NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Overview

Topotecan, pegylated liposomal doxorubicin hydrochloride, paclitaxel, trabectedin and gemcitabine for the treatment of recurrent ovarian cancer (including review of technology appraisal no. 91 and technology appraisal no. 222)

This overview is a summary of:

- the evidence and views submitted by the manufacturers, the consultees and their nominated clinical specialists and patient experts and
- the assessment report.

It highlights key issues for discussion at the first Appraisal Committee meeting and should be read with the full supporting documents for this appraisal.

Please note that this document is a summary of the information available before comments on the assessment report have been received.

Key issues for consideration

Clinical effectiveness

- Does the Committee consider that the estimates of progression-free survival and overall survival generated in the Assessment Group network meta-analyses are reflective of what would be seen in clinical practice?
- Does the Committee consider it appropriate that a network meta-analysis was not conducted for the full population because the analysis would not be clinically meaningful?
- Does the Committee consider that the network meta-analyses for each group were appropriately informed, including robust trials generalisable to the UK and adequately powered to detect a difference between treatments? The Assessment Group stated that subgroup data may not have been sufficiently powered to detect differences in overall survival or

progression-free survival. Statistical assessment of heterogeneity was not possible for any network because of the low number of trials identified and the predominantly linear nature of the networks constructed.

- What does the Committee think is the consequence of not being able to directly compare platinum and non-platinum regimens in the platinum-sensitive subgroup given that two separate networks (which cannot be directly compared) were constructed instead?
- To what extent does the Committee consider that including unadjusted hazard ratios from the literature in the network meta-analyses, in the absence of a consistent dataset for all comparisons, introduced bias?
- Does the Committee consider that people allergic to platinum-based treatment would have the same probability of response to therapy as patients without an allergy for the same non-platinum-containing treatments, and therefore did not need to be analysed separately?
- The manufacturer of trabectedin has suggested that treatment with trabectedin in combination with PLDH is eligible for consideration under the end-of-life criteria. Does the Committee consider trabectedin to be a life-extending treatment that fulfils the criteria in the supplementary advice on end-of-life treatments?

Cost -effectiveness

- Results for the full population are not presented. Does the Committee consider it appropriate that the results have been presented for platinum-sensitive and platinum-resistant or refractory groups separately?
- Following from this, does the Committee consider it appropriate to assess the results for the platinum-sensitive population separately based on whether platinum-containing regimens were included (network 1) or not (network 2)?
- Using summary hazard ratios based on the literature assumes proportional hazards but when this was explored, the log-cumulative

hazard plots indicated that this assumption may not be appropriate. What impact does the Committee think this has on the robustness of the analyses?

- The results for all groups are very sensitive to the relative treatment effect on overall survival. Does the Committee consider that the overall survival estimates included in the base-case analyses can be considered sufficiently robust given issues around crossover in trials, trials being inadequately powered to detect differences in overall survival and the proportional hazards assumption being inappropriate?
- For the platinum-resistant and platinum-refractory group, paclitaxel in combination with platinum was excluded from the base-case analyses because of lack of data. In addition, etoposide alone or in combination with platinum and best supportive care were also excluded as comparators due to lack of data. What impact does the Committee think this has on the relevance of the analyses in this population?
- Given that due to the absence of data it was not possible to compare treatments simultaneously, what is the Committees view on the relative clinical and cost effectiveness of topotecan, pegylated liposomal doxorubicin hydrochloride, paclitaxel, trabectedin and gemcitabine for the treatment of recurrent ovarian cancer?

1 Background: clinical need and practice

1.1 Ovarian cancer is a common gynaecological cancer which represents a group of different tumours that arise from diverse types of tissue contained within the ovary. The most common type of ovarian cancer arises from epithelial cells (the outside layer of cells) on the surface of the ovary, and can often spread from the ovary to any surface within the abdominal cavity including the fallopian tubes and peritoneal cavity. Fallopian tube cancer and primary peritoneal cancer are histologically equivalent diseases to epithelial ovarian cancer. 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.

1.2 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%.

1.3 Recurrent ovarian cancer may be categorised according to the response to first-line platinum chemotherapy as follows:

- fully platinum-sensitive (disease responds to first-line platinum-based therapy but relapses after 12 months or more)
- partially platinum-sensitive (disease responds to first-line platinum-based therapy but relapses between 6 and 12 months)
- platinum-resistant (disease which relapses within 6 months of completion of initial platinum-based chemotherapy)
- platinum-refractory (disease does not respond to initial platinum-based chemotherapy).

1.4 However, the ‘partially platinum-sensitive’ and ‘platinum resistant’ categories should not necessarily be defined rigidly. Although a significant percentage of women with ovarian cancer respond to initial chemotherapy, between 55% and 75% relapse within 2 years of completing treatment.

1.5 Standard treatment for ovarian cancer consists of surgery to determine the type and stage of the disease and to remove as

much of the cancer as possible. After surgery, chemotherapy is used to treat any residual disease. Increasingly chemotherapy is given before surgery. In people whose disease recurs, NICE technology appraisal guidance 91 recommends paclitaxel in combination with a platinum compound in platinum-sensitive or partially platinum-sensitive disease; pegylated liposomal doxorubicin hydrochloride (PLDH) in partially platinum-sensitive, platinum-resistant or platinum-refractory disease; paclitaxel alone in platinum-refractory or platinum-resistant disease; and topotecan in platinum-refractory or platinum-resistant disease for people for whom PLDH and single-agent paclitaxel are considered inappropriate. Some people with disease that is 'platinum resistant' may respond well to rechallenge with platinum-based chemotherapy so dose-dense platinum chemotherapy in combination with paclitaxel or etoposide is also an option for this sub-population.

2 The technologies

2.1 Gemcitabine (various manufacturers) is a chemotherapeutic agent that exerts its action by inhibiting DNA synthesis. It is a nucleoside analogue with anti-tumour activity against a number of solid tumours. Gemcitabine, in combination with carboplatin, has a UK marketing authorisation for the treatment of locally advanced or metastatic epithelial ovarian cancer in women with recurrent platinum-sensitive cancer after first-line platinum-based therapy.

2.2 Gemcitabine is administered by intravenous infusion. The recommended dose is 1000 mg/m² administered on Days 1 and 8 of each 21-day cycle. The summary of product characteristics lists the following as the most common adverse reactions associated with gemcitabine treatment: leucopenia,

thrombocytopenia, anaemia, dyspnoea, vomiting, nausea, elevation of liver transaminases (AST and ALT) and alkaline phosphatase, allergic skin rash, alopecia, haematuria, mild proteinuria, influenza-like symptoms and oedema/peripheral oedema.

2.3 Paclitaxel (various manufacturers) is a cytotoxic anticancer drug that belongs to the taxane group of drugs, which prevent the formation of mitotic spindles thus interfering with the process of cell division and resulting in cell death. Paclitaxel has a UK marketing authorisation for the second-line treatment of metastatic ovarian cancer after failure of standard platinum-containing therapy.

2.4 Paclitaxel is administered by intravenous infusion. The recommended dose is 175 mg/m² administered over a period of 3 hours, with a 3-week interval between treatment cycles (paclitaxel has also been evaluated in randomised controlled trials at a weekly interval between treatment cycles, and this dose is used to model the platinum refractory or resistant group in line with clinical practice). The summary of product characteristics lists the following as the most common adverse reactions associated with paclitaxel treatment: infection, myelosuppression, neutropenia, anaemia, thrombocytopenia, leucopenia, bleeding, mild hypersensitivity reactions, neurotoxicity, hypotension, diarrhoea, vomiting, nausea, mucositis, alopecia arthralgia and myalgia.

2.5 Pegylated liposomal doxorubicin hydrochloride (Caelyx, Jansen-Cilag) belongs to the class of drugs known as anthracyclines, which is a group of cytotoxic antibiotics that have antineoplastic activity. Anthracyclines intercalate with DNA, and so inhibit its synthesis. They also interact with cell membranes thereby

altering their function and generating cytotoxic chemical species. 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. In 2011 and 2012, there was a worldwide shortage in the supply of PLDH.

2.6 PLDH is administered by intravenous infusion. The recommended dose is 50 mg/m² once every 4 weeks for as long as the disease does not progress and the patient continues to tolerate treatment (Combination treatment at lower doses has been studied in clinical trials). The summary of product characteristics lists the following as the most common adverse reactions associated with treatment with pegylated liposomal doxorubicin hydrochloride: anorexia, nausea, stomatitis, vomiting, palmar-plantar erythrodysesthesia, alopecia, rash, asthenia, fatigue and mucositis.

2.7 Topotecan (various manufacturers) is a naturally-derived chemotherapeutic agent. It prevents DNA replication in cancer cells by inhibiting the enzyme topoisomerase I. Topotecan has a UK marketing authorisation for the treatment of women with metastatic cancer of the ovary after failure of first-line or subsequent chemotherapy. The recommended dose is 1.5 mg/m² body surface area per day, administered by intravenous infusion over 30 minutes daily for five consecutive days with a three week interval between the start of 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, leucopenia, nausea, vomiting and diarrhoea, constipation, abdominal pain, mucositis, alopecia, anorexia, infection, pyrexia, asthenia and fatigue.

2.8 Trabectedin (Yondelis, PharmaMar) is a synthetic, marine-derived anticancer agent that binds to the minor groove of the DNA and as a result bends the helix to the major groove, which results in perturbation of the cell cycle. Trabectedin, in combination with PLDH, has a UK marketing authorisation for the treatment of women with recurrent platinum-sensitive ovarian cancer. The recommended dose for trabectedin is 1.1 mg/ m^2, immediately after PLD 30 mg/ m^2, administered every three 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, alanine aminotransferase increase, aspartate aminotransferase increase, blood alkaline phosphatase increase, gamma-glutamyltransferase increase, fatigue, blood creatine phosphokinase increase, blood creatinine increase and blood albumin decrease.

