NICE National Institute for Health and Care Excellence

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) [ID468]

Assessment Report

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Topotecan, pegylated liposomal doxorubicin hydrochloride, paclitaxel, trabectedin and gemcitabine for advanced recurrent disease only (Review of TA 91 & TA 222)

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BMJ Technology Assessment Group

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Rider on responsibility for report
The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Contributions of authors:

Steve Edwards	Project lead: supervised the production of the final report; carried out the network meta-analyses; critical appraisal of the economic evidence and company submissions.
Samantha Barton	Devised and carried out the clinical literature searches; study selection; data extraction; report writing; and critical appraisal of the company submissions.
Elizabeth Thurgar	Devised and carried out the economic literature searches; study selection; data extraction; development of the economic model; report writing; and critical appraisal of the company submissions.
Nicola Trevor	Devised and carried out the economic literature searches; study selection; data extraction; development of the economic model; report writing; and critical appraisal of the company submissions.

All authors read and commented on draft versions of the Technology Assessment Group report

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DEFINITION OF TERMS AND LIST OF ABBREVIATIONS

Glossary of terms

Advanced ovarian cancer: Disease classified as International Federation of Gynaecologists and Obstetricians (FIGO) stages III–IV.

CA125: A cell surface marker found in serum. A response according to CA 125 has occurred if there is at least a 50% reduction in CA 125 levels from a pretreatment sample. The response must be confirmed and maintained for at least 28 days.

Chemotherapy: The use of drugs that are capable of killing cancer cells or preventing/slowing their growth.

Complete response: The total disappearance of all detectable malignant disease for at least 4 weeks.

Cost-effectiveness acceptability curve (CEAC): A graphical representation of the probability of an intervention being cost-effective over a range of monetary values for society's willingness to pay for an additional unit of health gain.

Debulking: Surgical removal of a substantial proportion of cancer tissue. Optimal debulking refers to the removal of the largest possible amount of tumour while limiting the damage to the surrounding normal tissue; interval debulking refers to the surgical removal of a tumour after chemotherapy, aimed at further reducing its bulk.

ECOG performance status: 0: Fully active, able to carry on all predisease performance without restriction. 1: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light housework, office work. 2: Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours. 3: Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. 4: Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. 5: Dead.

First-line therapy: The first chemotherapy regimen (usually administered with curative intent) given to patients who have been newly diagnosed with ovarian cancer, or who had an early stage of the disease which has been previously treated with surgery alone but has since relapsed and requires chemotherapy.

Histological grade: The degree of malignancy of a tumour as judged by histology.

Histological type: The type of tissue found in a tumour as determined by histology.

Incremental cost-effectiveness ratio: An expression of the additional cost of health gain associated with an intervention relative to an appropriate comparator. Expressed as the difference in mean costs (relative to the comparator) divided by the difference in mean effects. Sometimes expressed with confidence intervals.

Kaplan–Meier curves: Also called product limit method. A non-parametric method of compiling life or survival tables, developed by Kaplan and Meier in 1958. This combines calculated probabilities of survival and estimates to allow for censored observations, which are assumed to occur randomly. The intervals are defined as ending each time an event (e.g. death, withdrawal) occurs and are therefore unequal.

Karnofsky performance status scale: A performance measure for rating the ability of a person to perform usual activities, evaluating a patient's progress after a therapeutic procedure, and determining a patient's suitability for therapy. It is used most commonly in the prognosis of cancer therapy, usually after chemotherapy and customarily administered before and after therapy. A measure is given by a physician to a patient's ability to perform certain ordinary tasks: 100, normal, no complaints; 70, unable to carry on normal activity; 50, requires considerable assistance; 40, disabled; 30, hospitalisation recommended.

Partial response: At least a 50% decrease in tumour size for more than 4 weeks without an increase in the size of any area of known malignant disease or the appearance of new lesions.

Phase II trial: A study with a small number of patients diagnosed with the disease for which the drug is being studied. In this study, the safety of the new drug is tested. Early effectiveness data are also collected for varying doses of the drug.

Phase III trial: A study with a large number of patients diagnosed with the disease for which the drug is being studied and is unlicensed for the indication. In this study, the drug is tested against a placebo or alternative treatment.

Proportional hazards model: Regression method for modelling survival times. The outcome variable is whether or not the event of interest has occurred and, if so, after what period; if not, the duration of follow-up. The model predicts that hazard or risk of the event in question at any given time.

Quality-adjusted life-year (QALY): A term originally developed in cancer studies to balance poor quality of life (possibly with long life expectancy) with good quality of life (possibly with short life expectancy).

Quality of life (QoL): A concept incorporating all the factors that might impact on an individual's life, including factors such as the absence of disease or infirmity as well as other factors which might

affect their physical, mental and social well-being.

