc approach, and was not sufficiently reliable as a basis for estimating effectiveness.

- 4.19 The Committee also evaluated the impact of the retrospective adjustments suggested by the company in which the platinum-free interval was treated as a continuous variable. Using the company's adjusted results, and its new model, there was a calculated mean overall survival benefit of 9.7 months for trabectedin plus PLDH compared with PLDH alone. This contrasted with a mean 2.9 months overall survival gain as calculated by the Assessment Group. The Committee did not consider a 9.7 month overall survival gain to be plausible, given that no statistically significant

overall survival benefit was demonstrated in OVA-301. The Committee considered that the company's modelled overall survival benefit lacked credibility, and that this cast further doubt on the validity of the retrospective adjustment of treatment effects that had been introduced since the company's previous analyses presented for NICE technology appraisal guidance 222.

4.20 The Committee carefully considered the additional analyses for trabectedin plus PLDH compared with PLDH alone, and the comments received from the company for trabectedin during consultation on the post-appeal appraisal consultation document. It noted that the company had reiterated its view that the true benefit of trabectedin could only be captured if the results from the platinum-sensitive subgroup of the OVA-301 trial were retrospectively adjusted for imbalances in the platinum-free interval, and they had submitted further analyses retrospectively adjusting for the platinum-free interval as a categorical rather than a continuous variable. The Committee re-examined the evidence underpinning the company's adjustment. It noted that this was based on post-hoc analyses derived from OVA-301, using results presented in a 2012 publication by Monk et al. that was highlighted in the company's response. It agreed with the comments in the paper by Monk et al. that the analyses were 'hypothesis generating only', and that 'no firm conclusions could be made' because they were not pre-specified, and that 'these ad-hoc exploratory analyses' required 'prospective validation'. It also agreed with the Assessment Group that results from a second, independent study would be needed to demonstrate an association between duration of the platinum-free interval and response to non-platinum based treatments. After further consideration, the Committee confirmed its earlier view (see section 4.18) that the retrospective adjustment for platinum-free interval as presented by the company is currently not sufficiently reliable as a basis for estimating effectiveness.

Furthermore, the Committee remained concerned that the adjusted analyses resulted in a substantially higher mean overall survival gain for trabectedin plus PLDH of 8.36 months, compared with the mean of 2.9 months calculated by the Assessment Group. The Committee was not persuaded that the substantial overall survival benefit of 8.36 months was a reliable finding, given that no statistically significant overall survival benefit was demonstrated in OVA-301. It concluded that the retrospectively adjusted results did not provide a more robust estimate of the clinical effectiveness of trabectedin plus PLDH than the published unadjusted results from the properly conducted and randomised OVA-301 trial which had been incorporated into the Assessment Group's network meta-analysis.

- 4.21 The Committee considered the revised cost-effectiveness results submitted by the company that incorporated the retrospective adjustments for imbalances in the platinum-free interval as a categorical variable and an updated patient access scheme (see section 2.14). The Committee was not persuaded that the ICERs based on the retrospective adjustment were robust for the reasons set out in section 4.20. In addition, it was concerned that adjusting for the platinum-free interval led to substantially different ICERs depending on the method of adjustment (£28,600 per QALY gained in the company's analysis using patient level data and £59,800 per QALY gained in the Assessment Group's analysis using the company's adjusted hazard ratios, both incorporating the updated patient access scheme). The Committee considered that this further undermined the plausibility of the analyses. It agreed that the Assessment Group's ICERs, based on the unadjusted results, gave a more plausible estimate of the cost effectiveness of trabectedin plus PLDH compared with PLDH alone. It noted that taking into account the updated patient access scheme, the Assessment Group's ICER remained above £70,000 per QALY

gained. The Committee was not convinced that the ICER for trabectedin plus PLDH fell within the range which could be considered a cost effective use of NHS resources.