2.9 The acquisition costs of the technologies are described in table 1 below. Costs may vary in different settings because of negotiated procurement discounts. The manufacturer of trabectedin has agreed a patient access scheme with the Department of Health. The scheme will apply to patients who require more than 5 cycles of trabectedin plus PLDH; when an order is received for a patient on cycle 6 onwards, the manufacturer will authorise an appropriate rebate. Rebates will be in the form of either an adjustment to the invoice (free stock) or, if preferred, by credit note. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.

Table 1 Cost of the technologies

Non-proprietary name	Topetecan	Pegylated liposomal doxorubicin hydrochloride	Paclitaxel	Trabectedin	Gemcitabine
Proprietary name	Hycamtin	Caelyx	TAXOL	Yondelis	GEMZAR
Manufacturer	GSK	Janssen	Hospira	PharmaMar	Eli Lilly
Acquisition cost (BNF edition 64)	net price 1-mg vial = £97.65; 4-mg vial = £290.62	net price 10-mL vial = £360.23, 25-mL vial = £712.49	paclitaxel 6 mg/mL, net price 5-mL vial = £66.85, 16.7-mL vial = £200.35, 25-mL vial = £300.52, 50-mL vial = £601.03	net price 250-microgram vial = £363.00; 1-mg vial = £1366.00	£32.55 for a 200 mg vial and £162.76 for a 1 g vial (excluding VAT
Chemotherapy regimen	Topotecan 1.5 mg/m^2, day 1-5 every 21 day cycle	PLDH 40 mg/m2 day 1 every 28 day cycle	Paclitaxel 80mg/m2 weekly cycle for 18 weeks or until progression	Trabectedin 1.1 mg/m^2; PLDH 30 mg/m^2, day 1 every 21 day cycle	Gemcitabine 1,000 mg/m^2 day 1 and 8 every 21 day cycle, carboplatin target AUC of four day 1 every 21 day cycle
Chemotherapy cost per cycle (as in the model)	£1,305	£1,211	£306 – weekly dose £638- 3-weekly dose	£3,679	£706

3 Remit and decision problem

3.1 The remit from the Department of Health for this appraisal was: To appraise the clinical and cost effectiveness of topotecan, PLDH, paclitaxel, trabectedin and gemcitabine within their licensed indications for the treatment of recurrent ovarian cancer.

4 Clinical-effectiveness evidence

4.1 The Assessment Group carried out a systematic review and identified 16 randomised controlled trials, evaluating 14 different pairwise-comparisons, which met the inclusion criteria. The Assessment Group stated that 5 of these trials (Main et al. 2004, ten Bokkel et al. 1997, Gondzalez-Martin 2005, Gordon et al.2001, Pfisterer et al. 2006) evaluated the intervention and comparator within their licensed indications, dose and routes of administration. The remaining 11 trials included doses or routes of administration different from the relevant marketing authorisations. Only one trial previously included in TA91 (Cantu et al.) was excluded from the current review because the doxorubicin administered in the trial was the non-pegylated formulation whereas the scope specifies PLDH as the intervention of interest. The Assessment Group reviewed the clinical evidence submitted by the manufacturers' for gemcitabine and trabectedin and noted that the evidence presented in the submissions had been identified an included in the Assessment Group's systematic review. Two additional studies (JHRW and SO026) were presented in Eli Lilly's submission but these were excluded by the Assessment Group because they were single arm trials and therefore did not meet the inclusion criteria. In addition, no trials were specific to people who are allergic or intolerant to platinum-based treatments. Please see table 2 for a summary of the trial details.

Table 2 Summary description of the trials included in the Assessment Group systematic review.

Trial	Design	Population	Intervention	Comparator	Primary outcome measure	Comments from Assessment Group
ten Bokkel Huinik et al. (1997)	Phase III, open label N=235	Stage III/IV ovarian cancer, which had progressed	Topotecan 1.5 mg/m2 as a 30 min IV infusion for 5 consecutive	Paclitaxel 175 mg/m2 as a 3 hour IV infusion every 21	Response rate Duration of response	independent radiologist masked to treatment allocation

		during or after treatment with one platinum-based chemotherapy no minimum PFI specified	days every 21 days	days	Time to progression	results not based on ITT population crossover – potential confounding uncertainty as to whether the trial was adequately powered to detect a difference between treatments
Gordon et al. (2001)	Phase III, open label N=474	recurrent epithelial ovarian carcinoma that recurred after or did not respond to first-line platinum-based chemotherapy no minimum PFI specified	PLDH 50 mg/m2 as a 1 hour IV infusion every 28 days	Topotecan 1.5 mg/m2 as a 30 min infusion for 5 consecutive days every 21 days	PFS OS	Well-designed; independent radiological review Modified ITT analysis (results are based on patients who received at least a partial dose of study drug); Longer term OS results based on ITT analysis
Main et al. (Trial 30–57) Data and comments taken from TA91	Phase III, open label N=216	epithelial ovarian carcinoma after failure of first-line platinum-based chemotherapy no minimum PFI specified	PLDH 50 mg/m2 every 28 days	Paclitaxel 175 mg/m2 every 21 days	OS	Low recruitment rate (50%) – trial may be underpowered to detect differences Efficacy analysis in TA91 limited to OS Reasonably good quality trial
Gonzalez Martin et al.	Phase II, 'pick the winner design' N=81	platinum-sensitive recurrent ovarian cancer (>6 months), for which patients had received no more than two previous chemotherapy lines	Paclitaxel 175 mg/m2 as a 3 hour IV infusion plus carboplatin (AUC 5)every 3 weeks	Carboplatin (AUC 5) alone every 3 weeks	ORR (CR or PR)	Pick the winner" design trials are underpowered for hypothesis testing or comparisons of treatment effect on the outcomes of interest, such as survival Randomisation method not described
Pfisterer et al.	Phase III, open label N=356	platinum-sensitive recurrent ovarian cancer, with recurrence occurring at least 6 months after completion of	Gemcitabine 1,000 mg/m2 plus carboplatin (AUC 4) every 21 days	Carboplatin alone (AUC 5) every 21 days	PFS	Well-designed and conducted; ITT analysis Potential for bias with PFS as primary outcome and open label design; unclear

		first-line platinum-based therapy				if independent review
Gore et al.	Phase not clear, open label N=266	epithelial ovarian cancer that had either progressed during or relapsed within 12 months of completing first-line chemotherapy	Oral topotecan (2.3 mg/m2) given daily	IV topotecan 1.5 mg/m2 for 5 consecutive days every 21 days	RR	Well designed; ITT analysis Masked independent radiological review Randomisation method not described Unclear whether the study is adequately powered Population clinically homogenous
Sehouli et al.	Phase II; masking unclear N=194	Platinum-resistant (<6 months) recurrent epithelial ovarian or primary peritoneal cancer	Topotecan 4.0 mg/m2 IV each week applied on days 1, 8, and 15 of a 28 cycle	Topotecan 1.25 mg/m2 IV infusion for 5 consecutive days every 21 days	Clinical benefit rate -Composite of CR, PR and stable disease	Lower dose in comparator arm Primary outcome analysis not based on ITT population 80% patients evaluated by CA125 alone; not sufficient to confirm response to treatment Unclear whether investigator was masked to treatment allocation Trial not adequately powered
Alberts et al.	Phase II, masking unclear N=61	Stage III or IV epithelial or peritoneal ovarian carcinoma that recurred within 6–24 months of completing platinum-based chemotherapy (platinum-sensitive population)	PLDH 30 mg/m2 as a 1 hour IV infusion plus carboplatin (AUC 5) every 4 weeks	Carboplatin alone (AUC 5) every 4 weeks	OS	Method of randomisation and level of masking unclear; unlikely to introduce bias as primary outcome is OS Likely to have been underpowered as a result of early closure due to slow patient accrual (61 patients recruited out of a planned 900

						patients)
Bafaloukos et al.	Phase II; masking unclear N=204	Ovarian cancer that had recurred at least 6 months after platinum-based chemotherapy	PLDH (45 mg/m2 as a 90 min IV infusion) plus carboplatin (AUC 5) every 4 weeks	Paclitaxel (175 mg/m2 as a 3 hour IV infusion) plus carboplatin (AUC 5) every 21 days	RR	Method of randomisation not reported; level of masking unclear Primary analysis based on the ITT population Unclear whether radiological scans were evaluated by an independent review panel TTP was measured from date of treatment initiation rather than date of randomisation, which is a more commonly used definition for TTP in clinical trials
CALYPSO Pujade-Lauraine et al.	Phase III, non-inferiority, open-label N=976	Platinum-sensitive (>6 months) recurrent ovarian cancer	PLDH (30 mg/m2 as an IV infusion) plus carboplatin (AUC 5) every 28 days	Paclitaxel (175 mg/m2 as an IV infusion) plus carboplatin (AUC 5) every 21 days	PFS	Well-designed and well-conducted ITT analysis barring 3 patients who were judged to be ineligible because of absence of evidence of ovarian cancer post randomisation
Rosenberg et al.	Phase not clear N=208	Advanced ovarian cancer that had progressed during or relapsed after platinum-based treatment No minimum PFI specified	Paclitaxel (67 mg/m2) weekly	Paclitaxel (200 mg/m2) every 21 days	Clinical response rate	ITT analysis More patients in the paclitaxel weekly arm (32 vs 20) were taken off the study early due to either early progression or for administrative reasons Low recruitment rate (350 planned); may