RECIST (Response Evaluation Criteria for Solid Tumors) criteria: Complete response, disappearance of all target lesions and confirmed at 4 weeks; partial response, at least a 30% decrease in the sum of longest diameters (SLD) of target lesions (taking as reference the baseline SLD) and confirmed at 4 weeks; disease progression, at least a 20% increase in the SLD of target lesions (taking as reference the smallest SLD recorded since treatment started) with no documentation of complete response, partial response or stable disease before disease progression; stable disease, neither sufficient decrease in SLD to meet criteria for partial response nor sufficient increase in SLD to meet criteria for disease progression.

Staging: The allocation of categories (e.g. for ovarian cancer FIGO stages I–IV) to tumours, defined by internationally agreed criteria. Tumour stage is an important determinant of treatment and prognosis.

Abbreviations

Abbreviation	Description
ALT	Alanine transaminase
ASCO	American Society of Clinical Oncology
AST	Aspartate transaminase
AUC	Area under the curve
BMS	Bristol–Myers Squibb
BNF	British National Formulary
CEA	Carcinoembryonic antigen
CEAC	Cost-effectiveness acceptability curve
CI	Confidence interval
CR	Complete response
CRD	Centre for Reviews and Dissemination
CT	Computed tomography
CTC	Common Toxicity Criteria
CTU	Clinical Trials Unit
DSU	Decisions Support Unit
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organization for Research and Treatment of Cancer
FIGO	International Federation of Gynaecologists and Obstetricians
FPS	Fully platinum sensitive
GCIG	Gynecologic Cancer Intergroup
G-CSF	Granulocyte colony-stimulating factor
GFR	Glomerular filtration rate
GSK	GlaxoSmithKline
HR	Hazard ratio
HRT	Hormone replacement therapy
ICER	incremental cost-effectiveness ratio
IPD	Individual patient data
IRFMN	Istituto Mario Negri
ITT	Intention-to-treat
KPS	Karnofsky performance status
LYG	Life-year gained
MCAR	Missing completely at random
MeSH	Medical Subject Headings
MRC	Medical Research Council
MRI	Magnetic resonance imaging
MTC	Mixed-treatment comparison
NA	Not applicable
NCI	National Cancer Institute
NCI CTC	National Cancer Institute Common Toxicity Criteria
NE	Not evaluable
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis

NR	No response
OR	Odds ratio
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PFI	Platinum-free interval
PFS	Progression-free survival
PLDH	Pegylated liposomal doxorubicin hydrochloride
PPE	Palmar–plantar erythrodysesthesia
PPS	Partially platinum sensitive
PR	Partial response
PRR	Platinum resistant/refractory
QALY	Quality-adjusted life-year
QLQ-C30	Quality of life questionnaire C30
QoL	Quality of life
Q-TwiST	Quality-adjusted time without symptoms or toxicity
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumors
RR	Relative risk
SD	Stable disease
SWOG	Southwest Oncology Group
TTP	Time to progression
TwiST	Time without symptoms or toxicity
ULN	Upper limit of normal
UK	United Kingdom
WHO	World Health Organization
WTP	Willingness to pay

1 EXECUTIVE SUMMARY

1.1 Background

Ovarian cancer is the fifth most common cancer in the UK, and is the fourth most common cause of cancer death. It has been estimated that the lifetime risk (adjusting for multiple primaries) of developing ovarian cancer is 1 in 54 for women in the UK (based on data from 2008). Ovarian tumours are classified based on the cell type from which the tumour originates: surface epithelium; germ; or stroma. Most ovarian malignancies are epithelial in origin, accounting for 80–90% of ovarian cancers. Epithelial tumours can be further divided based on their histology (serous, mucinous, endometrioid, clear cell, and undifferentiated or unclassifiable). The most common type of ovarian cancer in the UK is serous carcinoma.

Ovarian cancer is predominantly a disease of older, post-menopausal women, with over 80% of cases being diagnosed in women over 50 years of age. Patients typically present with subtle symptoms, such as difficulty eating, abdominal bloating and feeling "full" quickly, all of which are suggestive of other, more minor conditions. As a result, many people (~60%) are diagnosed with ovarian cancer when their disease is in an advanced stage. Stage of disease at diagnosis is considered to be the strongest predictor of survival. Relative 5-year survival rate is more than 90% for early stage disease, but falls markedly to less than 10% for later stages.

Treatments for newly diagnosed ovarian cancer are given with curative intent and typically involve a combination of cytoreductive surgery and chemotherapy. Although first-line chemotherapeutic treatment achieves a response in approximately 70–80% of patients, some people do not respond to treatment and, of those who do respond, between 55% and 75% of people will relapse within 2 years of completing treatment. It is these populations, more specifically those people who have received prior platinum-based treatment, that are the focus of this systematic review and economic analysis.