4.22 The Committee was aware that the company had also reiterated other concerns, including that cost estimates were based on doses used in clinical practice instead of average doses from the clinical trials. However, the Committee maintained its view that this was appropriate because average doses were not uniformly available, and doses used in clinical practice are both generally agreed and consistent, and most relevant to the NHS (see section 4.8). Furthermore, it acknowledged that accounting for this had a minimal impact on the ICER. The Committee concluded that the most plausible ICER remained above £50,000 per QALY gained even if it had accepted the additional issues raised by the company.

4.23 The Committee noted that OVA-301 included only women with a first recurrence of ovarian cancer, and no clinical-effectiveness evidence for trabectedin was available for subsequent recurrences. It therefore concluded that trabectedin plus PLDH could not be considered a cost-effective use of NHS resources for treating a first recurrence of platinum-sensitive ovarian cancer. It further concluded that it could not make any recommendation about the clinical or cost effectiveness of trabectedin plus PLDH in later recurrences, and that clinicians should take this into account when considering trabectedin plus PLDH as a treatment option.

4.24 The Committee then discussed network 3 and the cost-effectiveness results for paclitaxel, PLDH and topotecan, all given as monotherapy for women with platinum-refractory or platinum-resistant disease. In the comparison between PLDH and paclitaxel, the Committee noted that paclitaxel was dominated by PLDH and therefore excluded from the incremental analysis. However, the

Committee noted the clinical experts' opinion that paclitaxel was considered standard care in this setting, and that the costs and QALYS associated with paclitaxel were similar to those of PLDH (£900 difference in total costs and 0.022 difference in QALYs). The Committee noted that the base case ICERs had been calculated on the assumption that PLDH would be given at a lower dose than specified in the marketing authorisation and that paclitaxel was assumed to be used in an unlicensed weekly regimen (80 mg/m²/week). It considered the additional analyses produced by the Assessment Group after appeal (see section 3.42). It noted that when the licensed 3-weekly paclitaxel regimen was assumed, the costs associated with paclitaxel were lower and it was no longer dominated. The ICER for PLDH relative to paclitaxel was £69,900 per QALY gained at a PLDH dose of 40 mg/m² of body surface area and £103,800 per QALY gained at a PLDH dose of 50 mg/m² of body surface area. The Committee considered that the substantial impact that varying the drug cost had on the ICER was because of small differences in costs and effects, resulting in unstable ICERs. It also considered that its previous opinion had been correct; that the best estimates of costs were those based on current clinical practice. The Committee concluded that these analyses did not change its previous conclusion that the costs and QALYs associated with paclitaxel and PLDH were similar. The Committee concluded that both paclitaxel and PLDH could be recommended for use in the NHS for women with platinum-refractory or platinum-resistant ovarian cancer.

- 4.25 The Committee noted that the incremental ICER for topotecan compared with PLDH was approximately £450,000 per QALY gained and remained above £50,000 per QALY gained in the sensitivity analyses. The Committee also noted the previous comments from the clinical experts that topotecan is rarely used in clinical practice for platinum-resistant disease because of low

response rates. The Committee therefore concluded that topotecan could not be considered a cost-effective use of NHS resources, for treating platinum-resistant or -refractory ovarian cancer.

4.26 The Committee considered supplementary advice from NICE that should be taken into account when appraising treatments that may extend the life of people with a 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.

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

4.27 The Committee was aware that the company for trabectedin had stated that using the adjusted trial results, the median life expectancy in the platinum-sensitive population was 19.4 months, and a gain in median life expectancy of 4 months was estimated with trabectedin for the platinum-sensitive and partially platinum-sensitive populations. However, the Committee did not accept that the adjusted trial results were sufficiently reliable as a basis for estimating effectiveness (see sections 4.14–4.19) and noted that estimates from OVA-301 discussed in NICE technology appraisal guidance 222 continued to be relevant. The Committee noted that

the median overall survival for people treated with PLDH in the entire platinum-sensitive population was more than 24 months, and that the overall survival gain was less than 3 months and not statistically significant. The Committee concluded that trabectedin in combination with PLDH did not fulfil the criteria for being a life-extending, end-of-life treatment and that, even if it had met the criteria, the cost-effectiveness estimates (see section 4.8) remained outside the range usually considered a cost-effective use of NHS resources.