						be underpowered
ICON4/AGO-OVAR-2.2 Parmar et al.	Phase III (2 trials run in parallel; separate protocols; minor differences) N=802	Relapsed epithelial ovarian cancer which had previously been treated with platinum-based chemotherapy and had been treatment-free for at least 6 months; patients in IRFMN were required to have been treatment-free for a minimum of 12 months	Paclitaxel (175 or 185 mg/m2) plus carboplatin (AUC 5) or cisplatin (50 mg/m2) every 21 days	Carboplatin (AUC 5) or cisplatin (minimum 75 mg/m2) alone every 21 days	OS	Level of masking unclear but with OS as the primary outcome bias is unlikely ITT analysis Well-conducted
CARTAXHY Lortholary et al.	Phase II, open label, 3-arm trial - combination of paclitaxel plus topotecan excluded N=165	Platinum resistant or refractory recurrent ovarian cancer	Paclitaxel 80 mg/m2 each week applied on days 1, 8, and 15 of a 28 cycle plus carboplatin (AUC 5) every 28 days	Paclitaxel 80 mg/m2 each week applied on days 1, 8, and 15 of a 28 cycle	PFS	ITT analysis Open label so potential for bias Randomisation methodology not reported Unclear if independent radiological review conducted
Piccart et al.	Phase II, open label N=86	Disease that progressed or stabilised after prior platinum-based treatment. For those experiencing relapse, relapse was to have occurred within 12 months of last platinum-based therapy	Paclitaxel 175 mg/m^2 as a 3 hour infusion every 21 days	Oxaliplatin 130 mg/m^2 as a 2 hour infusion every 21 days	Objective confirmed response rate	Open label design could bias results Unclear if independent radiologists were masked to treatment allocation Uncertainty around the power of the trial
OVA-301 Monk et al. (2010)	Phase III, open label N=672	Platinum-resistant (PFI <6 months) or platinum-sensitive (PFI ≥6 months) ovarian cancer; those who experienced progression during first-line therapy (platinum-refractory)	Trabectedin (1.1 mg/m2 as a 3 hour infusion) plus PLDH (30 mg/m2 as a 90 min infusion) every 21 days	PLDH (50 mg/m2 as a 90 min infusion) every 28 days	PFS	Robust design; methods well reported ITT analysis One potential area that affects the external validity of the trial is the omission of platinum-based chemotherapy

		were excluded				as a comparator, particularly as a large proportion of patients enrolled had platinum-sensitive disease. The authors commented that the inclusion of platinum-resistant patients contributed to the decision against use of a platinum-based control as platinum-based therapy would have been inappropriate in this setting This review does not include trabectedin plus PLDH as an intervention in patients with platinum resistant disease; only data from platinum-sensitive patients presented
Omura et al.	Phase III; masking unclear N=372	Recurrent epithelial ovarian cancer despite prior platinum therapy	Paclitaxel 250 mg/m2 (24 hour infusion) every 21 days (patients in this group also randomised to filgrastim 5 or 10 µg/kg subcutaneously)	Paclitaxel 175 mg/m2 (24 hour infusion) every 21 days	PFS OS	Randomisation robust; level of masking unclear Analyses not based on ITT population Low recruitment rate (540 planned), likely to be underpowered

4.2 Following feedback from clinical experts, the Assessment Group determined that it was appropriate to analyse patients with platinum-sensitive disease and patients with platinum resistant or refractory disease separately. Patients with platinum allergic disease were assumed to have the same probability of response

to therapy as patients without an allergy for the same non-platinum-containing treatments, and therefore treatments for patients with platinum allergic disease were not analysed separately. The Assessment Group stated that there was insufficient data for most comparisons to carry out a standard pair-wise 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 (MCMC) simulation. In the absence of individual patient data, the network meta-analysis synthesised summary measures of relative treatment effect in the form of hazard ratios from the literature.

4.3 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 two 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, platinum-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, platinum-resistant or refractory disease would not receive the same range of treatments and therefore the results of this analysis would not be clinically meaningful.

4.4 In general, the Assessment Group stated that the trials were well designed and conducted and the treatment groups within trials were well matched. Some differences in baseline characteristics between trials were identified, in particular with respect to length

of the progression-free interval, number of previous lines of chemotherapy and the method used to diagnose recurrence but 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 clinical effectiveness of treatments. However, the Assessment Group clarified that the assessment of clinical homogeneity was limited to the platinum sensitive network 1 in which platinum-based therapies were identified. For this network, the Assessment Group considered that as a result of the imbalance in ECOG status at baseline, the treatment effect associated with platinum may have been understated. Baseline characteristics were not reported for subgroups, and therefore an assessment of clinical heterogeneity was not possible for the 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 any network because of the low number of trials identified and the predominantly linear nature of the networks constructed.

4.5 The Assessment Group specified that unadjusted hazard ratios were used for progression free survival and overall survival within the network meta-analysis. It was 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. It was assumed that estimates of relative treatment effect based on unadjusted data would not meaningfully differ from estimates of relative treatment effect based on adjusted data.

Progression-free survival results

4.6 For the platinum-sensitive network 1 evaluating platinum-based regimens, the Assessment Group included 5 trials (Gonzalez Martin et al., ICON4/AGO-OVAR, CALYPSO, Alberts et al., Pfisterer et al.) evaluating progression-free survival in the network meta-analysis. The results from the individual trials are summarised on page 133 of the Assessment Report. Results from network meta-analysis found that paclitaxel in combination with carboplatin, gemcitabine in combination with carboplatin and PLDH in combination with carboplatin statistically significantly improved progression-free survival compared with platinum alone with hazard ratios of 0.73 (95% 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 in combination with carboplatin was found to be statistically significantly more effective at prolonging progression-free survival than paclitaxel in combination with carboplatin (HR=0.81, 95% C.I 0.71 to 0.92). No other statistically significant differences were identified between platinum-combination regimens.

4.7 For the platinum-sensitive network 2 evaluating non-platinum-based regimens, the Assessment Group included 3 trials (ten Bokkel et al., OVA-301, Gordon et al.) evaluating progression-free survival in the network meta-analysis. The results from the individual trials are summarised on page 133 of the Assessment Report. Results from network meta-analysis found that that trabectedin in combination with 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 amongst the monotherapies evaluated (that is, PLDH, topotecan, and paclitaxel).

4.8 For the platinum-resistant or platinum-refractory ovarian cancer group, the Assessment Group included 3 trials (ten Bokkel et al., Gordon et al., Sehouli et al.) evaluating progression-free survival for inclusion in the network meta-analysis. The results from the individual trials are summarised on page 135 of the Assessment Report. The Assessment Group also highlighted that trabectedin in combination with PLDH is outside of the scope for this subgroup and while the data have been included within the network to capture all the available evidence it is 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.

4.9 For the fully platinum-sensitive ovarian cancer subgroup, the Assessment Group stated that though 3 trials (OVA-301, Pfisterer et al., ICON4/AGO-OVAR) included subgroups with fully platinum-sensitive ovarian cancer only the OVA-301 trial reported data and therefore it was not possible to perform an indirect comparison. No statistically significant differences were reported in the OVA-301 trial. In addition, 4 trials (OVA-301, CALYPSO, ICON4/AGO-OVAR, 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 perform an indirect comparison. The OVA-301 trial reported a statistically significant improvement in progression-

free survival with trabectedin in combination with 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 in combination with carboplatin compared with paclitaxel in combination with carboplatin (HR=0.73, 95% CI 0.58 to 0.90; p=0.004).

Overall survival Results

4.10 For the platinum-sensitive network 1 evaluating platinum-based regimens, the Assessment Group included 6 trials (Alberts et al., Bafaloukos et al., ICON4/AGO-OVAR, CALYPSO, Gonzalez Martin et al., Pfisterer et al.) evaluating overall survival in the network meta-analysis. The results from the individual trials are summarised on page 102 of the Assessment Report. Results from the network meta-analysis indicated that PLDH in combination with carboplatin statistically significantly improved overall survival compared with platinum-therapy alone (HR=0.79, 95% C.I 0.64 to 0.97). Paclitaxel in combination with carboplatin was also found to statistically significantly improve overall survival compared with platinum alone (HR=0.77, 95% C.I 0.66 to 0.91). No other statistically significant differences in overall survival were identified between platinum-combination regimens.

4.11 For the platinum-sensitive network 2 evaluating non-platinum-based regimens, the Assessment Group included 4 trials (ten Bokkel et al., OVA-301, Gordon et al., Main et al.) evaluating overall survival in the network meta-analysis. The results from the individual trials are summarised on page 102 of the Assessment Report. Results from the network meta-analysis indicated that PLDH alone statistically significantly improved overall survival compared with topotecan alone (HR=0.73, 95% CI0.56 to 0.97). Trabectedin in combination with PLDH was also

found to statistically significantly improve overall survival compared with topotecan alone (HR=0.60, 95% C.I 0.43 to 0.86). No other statistically significant differences were identified between platinum-combination regimens.

4.12 For the platinum-resistant or platinum-refractory ovarian cancer group, the Assessment Group included 4 trials (ten Bokkel et al., Gordon et al., Sehouli et al., Main et al.) evaluating overall survival in the network meta-analysis. The results from the individual trials are summarised on page 105 of the Assessment Report. As for progression-free survival, the Assessment Group stated that trabectedin in combination with PLDH is outside of the scope for this subgroup and while the data have been included within the network to capture all the available evidence it is not included in the economic analysis. Results from the network meta-analysis found no statistically significant differences in overall survival among the treatments evaluated and these results were in line with results from the individual trials.

4.13 For the fully platinum sensitive ovarian cancer group, the Assessment Group identified 4 trials (Gordon et al, CALYPSO, ICON4/AGO-OVAR, OVA-301) evaluating overall survival. The results from the individual trials are summarised on page 117of the Assessment Report. The Assessment Group stated that it was not possible to perform a network meta-analysis because only 2 of the trials reported the required data for analysis and these trials did not have a common comparator. For the partially platinum-sensitive ovarian cancer group, the Assessment Group identified the same 4 trials evaluating overall survival. The results from the individual trials are summarised on page 120 of the Assessment Report. As before, the Assessment Group constructed 2 networks and network 1 evaluating platinum-

based regimens included only 1 trial (CALYPSO). No statistically significant difference in overall survival was identified for PLDH in combination with carboplatin compared with paclitaxel in combination with carboplatin in this trial. For network 2 evaluating non-platinum based regimens, results from the network meta-analysis indicated that trabectedin in combination with PLDH statistically significantly improved overall survival compared with PLDH alone (HR=0.83, 95% C.I 0.667 to 1.032). Trabectedin in combination with PLDH was also found to statistically significantly improve overall survival compared with topotecan alone (HR=0.60, 95% CI 0.43 to 0.86).

Overall response rate

4.14 Overall response rate was defined in the Assessment Group network meta-analysis as the number of patients achieving complete response, or partial response as their best response. For the platinum-sensitive network 1 evaluating platinum-based regimens, the Assessment Group included 5 trials (Alberts et al., Bafaloukos et al., ICON4/AGO-OVAR, CALYPSO, Gonzalez Martin et al., Pfisterer et al.) evaluating overall response rate in the network meta-analysis. The results from the individual trials are presented on page 160 of the Assessment Report. Results from the network meta-analysis indicated that paclitaxel in combination with carboplatin compared with than platinum alone had a statistically significant overall response rate with an odds ratio (OR) of 1.50 (95% CI 1.10 to 2.10). Similarly, gemcitabine in combination with carboplatin was found to have a significantly higher overall response rate than platinum alone (OR=2.05, 95% CI 1.30 to 3.01). There were no other statistically significant differences between the treatments assessed.

4.15 For the platinum-sensitive network 2 evaluating non-platinum-based regimens, the Assessment Group included 5 trials (Gordon et al., ten Bokkel et al., OVA0301, Gore et al., Rosenberg et al.), evaluating overall response rate in the network meta-analysis. The results from the individual trials are presented on page 160 of the Assessment Report. Results from the network meta-analysis indicated that trabectedin in combination with PLDH statistically significantly improves overall response rate compared with PLDH alone (OR=1.93, 95% CI 1.23 to 2.90), and also when compared with oral topotecan alone (OR=3.81, 95% CI 1.48 to 14.08). Intravenous topotecan was found to be associated with a statistically significantly higher overall response rate compared with oral topotecan (OR=2.21, 95% CI 1.05 to 5.88). No other statistically significant differences were identified.

4.16 For the platinum-resistant or platinum-refractory ovarian cancer group, the Assessment Group included 5 trials (Gordon et al., ten Bokkel et al., Sehouli et al., Gore et al., Rosenberg et al.), evaluating overall response rate in the network meta-analysis. The results from the individual trials are presented on page 183 of the Assessment Report. Results from the network meta-analysis found that all the chemotherapy regimens evaluated were associated with statistically significantly lower overall response rates than PLDH alone. For the partially platinum-sensitive group, the Assessment group stated that only the CALYPSO trial was identified and therefore a network meta-analysis was not possible. Results from the CALYPSO trial indicated that there was no statistically significant differences in overall response rate for PLDH in combination with carboplatin compared with paclitaxel in combination with carboplatin (OR=0.863; 95% CI 0.584 to 1.274). The Assessment Group did

not make any comment regarding overall response rates for the fully platinum-sensitive population.

Health related quality of life

4.17 Of the 16 trials identified, 10 reported data on quality of life. The most commonly used scale in trials identified was EORTC QLQ-C30 questionnaire. However, the Assessment Group reported that there was considerable disparity in the level of reporting of results, the questionnaires used to evaluate quality of life, and the time points for evaluation. Therefore, due to lack of comparable data, the Assessment Group only provided a summary of the results from the individual trials; please see page 189 onwards for details. A brief outline is presented below.

- PLDH in combination with carboplatin compared with paclitaxel in combination carboplatin: the CALYSO trial used the EORTC QLQ-C30 questionnaire in addition to the ovarian cancer-specific OV28 module. At baseline, 90% of patients completed the questionnaires, but compliance steadily decreased over the 9 month period and 50% of patients completed questionnaires at end of the study period. At 3 months, PLDH in combination with platinum was associated with a significant improvement in global health compared with paclitaxel plus platinum. However, this benefit was not maintained at 6 months at which time the difference between groups was not statistically significant.

- Trabectedin in combination with PLDH compared with PLDH alone: the OVA-301 trial incorporated the EORTC QLQ-C30 and QLQ-OV28 questionnaires, together with the EQ-5D questionnaire. At most time points more than 90% of patients completed questionnaires, and 66% of patients had completed questionnaires at the end of the study period. No

statistically significant difference in health related quality of life between treatments was identified. In the manufacturer's submission, health-related quality of life data was reported for the subgroup of patients with partially platinum-sensitive ovarian cancer, which indicated that for people responding beyond cycle 5, trabectedin in combination with PLDH resulted in higher global health status scores than the PLDH alone.

- PDHL compared with topotecan: the Gorden (2001) study used the EORTC QLQ-C30 questionnaire. At baseline approximately 82% of patients completed questionnaires, and 50% of patients had completed questionnaires at the end of the study period. No statistically significant difference in health related quality of life between treatments was identified except for the pain-sub scale score which favored topotecan.

- Gemcitabine in combination with carboplatin compared with carboplatin monotherapy: the Pfisterer study incorporated the EORTC QLQ-C30 and QLQ-C28 questionnaires. The rate of completion of questionnaires remained approximately 82% of patients throughout the study period. No statistically significant differences in health-related quality of life between treatments were identified.

- Paclitaxel in combination with carboplatin compared with platinum alone: the ICON4/AGO-OVAR trial used the EORTC QLQ-C30 questionnaire; and the Gonzalez-Martin study incorporated the QLQ-C30 questionnaire. Rates of questionnaire completion at the end of the study period were not reported. In the ICON4/AGO-OVAR trial, people receiving platinum alone scored significantly worse on the

nausea and vomiting symptom scale than the paclitaxel in combination with platinum group. However, the Assessment Group stated that this difference was observed for only the first 15 weeks after randomisation. The Gonzalez-Martin study found no statistically significant difference in health related quality of life between treatments.

- Paclitaxel in combination with carboplatin compared with paclitaxel alone: the Lorthalary study incorporated the EORTC QLQ-30 and QLQ-OV28 questionnaires. The completion rate of questionnaires ranged from 40 to 70% after 2, 4 and 6 cycles of treatment.

- People receiving weekly paclitaxel in combination with platinum experienced improvements in constipation, abdominal/gastrointestinal symptoms, appetite, pain, and emotional functioning compared to people receiving paclitaxel alone. Patients treated with weekly paclitaxel alone experienced improvements in attitude to disease and insomnia, but worsening of dyspnoea and peripheral neuropathy.

Adverse events

4.18 The Assessment Group stated that the most frequently reported adverse reactions reported in the trials were reflective of those reported in the individual summary of product characteristics and details are available on page 165 to 221 of the Assessment Report. Consequently, based on advice from clinical experts, the Assessment Group limited their network-meta-analyses to the following severe grade 3-4 adverse events which they considered to be the most problematic for patients: allergic reaction, alopecia, anemia, 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 where a network meta-analysis was not possible, indicated that the likelihood of adverse events were not statistically significantly different across treatment regimens. However, in some instances, chemotherapies were estimated as having significantly lower risks of one or more adverse events but significantly higher risks of other adverse events. For example, when compared to paclitaxel in combination with platinum, PLDH in combination with platinum is associated with significantly lower risks of allergic reaction and alopecia but significantly higher risks of anaemia and nausea and vomiting. Overall, no chemotherapy was consistently associated with either a lower risk or a higher risk of the adverse events assessed.

5 Comments from other consultees

5.1 The professional group stated that while previously it was considered that ovarian cancers arise within ovarian surface epithelial cells, it is now understood that the major subtypes of ovarian cancer are not one disease, but a collection of tumours with different clinical behavior, many arising from non-ovarian tissues, linked only by a common anatomical location. It was emphasised that many patients benefit from a number of different courses of treatment and must have options available to them. It was highlighted that most data on chemotherapy responsiveness and survival is derived from trials in which most patients have high grade serous cancer and decisions about treatment choices are based on broad categorisation of ‘platinum-sensitivity’ and discussion of side-effects and benefits with patients. However, it was noted that subtype-specific trials in low grade serous and clear cell carcinomas (as well as

specific high grade serous studies) are either ongoing or in development and the future treatment of ovarian cancer will be determined by subtype. The professional and patient groups stated that there was a high level of clinical need for a range of options for the treatment of recurrent ovarian cancer.