4.28 The Committee was aware of NICE's position statement on the Pharmaceutical Price Regulation Scheme (PPRS) 2014, and in particular the PPRS payment mechanism. It 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 about the relevance of the PPRS to this appraisal. It therefore concluded that the PPRS payment mechanism was not relevant in considering the cost effectiveness of any of the technologies in this appraisal.

Summary of Appraisal Committee's key conclusions

TAXXX	Appraisal title: Topotecan, pegylated liposomal doxorubicin hydrochloride, paclitaxel, trabectedin and gemcitabine for treating recurrent ovarian cancer	Section
Key conclusion		
Paclitaxel in combination with platinum or as monotherapy is recommended within its marketing authorisation as an option for treating recurrent ovarian cancer.	1.1 to 1.5	

<p>Pegylated liposomal doxorubicin hydrochloride (PLDH) as monotherapy is recommended within its marketing authorisation as an option for treating recurrent ovarian cancer.</p> <p>PLDH in combination with platinum is recommended as an option for treating recurrent ovarian cancer.</p> <p>The following are not recommended within their marketing authorisations for treating the first recurrence of platinum-sensitive ovarian cancer:</p> <ul style="list-style-type: none"> • gemcitabine in combination with carboplatin • trabectedin in combination with PLDH • topotecan. <p>The Appraisal Committee was unable to make recommendations on the use of these technologies for treating platinum-sensitive ovarian cancer beyond the first recurrence.</p> <p>Topotecan is not recommended within its marketing authorisation for treating recurrent platinum-resistant or platinum-refractory ovarian cancer.</p> <p>The Committee concluded that paclitaxel plus platinum was the most cost-effective option for women with recurrent platinum-sensitive ovarian cancer, but that PLDH plus platinum could also be considered cost effective, noting that the combination dose of PLDH is based on that used in the CALYPSO trial, which is lower than that specified in the marketing authorisation for PLDH (Caelyx). The Committee understood that the recommendation for PLDH plus platinum was made following Ministerial agreement to direct NICE to make a recommendation under regulation 5 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations</p>	<p>4.6, 4.7</p>
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<p>2013. The Committee was aware that under regulation 5, its recommendation would not be associated with mandatory funding.</p> <p>The Committee was aware that the cost-effectiveness estimates based on the network 1 meta-analysis showed that gemcitabine plus carboplatin resulted in an incremental cost-effectiveness ratio (ICER) compared with platinum alone of £114,000 per quality-adjusted life year (QALY) gained, which could not be considered a cost-effective use of NHS resources. Although the Committee accepted the results of the network meta-analysis, it noted that the clinical evidence for gemcitabine plus platinum that informed the cost-effectiveness analysis only included women with a first recurrence of ovarian cancer, at which stage paclitaxel plus platinum or PLDH plus platinum would be alternative treatment options. It considered that it could not assume that identical results for relative clinical effectiveness would be found in women who had a second or subsequent recurrence. The Committee concluded that it could not make any recommendation about the clinical or cost effectiveness of gemcitabine beyond the first recurrence of platinum sensitive ovarian cancer.</p>	<p>4.8 to 4.9</p>
<p>The Committee noted that the ICER for PLDH monotherapy compared with paclitaxel monotherapy was approximately £23,700 per QALY gained. It also noted the Assessment Group's comments that the costs and QALYs associated with paclitaxel were similar to those of PLDH. Topotecan produced the fewest QALYs compared with PLDH monotherapy, trabectedin plus PLDH, and paclitaxel but was associated with higher costs than both PLDH and paclitaxel monotherapy. The Committee concluded that paclitaxel and PLDH could be recommended for use in the NHS for women with platinum-sensitive disease for whom platinum-based treatment was unsuitable, but topotecan had not been demonstrated to be cost effective for the treatment of platinum-sensitive ovarian cancer in</p>	<p>4.11, 4.12</p>