5.2 The professional group stated that for platinum-resistant ovarian cancer, the major change in clinical practice since TA91 has been the use of weekly paclitaxel. It was noted that while there have been no studies directly comparing single agent weekly paclitaxel with either single agent PLDH or topotecan, it has been used as the comparator in randomised studies and retrospective comparisons and denying access to paclitaxel would be a disadvantage to patients. However, it was noted that if paclitaxel were to become the standard of care in the first-line setting, which was likely, it was unclear whether patients would continue to benefit in the relapsed, platinum-resistant setting.

5.3 The professional group stated that for platinum sensitive ovarian cancer, standard practice is platinum-containing chemotherapy. Combination regimes of carboplatin and gemcitabine, carboplatin and PLDH as well as carboplatin and paclitaxel are widely used to treat platinum-sensitive relapsed ovarian cancer. It was highlighted that single agent carboplatin is only used if patients have significant pre-existing paclitaxel neuropathy or cannot tolerate combination regimes. The professional group also indicated that trabectedin could be used to treat partially platinum sensitive subgroups of patients, based on the findings of the OVA-301 trial. The forthcoming INOVATYON trial (completion date December 2013) was noted which will directly compare PLDH in combination with trabectedin with PLDH in combination with carboplatin in the partially platinum-sensitive population.

5.4 The patient experts highlighted the emotional impact on women related to the fear of recurrence and subsequent treatment, particularly for women with platinum refractory disease. It was noted that disease recurrence is associated with poorer prognosis and limitations in treatment options available and this can have a devastating impact on patients. They echoed the comments from the professional group that different sub-types require different treatments and patients would benefit from a targeted treatment plan. They emphasized the importance of ensuring all possible treatment options are available to clinicians and patients. In general, it was noted that some treatments may result in mild to moderate side effects whereas others such as PLDH and gemcitabine are well tolerated with only minor side effects. It was noted that as recurrent ovarian cancer is often incurable it is very importanct that the treatments do not worsen quality of life, but also recognising that any improvement in survival is valued so patients so may consider mild or moderate side effects to be worth the extension to their life.

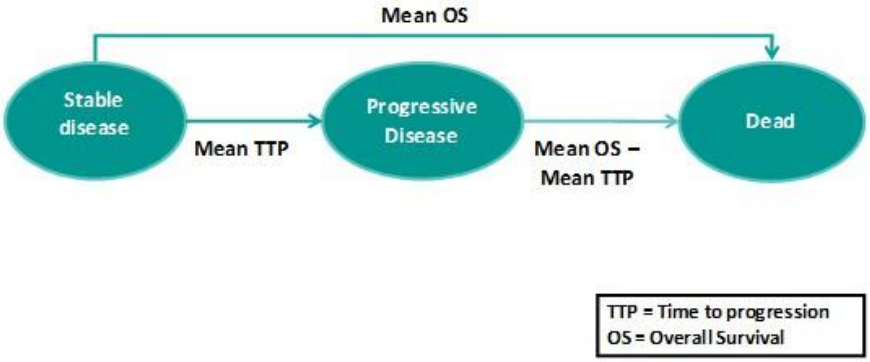
6 Cost-effectiveness evidence

6.1 One manufacturer (trabectedin, PharmaMar) submitted cost-effectiveness evidence as part of their submission. The manufacturer developed a decision analytic model comparing trabectedin in combination with PLDH with PLDH alone in people with recurrent platinum-sensitive ovarian cancer who are not suitable for platinum based chemotherapy because of allergy or intolerance or because they have partially platinum-sensitive disease. The manufacturer stated that this population was chosen to align with the inclusion criteria for OVA-301 and to address the clinical unmet need in this population. The Assessment Group stated that while it was unclear what proportion of patients in the OVA-301 trial were allergic or

intolerant to platinum-based therapy, the efficacy of non-platinum-based treatments were unlikely to differ between people with or without the presence of an allergy or intolerance. The cohort had received only one prior platinum-based chemotherapy regimen, and experienced recurrence or progression. Patients were stratified by the ECOG performance score (0-1 or 2) and platinum-sensitivity (sensitive: PFI ≥ 6 months, or resistant: PFI < 6 months). The dosing schedule was an IV infusion of PLDH 30 mg/m2 followed by a 3-hour infusion of trabectedin 1.1 mg/m2 every 3 weeks or PLDH 50 mg/m2 every 4 weeks.

6.2 The model structure developed by the manufacturer was identical to the model developed within TA91; disease was classified into three distinct periods: stable disease, progressive disease, and death (Figure 1 below). The time spent within each health state was determined by the mean time to progression and mean overall survival data from OVA-301. Costs and QALYs accumulated for each treatment were calculated based upon the mean time spent in each health state. The model had a life-time time horizon. An NHS and personal social services perspective was taken and costs and benefits were discounted at 3.5%. The Assessment Group stated that this model structure was appropriate but noted that this assessment included a comparison with only 1 of 5 potentially relevant comparators listed in the NICE scope. Specifically, platinum-based chemotherapies were not included as comparators but the Assessment Group highlighted that these would be important treatment options for people with partially platinum-sensitive disease. However, it was acknowledged that no comparative data was identified for this comparison.

Figure 1 Schematic of the model structure



6.3 The manufacturer stated that because the OVA-301 trial was not powered for post-hoc analysis of subgroups within the platinum-sensitive stratum, data for the entire platinum-sensitive population was considered appropriate for the cost-effectiveness analyses. The manufacturer fitted five parametric survival distributions (Exponential, Weibull, Gompertz, Log-logistic and Lognormal) by treatment arm to the progression-free survival and overall survival data from OVA-301 separately, adjusting for potential covariates, in order to extrapolate the data over a lifetime horizon and obtain the mean progression-free survival and overall survival for each treatment. Explanatory variables were also used to control for baseline characteristics. Goodness of fit criteria based on Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) of each survival distribution was used to select the preferred distribution. Based on the Weibull distributions, the mean progression-free survival for trabectedin in combination PLDH and PLDH alone was 11.26 and 8.25 months respectively. Based on the Log-logistic distributions, the mean overall survival for trabectedin in combination PLDH and PLDH alone was 44.69 and 34.97 months respectively.

6.4 The Assessment Group highlighted that a key limitation of the analysis was the degree of censoring observed within the progression-free survival and overall survival data and stated that this reduced the validity of the data used in the model. With regard to progression-free survival, in OVA-301, 38.8% and 40.5% of people receiving treatment with PLDH and trabectedin in combination with PLDH were censored respectively. The manufacturer did not include details around the reasons for censoring or provide an explanation for the quantity of censoring encountered. In addition, limited details around censoring within the overall survival analysis were presented.

6.5 The model included Grade 3 or 4 adverse events with an incidence equal or greater than 5% in the OVA-301 trial and were considered to have a significant cost associated with them. The frequencies of adverse events in the OVA-301 trial for patients with platinum-sensitive disease were utilised in the model. These are summarised on page 254 of the Assessment Report.

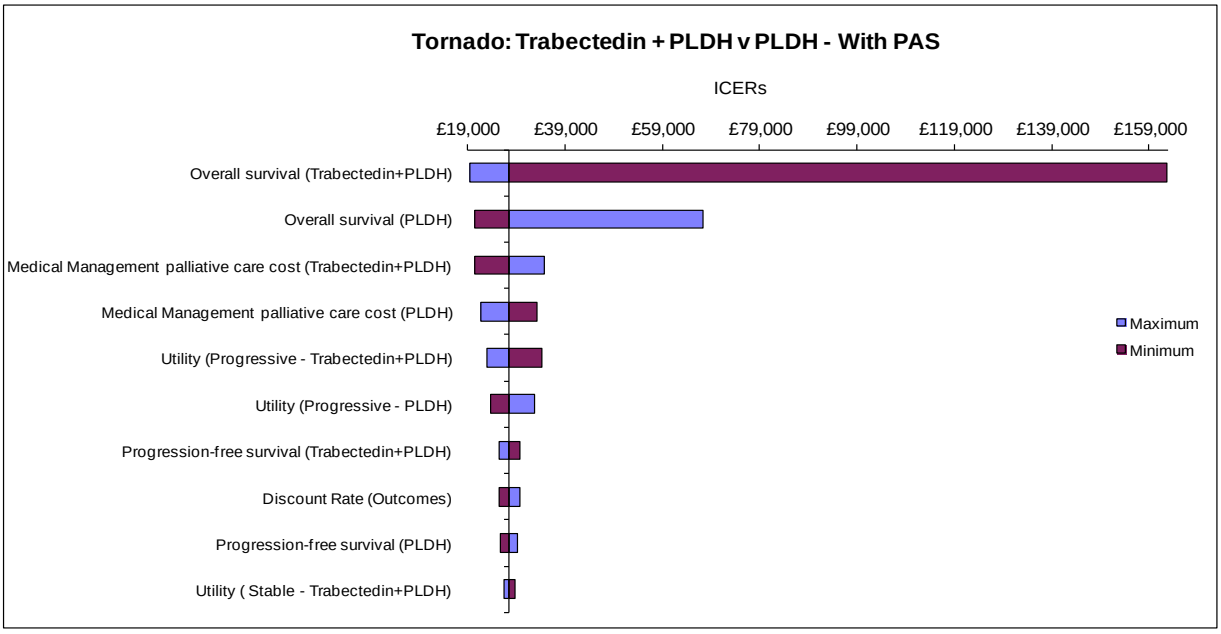
6.6 Utility estimates were obtained from the EQ-5D data from the OVA-301 trial. The mean utility in the stable and progressive states were 0.718 and 0.649 respectively. Disutilities associated with adverse events were not included in the model as it was considered that the impact of adverse events on quality of life would be captured within the mean estimates obtained from trial data. Costs incorporated in the model related to drug costs, drug administration costs, medical management and cost of adverse events. These are summarised on page 255 of the Assessment Report. As noted in section 2.9, the manufacturer of trabectedin has agreed a patient access scheme with the Department of Health. The scheme will apply to patients who require more than 5 cycles of trabectedin plus PLDH. Without the patient access

scheme it was assumed that on average a patient would receive 6.86 cycles of trabectedin. However, incorporating the patient access scheme assumes that the cost to the NHS for trabectedin would be for 4.28 cycles of treatment on average. In addition, a total discounted implementation cost of the patient access scheme of £560.74 was included in the model.