<p>women unable to take platinum and that this remained the case in the sensitivity analyses.</p>	
<p>The Committee agreed that the Assessment Group’s ICERs, based on the unadjusted results, gave the most plausible estimate of the cost effectiveness of trabectedin plus PLDH compared with PLDH alone, rather than the company’s ICERs, and it was not convinced that these were within the range that could be considered a cost-effective use of NHS resources. Because the OVA-301 trial included only women with a first recurrence of ovarian cancer, the Committee concluded that trabectedin plus PLDH could not be considered a cost-effective use of NHS resources for treating a first recurrence of platinum-sensitive ovarian cancer but that it could not make any recommendation about the clinical or cost effectiveness of trabectedin plus PLDH in later recurrences, and that clinicians should take this into account when considering trabectedin plus PLDH as a treatment option.</p>	<p>4.21, 4.23</p>
<p>The Committee discussed the cost-effectiveness results for paclitaxel, PLDH and topotecan, all given as monotherapy for platinum-refractory or platinum-resistant disease. In the comparison between PLDH and paclitaxel, the Committee noted that the costs and QALYS associated with paclitaxel were similar to those of PLDH (£900 difference in total costs and 0.022 difference in QALYs). The Committee noted that the incremental ICER for topotecan compared with PLDH was approximately £450,000 per QALY gained and remained above £50,000 per QALY gained in the sensitivity analyses. The Committee concluded that PLDH and paclitaxel could be recommended for use, but that topotecan could not be considered a cost-effective use of NHS resources, for treating platinum-resistant or -refractory ovarian cancer.</p>	<p>4.24, 4.25</p>

Current practice		
<p>Clinical need of patients, including the availability of alternative treatments</p>	<p>The Committee heard from clinical experts that women with recurrent ovarian cancer can experience several relapses after initial treatment with platinum-based chemotherapy, and it is very important to have a range of treatment options available at each relapse.</p> <p>The Committee heard that standard treatment for women with platinum-sensitive disease, including those with partially platinum-sensitive disease, is platinum-combination chemotherapy and that paclitaxel is used for treating platinum-refractory or platinum-resistant disease. The Committee heard from the clinical experts that only a small proportion of women are allergic to a particular platinum agent such as carboplatin, and that these women are offered either an alternative platinum agent (cisplatin) or non-platinum regimens.</p>	<p>4.14.1, 4.34.2</p>
The technology		
<p>Proposed benefits of the technology</p> <p>How innovative is the technology in its potential to make a significant and substantial impact</p>	<p>Not applicable.</p>	

on health-related benefits?		
What is the position of the treatment in the pathway of care for the condition?	The clinical experts stated that treatment is tailored to individuals, taking into account factors such as previous treatment and the potential for developing platinum resistance.	4.14.1
Adverse reactions	The results of the Assessment Group’s network meta-analyses found that overall, none of the treatments were consistently associated with either a lower or a higher risk of adverse events.	3.20
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	The Committee expressed disappointment with the quality and breadth of the trial evidence, and also with some of the trial design and reporting, but on balance concluded that the Assessment Group’s approach was reasonable given the data available, and accepted the clinical-effectiveness results from the network meta-analyses.	4.5
Relevance to general clinical practice in the NHS	The Committee agreed that the Assessment Group’s approach of presenting results separately for women with platinum-sensitive disease and platinum-resistant or platinum-refractory disease was appropriate. The clinical experts stated that in clinical practice, the licensed dose may not be	4.24.2 4.34.3

	<p>adhered to. The Committee concluded that in clinical practice the licensed dose is frequently adjusted to balance efficacy against toxicity, and that there was strong clinical opinion that using 40 mg/m² PLDH as monotherapy in platinum sensitive or resistant disease, or a weekly regimen of paclitaxel in platinum-resistant or refractory disease does not reduce the clinical effectiveness of the treatments.</p> <p>The Committee appreciated that the doses used in clinical practice, even when these are well established, may not be identical to the average doses in the trials, but it was reassured that there was no clinical expectation that the effectiveness achieved by the treatments as currently administered in the NHS would be significantly different to the effectiveness demonstrated in the trials.</p>	<p>4.11</p>
<p>Uncertainties generated by the evidence</p>	<p>The Committee discussed the limitations of the network meta-analyses, particularly the differences in baseline characteristics between trials, uncertainty around whether trials were adequately powered to detect differences in overall survival and progression-free survival, and concerns about confounding because of crossover. The Committee acknowledged that the analyses had methodological limitations and that some assumptions had to be accepted.</p>	<p>4.5</p>

<p>Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?</p>	<p>None was identified.</p>	
<p>Estimate of the size of the clinical effectiveness including strength of supporting evidence</p>	<p>The Committee concluded that for women with platinum-sensitive disease, paclitaxel, gemcitabine and PLDH (all plus carboplatin) improved progression-free survival compared with platinum alone and that PLDH and paclitaxel (both plus carboplatin) also improved overall survival. It also concluded that trabectedin plus PLDH improved progression-free survival compared with PLDH, paclitaxel and topotecan (all given alone), and that there was evidence that PLDH alone and trabectedin plus PLDH increased overall survival compared with topotecan. Finally, it accepted that for women with platinum-resistant or platinum-refractory disease, there were no statistically significant differences in progression-free and overall survival between PLDH, paclitaxel and topotecan.</p>	<p>4.5</p>
<p>For reviews (except rapid reviews): How has the new clinical evidence that has emerged since</p>	<p>Topotecan is no longer recommended for second-line (or subsequent) treatment for women with platinum-refractory or platinum-resistant advanced ovarian cancer, or those who are allergic to platinum-based</p>	

<p>the original appraisals (TA91 and TA222) influenced the current (preliminary) recommendations?</p>	<p>compounds, for whom PLDH and single-agent paclitaxel are considered inappropriate.</p>	
<p>Evidence for cost effectiveness</p>		
<p>Availability and nature of evidence</p>	<p>The company for trabectedin submitted cost-effectiveness evidence as part of its submission.</p> <p>The Assessment Group developed a de novo model.</p>	<p>3.21</p> <p>3.26</p>
<p>Uncertainties around and plausibility of assumptions and inputs in the economic model</p>	<p>There was uncertainty around estimates generated by the Assessment Group's network meta-analyses that were incorporated into the model. The Committee noted that no evidence was available for gemcitabine plus carboplatin, topotecan, and trabectedin plus PLDH for treating second and subsequent recurrences of ovarian cancer in women with platinum-sensitive disease. The recommendations are therefore limited to a first recurrence of ovarian cancer and do not stop clinicians and patients from considering these treatments for second or subsequent recurrences of platinum-sensitive ovarian cancer.</p>	<p>4.5, 4.10, 4.12, 4.23</p>
<p>Incorporation of health-related</p>	<p>The Committee did not draw any specific conclusions about the health-related quality-</p>	

<p>quality-of-life benefits and utility values</p> <p>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?</p>	<p>of-life benefits and utility values.</p>	
<p>Are there specific groups of women for whom the technology is particularly cost effective?</p>	<p>None was identified.</p>	
<p>What are the key drivers of cost effectiveness?</p>	<p>The ICER estimates were most sensitive to the relative effect of treatment on overall survival.</p>	<p>3.35 3.38 3.41</p>
<p>Most likely cost-effectiveness estimate (given as an ICER)</p>	<p>For women with platinum-sensitive recurrent ovarian cancer, the Committee agreed that:</p> <ul style="list-style-type: none"> • the ICER for paclitaxel plus PLDH compared with platinum alone was approximately £24,400 per QALY gained • PLDH plus platinum was dominated by paclitaxel plus platinum in the fully incremental analysis but the Committee 	<p>4.6 to 4.12, 4.21, 4.24, 4.25</p>