6.7 Base case deterministic results, incorporating a patient access scheme for trabectedin, indicated incremental costs of £13,397 and incremental QALYs of 0.49 for trabectedin in combination with 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.

6.8 The manufacturer undertook a series of deterministic sensitivity analyses on various model parameters. The key driver of the cost-effectiveness estimates was the estimate of overall survival. The manufacturer reported that the cost-effectiveness estimate was also sensitive to medical management and palliative care costs and utility estimates for progressed disease (figure 2).

Figure 2 Parameters affecting the ICER



6.9 Scenario analyses indicated that results were most sensitive to the adjustment of progression-free interval as an explanatory variable and alternative survival distributions for progression-free survival and overall survival. When the second best fitting distributions based on AIC and BIC were chosen (Gompertz and Weibull), the ICER increased to over £35,000 per QALY gained.

Table 3. Sensitivity analysis with progression-free interval adjustment and choosing different survival distributions (with PAS analyses)

Scenario	Trabectedin plus PLDH (PFS)	PLDH monotherapy (PFS)	Trabectedin plus PLDH (OS)	PLDH monotherapy (OS)	ICER (£)
Base case	Weibull AIC = 451.2	Weibull AIC = 380.9	Log-logistic AIC = 508.	Log-logistic AIC = 472.7	27,573
No PFI adjustment	Weibull AIC = 456.3	Weibull AIC = 385.8	Log-logistic AIC = 514.3	Log-logistic AIC = 504.7	70,222
Distribution 1	Gompertz AIC = 457.7	Gompertz AIC = 384.0	Log-logistic AIC = 508.0	Log-logistic AIC = 472.7	27,572
Distribution 2	Weibull AIC = 451.2	Weibull AIC = 380.	Weibull AIC = 508.1	Weibull AIC = 478.6	35,485
Distribution 3	Gompertz AIC = 457.7	Gompertz AIC = 384.0	Weibull AIC = 508.1	Weibull AIC = 478.6	35,485

6.10 The manufacturer also conducted a range of additional scenario analyses. Increasing the cost of neutropenia from nil in the base case to £122 per patient for a grade 3 event and £2,346 per patient for a grade 4 event resulted in the greatest increase in the ICER from £27,573 to £29,033 per QALY gained. Results of the probabilistic sensitivity analysis showed that, at a cost-effectiveness threshold range of £20,000 to £30,000 per QALY gained; trabectedin in combination with PLDH had a 11% and 53% probability of being cost effective.

6.11 The manufacturer stated that trabectedin was eligible for consideration under the end-of-life criteria. The manufacturer stated that trabectedin in combination with PLDH was indicated for people with a life expectancy of less than 2 years without treatment: median overall survival in the platinum-sensitive and partially-platinum sensitive populations was 24.1 months and 16.4 months for patients treated with PLDH alone. Accounting for the imbalance in progression-free interval and other prognostic factors in the platinum-sensitive population reduced the median to 19.4 months. In addition, for people with platinum-sensitive and partially platinum-sensitive relapsed ovarian cancer, median survival (after correction of prognostic factors including PFI) shows an extension in life of 4 months, and estimated mean survival suggests this extension of life could be in excess of 9 months. The manufacturer also estimated that trabectedin would be indicated for approximately 500 people with relapsed platinum-sensitive ovarian cancer in 2014.

The Assessment Group model

6.12 The Assessment Group conducted a systematic review and stated that no cost-effectiveness analysis including the full range of interventions and comparators was available in the literature.

It was noted that the majority of analyses available were based on the model developed for TA91. The Assessment Group stated that this model structure, also adopted by the manufacturer for trabectedin (see section 6.2) was considered by the Assessment Group to be most appropriate for the decision problem and therefore used it to develop a de-novo model (see figure 1). 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 were in the dead health state. The NHS and personal social services perspective was adopted and costs and benefits were discounted at 3.5%. Within TA91, 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; however, 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 within the economic model, and facilitate the assignment of costs, utilities and discounting.

6.13 The model included the population with platinum-sensitive disease and platinum-resistant or refractory disease separately and there was no explicit analysis of the full population. The Assessment Group explained that this was because disaggregation of the results by platinum sensitivity is more clinically relevant because progression-free interval was a key prognostic factor, as confirmed by experts, and this approach was also in line with the date available to inform the analysis. The Assessment Group stated that data for people with fully or

partially platinum-sensitive disease was insufficient so these groups were considered in sensitivity rather than base-case analysis. As noted in section 5.2.3, 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 the platinum-sensitive network 2 and platinum-resistant and platinum refractory-subgroups.

6.14 Table 4 below outlines the interventions and comparators outlined in the NICE scope for people with platinum-sensitive and platinum-resistant or platinum-refractory ovarian cancer, highlighting to what extent the de novo analysis carried out by the Assessment Group satisfies the scope.

Table 4. Comparison of the Assessment Group de novo analysis and the NICE scope

NICE scope		TAG *de novo* analysis
Interventions	For people with platinum-sensitive ovarian cancer: • paclitaxel alone or in combination with platinum chemotherapy; • pegylated liposomal doxorubicin hydrochloride alone or in combination with platinum chemotherapy; • gemcitabine in combination with carboplatin; • trabectedin in combination with pegylated liposomal doxorubicin hydrochloride • topotecan.	All interventions of interest were considered; however, as noted in the clinical-effectiveness section, two independent networks were constructed evaluating platinum and non-platinum based regimens separately.
	For people with platinum-resistant or platinum-refractory ovarian cancer: • paclitaxel alone or in combination with platinum chemotherapy; • pegylated liposomal doxorubicin hydrochloride; • topotecan.	Data for paclitaxel in combination with platinum was not available from the literature. Therefore, this intervention was omitted from the base case analysis.

Comparators	For people with platinum-sensitive ovarian cancer: • the interventions listed above in comparison with each other • bevacizumab in platinum-containing chemotherapy (subject to NICE appraisal) • single-agent platinum chemotherapy.	All comparators of interest were considered; however, due to the data available from the literature, two independent networks were constructed. Bevacizumab in platinum-containing chemotherapy was not recommended for use in TA285 and therefore was not considered in this analysis.
	For people with platinum-resistant or platinum-refractory ovarian cancer: • the interventions listed above in comparison with each other; • etoposide alone or in combination with platinum chemotherapy; • best supportive care.	Data for paclitaxel in combination with platinum was not available from the literature. Therefore, this intervention was omitted from the base case analysis. Data for etoposide alone or in combination with platinum chemotherapy and data for best supportive care were not available. Therefore, these comparators were omitted from the base case analysis.
Abbreviations used in table: NICE, National Institute for Health and Care Excellence; TAG, Technology Assessment Group.		

6.15 Clinical effectiveness data from the Assessment Group's network-meta-analysis was included in the model (see Table 5 below). The Assessment Group noted 3 main concerns with the use of this data in the model. First, due to lack of individual patient data, the network meta-analysis synthesised hazard ratios from the literature. Individual patient data would have allowed for differences in baseline characteristics within and between trials to be incorporated. In addition, as discussed in section 4.5 above, unadjusted hazard ratios were incorporated which could include potential bias. Second, using summary hazard ratios based on the literature assumes proportional hazards, that is, the relative treatment effects captured by the hazard ratios holds true across all time points. However, when this assumption was explored, the log-cumulative hazard plots indicated that this assumption may not be appropriate. The Assessment Group highlighted that the where the relative hazard decreases over time for both PFS and OS, the model is

likely to overestimate the relative benefit of treatment and vice-versa. Third, it was noted that several trial included allowed for crossover which could have confounded overall survival data. The Assessment Group was unable to assess the degree of crossover bias because all the trials did not describe further treatment received and due to lack of individual patient data.

Table 5. Clinical effectiveness data from the Assessment Group's network meta-analysis

	Progression free survival		Overall survival	
	Mean HR versus baseline	95% credible interval	Mean HR versus baseline	95% credible interval
PS; network 1 (paclitaxel plus carboplatin baseline)				
Paclitaxel plus platinum [carboplatin] (baseline treatment)	1.000	-	1.000	-
PLDH plus platinum [carboplatin]	0.817	0.717, 0.927	1.023	0.889, 1.172
Gemcitabine plus carboplatin	0.985	0.748, 1.273	1.247	0.921, 1.652
Platinum [carboplatin]	1.361	1.182, 1.559	1.290	1.096, 1.509
PS; network 2 (PLDH baseline)				
PLDH (baseline treatment)	1.000	–	1.000	–
PLDH plus trabectedin	0.736	0.560, 0.949	0.835	0.667, 1.032
Paclitaxel	1.615	0.939, 2.586	1.219	0.850, 1.690
Topotecan	1.298	0.979, 1.688	1.367	1.035, 1.770
Platinum resistant/refractory; network (PLDH baseline)				
PLDH (baseline treatment)	1.000	–	1.000	–
Paclitaxel	1.360	0.817, 2.123	1.053	0.783, 1.382
Topotecan	0.998	0.767, 1.277	0.973	0.764, 1.221
HR>1 favours baseline treatment Abbreviations used in table: HR, hazard ratio; PLDH, pegylated liposomal doxorubicin hydrochloride; PS, platinum sensitive.				