	<p>accepted that the ICER for PLDH plus platinum compared with platinum alone was approximately £30,200 per QALY gained and it could also be considered cost-effective</p> <ul style="list-style-type: none"> • for women who cannot have platinum treatment, the ICER for PLDH monotherapy compared with paclitaxel monotherapy was approximately £23,700 per QALY gained • gemcitabine plus carboplatin was extendedly dominated and excluded from the fully incremental analysis. The Committee agreed that the ICER for gemcitabine plus carboplatin compared with platinum alone was £114,000 per QALY gained • the ICER for trabectedin plus PLDH compared with PLDH alone, as estimated by the Assessment Group and incorporating the updated patient access scheme, was above £70,000 per QALY gained • topotecan was dominated and excluded from the fully incremental analysis. <p>For women with platinum-resistant or refractory ovarian cancer, the Committee agreed that:</p> <ul style="list-style-type: none"> • the ICER for topotecan compared with PLDH was approximately £450,000 per 	
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	<p>QALY gained</p> <ul style="list-style-type: none"> • paclitaxel was dominated by PLDH, but the Committee noted that the costs and QALYS associated with paclitaxel are similar to those of PLDH and concluded that both could be considered cost-effective • the additional analyses produced by the Assessment Group after appeal showing the impact of varying the drug cost for paclitaxel and PLDH did not change its conclusion that the costs and QALYS associated with paclitaxel and PLDH were similar. 	
<p>For reviews (except rapid reviews):</p> <p>How has the new cost-effectiveness evidence that has emerged since the original appraisals (TA91 and TA222) influenced the current (preliminary) recommendations?</p>	<p>For women with platinum-refractory or platinum-resistant disease, or who are allergic to platinum-based compounds, for whom PLDH and single-agent paclitaxel are considered inappropriate, topotecan is now not considered to be a cost-effective use of NHS resources.</p>	
<p>Additional factors taken into account</p>		
<p>Patient access schemes (PPRS)</p>	<p>A patient access scheme for trabectedin was submitted, and this was updated during the</p>	<p><u>2.143.1</u> 4</p>

	appraisal.	
End-of-life considerations	The Committee concluded that trabectedin in combination with PLDH did not fulfil the criteria for being a life-extending, end-of-life treatment.	4.264.2 6, 4.27
Equalities considerations and social value judgements	Not applicable.	

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 paragraph above. This means that, if a patient has recurrent ovarian cancer and the doctor responsible for their care thinks that paclitaxel or

pegylated liposomal doxorubicin hydrochloride (PLDH) is the right treatment, they should be available for use, in line with NICE's recommendations.

6 Related NICE guidance

Details are correct at the time of publication. Further information is available on the [NICE website](#).

Published

- [Bevacizumab in combination with gemcitabine and carboplatin for treating the first recurrence of platinum-sensitive advanced ovarian cancer](#). NICE technology appraisal guidance 285 (2013).
- [Bevacizumab for treating relapsed, platinum-resistant epithelial ovarian, fallopian tube or primary peritoneal cancer \(terminated appraisal\)](#). NICE technology appraisal guidance 353 (2015).
- [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](#). NICE technology appraisal guidance 38 (2016).
- [Trabectedin for the treatment of relapsed ovarian cancer](#). NICE technology appraisal guidance 222 (2011).
- [Paclitaxel, pegylated liposomal doxorubicin hydrochloride and topotecan for second-line or subsequent treatment of advanced ovarian cancer](#). NICE technology appraisal guidance 91 (2005).
- [Ovarian cancer: recognition and initial management](#). NICE guideline CG122 (2011).

7 Review of guidance

- 7.1 The guidance on this technology will be considered for review 3 years after publication of the guidance. The Guidance Executive will decide whether the technology should be reviewed based on

information gathered by NICE, and in consultation with consultees
and commentators

Jane Adam
Chair, Appraisal Committee
February 2016

8 Appraisal Committee members, guideline representatives and NICE project team

8.1 *Appraisal Committee members*

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are 4 Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

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

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

Dr Jane Adam (Chair)

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Professor Iain Squire (Vice-Chair)

Consultant Physician, University Hospitals of Leicester

Dr Graham Ash

Consultant in General Adult Psychiatry, Lancashire Care NHS Foundation Trust

Dr Jeremy Braybrooke

Consultant Medical Oncologist, University Hospitals Bristol NHS Foundation Trust

Dr Gerardine Bryant

General Practitioner, Swadlincote, Derbyshire

Professor Aileen Clarke

Professor of Public Health & Health Services Research, University of Warwick

Dr Justin Daniels

Consultant Paediatrician, North Middlesex University Hospital

Dr Andrew England

Senior Lecturer, Directorate of Radiography, University of Salford

Dr Rachel Hobson

Formulary Pharmacist, NHS Wiltshire CCG

Dr Mohit Misra

General Practitioner, Queen Elizabeth Hospital, London

Ms Sarah Parry

Clinical Nurse Specialist - Paediatric Pain Management, Bristol Royal Hospital for Children