6.16 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 lack of data; instead, adverse event data from any population (platinum sensitive or platinum resistant/refractory) were included in analysis therefore assuming that the likelihood of an adverse reaction is independent of the progression-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. While 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. The details are available on page 305 to 307 of the Assessment Report.

6.17 The Assessment Group conducted a systematic review and identified 22 studies measuring health-related quality of life. It was noted that the utility values included in TA222 from the OVA-301 trial were most relevant because EQ-5D utility values in the recurrent ovarian cancer population by the health states required for the economic model were reported, and were based on a large sample of patients (n=600). The manufacturer 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 within TA222, 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 and also to avoid double-counting because events on patient quality of life

associated with trabectedin in combination with PLDH and PLDH alone are already implicitly included within health state EQ-5D estimates from TA222. This was explored in sensitivity analyses.

6.18 The Assessment Group model included costs associated with the technologies, administration costs, health state related costs and adverse events costs. Chemotherapy costs per cycle were estimated based on drug costs in the BNF and regimens as per the summary of product characteristics with verification and amendment from clinical experts. The Assessment Group clarified that uncertainty associated with patient characteristics had been accounted for in the base-case analysis because data from 321 ovarian cancer patients described by Sacco *et al.* has been used to estimate dose, and therefore cost, at an individual level. The costs per cycle outlined in Table 6 were applied within the model to people within the stable disease health state, for up to the stated maximum number of cycles. However, for trabectedin in combination with PLDH, although the maximum number of cycles likely to be used in clinical practice is 6 cycles, the manufacturer for trabectedin submitted a patient access scheme (PAS) which limits the number of cycles for which the NHS would bear the cost to 5 cycles. Therefore, in the base-case analysis, for trabectedin in combination with PLDH, costs for a maximum of 5 cycles were included. In addition, the implementation of such a PAS would result in an administration cost which would be borne by the NHS. Therefore, a PAS implementation cost was included within the model. The non-discounted estimate of £598 was included in the model because it would occur only in the first year of the model.

6.19 The model assumed that with the exception of oral etoposide, all treatment regimens would be administered as an infusion in a hospital and associated administration costs were included in

the model. The costs associated with the stable disease health state comprised the cost of monitoring via one hospital outpatient visit every 3 months with costs based on NHS reference costs. It was assumed that for disease that progressed following treatment for platinum-resistant or platinum-refractory disease, subsequent treatment would be palliative in intent. Therefore, a cost associated with palliative care was applied for each month in the progressed heath state. For disease that progressed following treatment for platinum-sensitive disease, a cost associated with a further line of chemotherapy was applied for 6 months following progression. After this point, a cost associated with palliative care was applied for each month spent in the progressed health state. The Assessment Group stated that this approach was simplistic but captured the key aspects of costs associated with progressed disease. For the base-case analyses, it was assumed that no vial sharing would occur.

Table 6. Estimated chemotherapy costs applied within the Assessment Group's base case de novo economic evaluation

Chemotherapy regimen	Chemotherapy cost per cycle	Admin cost cycle 1	Admin cost cycle 2 onwards	Cost of adverse events (during treatment)	Health state costs (per month)		
					Stable period	Progressed period, PS patients, months 1-6	Progressed period, PS patients months 6+ or PRR patients from progression
Paclitaxel 80mg/m^2 weekly (cycle) for 18 weeks or until progression	£306	£215	£286	£111	£45	£796	£531
Paclitaxel 175 mg/m^2 day 1 every 21 day cycle	£638	£347	£286	£111	£45	£796	£531
Paclitaxel 80mg/m^2 plus carboplatin AUC three, weekly for 18 weeks or until progression	£442	£231	£302	£78	£45	£796	£531
Paclitaxel 175 mg/m^2 and carboplatin AUC	£855	£363	£302	£78	£45	£796	£531

five, day 1 every 21 day cycle							
PLDH 40 mg/m^2 day 1 every 28 day cycle	£1,211	£265	£286	£69	£45	£796	£531
PLDH 30 mg/m^2; carboplatin target AUC of five, day 1 every 28 day cycle	£1,137	£363	£302	£97	£45	£796	£531
Gemcitabine 1,000 mg/m^2 day 1 and 8 every 21 day cycle, carboplatin target AUC of four day 1 every 21 day cycle	£706	£567	£588	£172	£45	£796	£531
Trabectedin 1.1 mg/m^2; PLDH 30 mg/m^2, day 1 every 21 day cycle	£3,679	£363	£302	£198	£45	£796	£531
Topotecan 1.5 mg/m^2, day 1-5 every 21 day cycle	£1,305	£1,359	£1,430	£200	£45	£796	£531
Carboplatin target AUC5, day 1 every 21 day cycle	£217	£215	£286	£33	£45	£796	£531
*Etoposide 50 mg (oral) days 1-21 every 28 day cycle**	*£200*	*£0*	*£0*	*£39*	*£45*	*£796*	*£531*
*Etoposide 50 mg (oral) days 1-21 and cisplatin 50 mg/m^2 days 1,8 and 15 every 28 day cycle**	*£340*	*£919*	*£858*	*£53*	*£45*	*£796*	*£531*
* Sensitivity analysis only Abbreviations used in table: AUC, area under the curve; m, metre; mg, milligram, PLDH, pegylated liposomal doxorubicin hydrochloride; PS, platinum sensitive; PRR, platinum resistant/refractory.							

6.20 The impact of parameter uncertainty on model results was investigated in both probabilistic sensitivity analyses and deterministic one-way sensitivity analyses. In addition, structural assumptions were varied in deterministic scenario analyses. The results for the base-case and sensitivity analyses each of the networks are presented below.

Results Network 1 – Platinum-based regimens in people with platinum-sensitive sensitive disease

6.21 The fully incremental results from the Assessment Group's base-case deterministic cost-effectiveness analysis for network 1

evaluating platinum-based regimens in people with platinum sensitive disease are presented in table 7 below. Both deterministic and probabilistic results indicated that PLDH in combination with platinum is dominated by (that is, it is more costly and less effective than) paclitaxel in combination with platinum. Similarly, gemcitabine in combination with carboplatin was extendedly dominated (that is, it is more costly and less effective than) by paclitaxel in combination with platinum. Therefore, PLDH in combination with platinum and gemcitabine in combination with carboplatin were excluded, leaving paclitaxel in combination with 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 in combination with platinum was associated with an estimated incremental cost of £5,694 and an additional 0.23 quality-adjusted life years (QALYs) when compared with platinum alone. The probabilistic ICER for paclitaxel in combination with platinum compared with platinum alone was £24,539 per QALY gained.

6.22 One-way sensitivity analyses on various model parameters indicated that the comparisons of paclitaxel in combination with platinum and PLDH in combination with platinum compared with platinum alone were most sensitive to the relative effect of treatment on overall survival resulting in an increase in the ICER by up to £20,000 per QALY gained. For example, use of the lower bound of the 95% credible interval (estimated from the network meta-analysis) for the hazard ratio for overall survival (platinum alone compared with paclitaxel in combination with platinum platinum) increased the deterministic base case ICERs by over £20,000 per QALY gained. Please see table 9 for further details. 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.

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

Table 7. Network 1- Results of the Assessment Group base case de novo economic evaluation

Treatment	Incremental cost (discounted)	Incremental QALYs (discounted)	Incremental ICER (cost/QALY)	Incremental ICER (cost/QALY) (excluding dominated options)
Probabilistic results				
Platinum	–	–	–	–
Gemcitabine plus carboplatin	£4,491	0.047	£94,984	Extendedly dominated
Paclitaxel plus platinum	£1,178	0.184	£6,411	£24,539
PLDH plus platinum	£1,021	-0.009	Strictly dominated	
Deterministic results				
Platinum	–	–	–	–
Gemcitabine plus carboplatin	£4,432	0.039	£114,410	Extendedly dominated
Paclitaxel plus platinum	£1,262	0.195	£6,472	£24,361

PLDH plus platinum	£977	-0.015	Strictly dominated
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; PLDH, pegylated liposomal doxorubicin hydrochloride; vs, versus.			

Results Network 2 – Non-platinum-based regimens in people with platinum-sensitive disease

6.24 Base-case results (deterministic and probabilistic) indicated that topotecan was strictly dominated by PLDH. Topotecan was therefore removed from the analysis and the relevant fully incremental comparisons of PLDH compared with paclitaxel, and trabectedin in combination with PLDH compared with PLDH alone were presented. When compared with paclitaxel, PLDH was associated with an incremental cost of approximately £3,900 and approximately 0.16 additional QALYs. This resulted in ICERs of £23,733 and £25,931per QALY gained in the deterministic and probabilistic analyses, respectively. When compared with PLDH alone, trabectedin in combination with PLDH was associated with an incremental cost of approximately £13,000 and 0.16 additional QALYs. The resulting ICERs for trabectedin in combination with PLDH compared with PLDH alone were £85,212 and £81,353 per QALY gained in the deterministic and probabilistic analyses, respectively.

Table 8. Network 2 - Results of the Assessment Group base case de novo economic evaluation

Treatment	Incremental cost (discounted)	Incremental QALYs (discounted)	Incremental ICER (cost/QALY)	Incremental ICER (cost/QALY) (excluding dominated options)
Probabilistic results				
Paclitaxel	–	–		
PLDH	£3,814	0.147	£25,931	£25,931
Topotecan	£4,298	-0.238	Strictly dominated	
Trabectedin	£8,798	0.399	£54,893	£81,353

plus PLDH				
Deterministic results				
Paclitaxel	–	–	–	–
PLDH	£3,931	0.166	£23,733	£23,733
Topotecan	£4,194	-0.247	Strictly dominated	
Trabectedin plus PLDH	£8,847	0.400	£22,131	£85,212
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; PLDH, pegylated liposomal doxorubicin hydrochloride; vs, versus.				

6.25 The Assessment Group undertook a series of one-way sensitivity analyses on various model parameters. As for network 1, the key driver of the cost-effectiveness estimates for all 3 comparisons (PLDH compared with paclitaxel, trabectedin plus PLDH compared with paclitaxel, trabectedin plus PLDH compared with PLDH) was the relative effect of treatment on overall survival. Please see table 9 for further details. For example, for the comparison of PLDH with paclitaxel, use of the lower bound of the 95% credible interval for the hazard ratio for overall survival (paclitaxel compared with PLDH) resulted in a move from an ICER of approximately £25,000 (PLDH compared with paclitaxel) to PLDH being dominated by paclitaxel. The Assessment Group undertook a series of scenarios analyses and noted that the base-case results were robust in the majority of the scenarios modeled, with the exception of the scenario where the dose of PLDH was increased from 40mg/m2 to 50mg/m2, increasing the ICER for PLDH compared with paclitaxel from £23,733 to £31,222 per QALY gained. The Assessment Group stated that apart from this scenario, the ICER remained below £30,000 per QALY gained and highlighted that topotecan was dominated by trabectedin in combination with PLDH in every scenario.

6.26 The Assessment group also carried out an exploratory scenario analysis using clinical effectiveness data from the PharmaMar

submission for a head to head comparison of trabectedin in combination with PLDH compared with PLDH alone. This resulted in an ICER of £35,363 per QALY gained compared with an ICER of £85,212 and £27,573 estimated by the Assessment Group and the manufacturer's base-case analysis respectively. The Assessment Group stated that this difference was predominantly a consequence of the use of adjusted clinical effectiveness data, acknowledging that adjustment of clinical effectiveness data for key prognostic factors such was likely to result in more accurate estimates of progression-free survival and overall survival. See page 357 of the Assessment Report for further details.

Results – platinum-resistant and platinum-refractory group

6.27 Base-case results for the platinum-refractory and platinum-resistant group (deterministic and probabilistic) indicated that paclitaxel was dominated by PLDH alone. Therefore, topotecan compared with PLDH was the only comparison considered in the final cost-effectiveness results. Topotecan in combination with PLDH was associated with an incremental cost of approximately £7,000 and 0.02 additional QALYs. The resulting ICERs for topotecan in combination with PLDH compared with PLDH alone were £499,553 and £324,188 per QALY gained in the deterministic and probabilistic analyses, respectively.

6.28 As with platinum-sensitive network 1 and 2, the relative effect of treatment on overall survival was the key driver of cost-effectiveness results. Please see table 9 for further details. For the comparisons of both topotecan and paclitaxel with PLDH, sensitivity analyses around the relative effect of overall survival altered results: for example, when the lower bounds of the overall survival hazard ratios were used for topotecan compared

with PLDH and paclitaxel compared with PLDH, the ICERs were £53,288 and £17,903 per QALY gained respectively. The Assessment Group undertook a series of scenarios analyses and noted that the base-case results were robust in the majority of the scenarios modeled. They highlighted that the ICER for topotecan compared with PLDH ranged from £374,963 and £503,885 in all scenarios. Paclitaxel was dominated in all scenarios except when the cost associated with a 50mg 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.

Table 9. Impact of uncertainty associated with overall survival hazard ratios on the Assessment Group deterministic ICER estimates

Comparison	HR	Mean (95% CrI)	ICER (Mean)	ICER (lower 95% CrI)	ICER (upper 95% CrI)
Platinum sensitive - network 1 (all HRs versus paclitaxel plus platinum)					
Gemcitabine plus carboplatin vs platinum	Gemcitabine plus carboplatin	0.985 (0.748, 1.273)	£114,410	£23,578	Dominated
	Platinum	1.361 (1.182, 1.559)		Dominated	£33,608
Paclitaxel plus platinum vs platinum	Platinum	1.361 (1.182, 1.559)	£24,361	£46,435	£19,283
PLDH plus platinum vs platinum	PLDH plus platinum	0.817 (0.717, 0.927)	£30,439	£23,175	£54,776
	Platinum	1.361 (1.182, 1.559)		£68,315	£22,829
Paclitaxel plus platinum vs gemcitabine plus carboplatin	Gemcitabine plus carboplatin	0.985 (0.748, 1.273)	£6,472	Less costly and less effective	£8,719
PLDH plus platinum vs gemcitabine plus carboplatin	PLDH plus platinum	0.817 (0.717, 0.927)	£12,410	£11,617	£16,236
	Gemcitabine plus carboplatin	0.985 (0.748, 1.273)		Less costly and less effective	£11,345
PLDH plus platinum vs paclitaxel plus platinum	PLDH plus platinum	0.817 (0.717, 0.927)	Dominated	£20,672	Less costly and less effective

Platinum sensitive - network 2 (all HRs versus PLDH)					
PLDH vs paclitaxel	Paclitaxel	1.615 (0.939, 2.586)	£23,733	Dominated	£15,900
Topotecan vs paclitaxel	Topotecan	1.298 (0.979, 1.688)	Dominated	£78,398	Dominated
	Paclitaxel	1.615 (0.939, 2.586)		Dominated	£67,465
Trabectedin plus PLDH vs paclitaxel	Trabectedin plus PLDH	0.736 (0.560, 0.949)	£53,258	£37,519	£102,032
	Paclitaxel	1.615 (0.939, 2.586)		£413,936	£34,938
Topotecan vs PLDH	Topotecan	1.298 (0.979, 1.688)	Dominated	Dominated	Dominated
Trabectedin plus PLDH vs PLDH	Trabectedin plus PLDH	0.736 (0.560, 0.949)	£85,212	£44,266	Dominated
Trabectedin plus PLDH vs topotecan	Trabectedin plus PLDH	0.736 (0.560, 0.949)	£22,131	£18,437	£30,754
	Topotecan	1.298 (0.979, 1.688)		£35,482	£18,478
Platinum resistant/refractory (all HRs versus PLDH)					
Paclitaxel vs PLDH	Paclitaxel	1.360 (0.817, 2.123)	Dominated	£17,904	Q3
Topotecan vs PLDH	Topotecan	0.998 (0.767, 1.277)	£449,553	£53,288	Dominated
Topotecan vs paclitaxel	Topotecan	0.998 (0.767, 1.277)	£127,117	£39,903	Dominated
	Paclitaxel	1.360 (0.817, 2.123)		Dominated	£39,485
Abbreviations used in table: CrI, credible interval; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; OS, overall survival; PLDH, pegylated liposomal doxorubicin hydrochloride; TAG, Technology Assessment Group.					

7 Equalities issues

7.1 No potential equality issues have been identified

8 Innovation

8.1 ***n/a***

9 Authors

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Related NICE guidance

Technology Appraisal No. 91, May 2005, ‘Topotecan, pegylated liposomal doxorubicin hydrochloride and paclitaxel for the treatment of advanced ovarian cancer’

For women for whom the cancer is:

- platinum-sensitive or partially platinum-sensitive, except women who are allergic to platinum-based drugs, paclitaxel in combination with a platinum-based drug (carboplatin or cisplatin) as an option for second-line (or subsequent) treatment should be considered.
- partially platinum-sensitive, platinum-resistant or platinum-refractory, and women who are allergic to platinum-based compounds, PLDH as an option for second-line (or subsequent) treatment should be considered.
- platinum-refractory or platinum-resistant, and women who are allergic to platinum-based compounds, paclitaxel on its own as an option for second-line (or subsequent) treatment should be considered.
- platinum-refractory or platinum-resistant, or women who are allergic to platinum-based compounds, for whom PLDH and single-agent paclitaxel are considered inappropriate, topotecan as an option for second-line (or subsequent) treatment should be considered.

These recommendations also apply to ovarian cancer that relapses after second-line chemotherapy; this is called ‘subsequent’ chemotherapy.

Technology Appraisal No. 222, Apr 2011, ‘Trabectedin for the treatment of relapsed ovarian cancer’.

- Trabectedin in combination with pegylated liposomal doxorubicin hydrochloride (PLDH) is not recommended for the treatment of women with relapsed platinum-sensitive ovarian cancer.

Ovarian cancer: The recognition and initial management of ovarian cancer. Nice clinical Guideline 122 (2011)

NICE pathways

- There is a NICE pathway on ovarian cancer, which is available from http://pathways.nice.org.uk/pathways/ovarian-cancer

Appendix B: Clinical efficacy section of the draft European public assessment report

Topotecan:

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000123/WC500051538.pdf

Pegylated liposomal doxorubicin hydrochloride:

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000089/WC500020175.pdf

Paclitaxel:
http://www.hma.eu/fileadmin/dateien/pipar/dk879paclitaxel/par_DK879_Paclitaxel_MEDA.pdf

Trabectedin:

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000773/WC500045836.pdf

Gemcitabine:
http://www.hma.eu/fileadmin/dateien/pipar/dk11571329gemcitabine/parmod5_dk1157gemcitabine.pdf