Ms Pamela Rees

Lay Member

Dr Paul Robinson

Medical Director, Merck Sharp & Dohme

Ms Ellen Rule

Director of Transformation and Service Redesign, Gloucestershire Clinical Commissioning Group

Mr Stephen Sharp

Senior Statistician, University of Cambridge MRC Epidemiology Unit

Dr Brian Shine

Consultant Chemical Pathologist, John Radcliffe Hospital, Oxford

Dr Eldon Spackman

Research Fellow, Centre for Health Economics, University of York

Mr David Thomson

Lay member

Dr John Watkins

Clinical Senior Lecturer, Cardiff University; Consultant in Public Health
Medicine, National Public Health Service Wales

Professor Olivia Wu

Professor of Health Technology Assessment, University of Glasgow

Dr Nerys Woolacott

Senior Research Fellow, Centre for Reviews and Dissemination, University of
York

8.2 NICE project team

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

Helen Tucker

Technical Lead

Raisa Sidhu and Zoe Charles

Technical Advisers

Bijal Joshi

Project Manager

9 Sources of evidence considered by the Committee

A. The assessment report for this appraisal was prepared by BMJ-TAG:

- Edwards SJ, Barton S, Thurgar E et al. Topotecan, pegylated liposomal doxorubicin hydrochloride, paclitaxel, trabectedin and gemcitabine for the treatment of recurrent ovarian cancer: A Multiple Technology Appraisal. BMJ-TAG, London, July 2013.

B. The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, assessment report and the appraisal consultation document (ACD). Organisations listed in I, II and III were also invited to make written submissions and have the opportunity to appeal against the final appraisal determination.

I. Companies/sponsors:

- Eli Lilly (gemcitabine)
- GlaxoSmithKline (topotecan)
- Janssen-Cilag (pegylated liposomal doxorubicin hydrochloride)
- PharmaMar (trabectedin)

II. Professional/expert and patient/carer groups:

- Ovacome
- Ovarian Cancer Action
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians
- Target Ovarian Cancer

III. Other consultees:

- Department of Health
- Welsh Government

IV. Commentator organisations (without the right of appeal):

- BMJ-TAG
- Commissioning Support Appraisals Service
- Department of Health, Social Services and Public Safety for Northern Ireland
- Health Improvement Scotland
- Merck Sharp & Dohme (vintafolide)
- National Collaborating Centre for Cancer
- National Institute for Health Research Health Technology Assessment Programme
- Pfizer (cisplatin)
- Roche Products (bevacizumab)

C. The following individuals were selected from clinical expert and patient expert nominations from the consultees and commentators. They participated in the Appraisal Committee discussions and provided evidence to inform the Appraisal Committee's deliberations. They gave their expert personal view on topotecan, pegylated liposomal doxorubicin hydrochloride, paclitaxel, trabectedin and gemcitabine for the treatment of recurrent ovarian cancer by attending Committee discussions and/or providing written evidence to the Committee.

- Professor Charlie Gourley, Professor and Honorary Consultant in Medical Oncology, nominated by organisation representing Healthcare Improvement Scotland – clinical expert (attended first discussion only)
- Professor Jonathan A Ledermann, Professor of Medical Oncology, UCL Cancer Institute & Clinical Director Cancer Services UCL Hospitals, London, nominated by organisation representing Royal College of Physicians – clinical expert

- Mrs Tilean Clarke, Professional Support Manager, nominated by organisation representing Target Ovarian Cancer – patient expert
- Ms Wendy Fisher, Retired University Lecturer, nominated by organisation representing Ovarian Cancer Action – patient expert

D. Representatives from the following company attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- PharmaMar