A patient's response to first-line platinum-based therapy is indicative of their response to second and subsequent lines of platinum-based treatment, with the length of the platinum-free interval (PFI) and the extent of relapse (site and number of tumours) particularly prognostic of response. The choice of second and subsequent line of treatment has long been based on a patient's PFI, that is, the period of time between the last treatment of one regimen and the first treatment of the next regimen. Categorisations of platinum sensitivity used in the choice of second and subsequent lines of treatment of ovarian cancer are defined as follows:

- Platinum sensitive: disease that responds to first-line platinum-based therapy but relapses 6 months or more after completion of initial platinum-based chemotherapy;
    - Partially platinum-sensitive: disease that responds to first-line platinum based therapy but relapses between 6 and 12 months after completion of initial platinum-based chemotherapy;
    - Fully platinum-sensitive: disease that responds to first-line platinum based therapy but relapses 12 months or more after completion of initial platinum-based chemotherapy;
- Platinum resistant: disease that relapses within 6 months of completion of initial platinum-based chemotherapy;
- Platinum refractory: disease that does not respond to initial platinum-based chemotherapy.

Current NICE guidance on second-line or subsequent treatment of advanced ovarian cancer is based on the duration of time since last platinum-based therapy. The recommended options for patients with platinum-sensitive or partially platinum-sensitive advanced ovarian cancer are paclitaxel in combination with a platinum-based compound (carboplatin or cisplatin), or single-agent PLDH (only for partially platinum-sensitive ovarian cancer). Trabectedin in combination with PLDH is not recommended. The recommended options for patients with platinum-resistant or platinum-refractory ovarian cancer are single-agent paclitaxel, PLDH, or topotecan (for patients for whom PLDH and paclitaxel are considered inappropriate). At present there is no published guidance regarding the use of gemcitabine for treatment of ovarian cancer. However, combined with carboplatin, gemcitabine is licensed for the treatment of relapsed ovarian cancer in patients with platinum-sensitive or partially platinum-sensitive disease. In a recently completed Technology Appraisal, NICE did not recommend bevacizumab in combination with gemcitabine and carboplatin for the treatment of recurrent ovarian cancer.

1.2 Objectives

The following question is addressed by this technology assessment report: "what is the clinical and cost-effectiveness of topotecan, pegylated liposomal doxorubicin hydrochloride (PLDH), paclitaxel, trabectedin and gemcitabine for the treatment of advanced, recurrent ovarian cancer."

The five pharmaceutical interventions that are the focus of this MTA all have marketing authorisations in the UK for the treatment of several types of cancer, including ovarian cancer. Paclitaxel (various manufacturers) is licensed for first-line treatment of ovarian cancer in combination with platinum-based chemotherapy, and as second-line treatment of ovarian cancer after failure of standard platinum-based therapy. PLDH (Caelyx®, Jansen-Cilag) and topotecan (various manufacturers) are licensed for the treatment of advanced ovarian cancer after failure of first-line platinum-based therapy. Gemcitabine (Gemzar®, Lilly) is licensed in combination with carboplatin (platinum-based chemotherapy), and trabectedin (Yondelis®, PharmaMar) is licensed in combination

with PLDH, as second-line treatment of ovarian cancer in patients with relapsed platinum-sensitive disease.

For patients with platinum-sensitive ovarian cancer the relevant comparators are:

- the interventions licensed for platinum-sensitive disease in comparison with each other;
- single-agent platinum chemotherapy.

For patients with platinum-resistant or platinum-refractory ovarian cancer the relevant comparators are:

- the interventions licensed for platinum-resistant or platinum-refractory disease in comparison with each other;
- etoposide alone or in combination with platinum chemotherapy;
- best supportive care.

For patients with ovarian cancer, who are allergic to platinum-based chemotherapy the relevant comparators are:

- the interventions, without platinum-containing chemotherapy, in comparison with each other;
- etoposide;
- best supportive care.

1.3 Methods

The assessment comprises a systematic review of clinical and cost-effectiveness studies, a review and critique of manufacturer submissions, and a *de novo* economic analysis.

1.3.1 Clinical effectiveness systematic review

Evidence for the clinical effectiveness of the interventions outlined in the NICE scope (topotecan, PLDH, trabectedin, paclitaxel and gemcitabine) was assessed by conducting a systematic review of published research evidence. The review was undertaken following the general principles published by the Centre for Reviews and Dissemination (CRD).

The literature search was designed to update and expand the systematic search carried out in Technology Appraisal 91 (TA91), which evaluated the clinical and cost effectiveness of topotecan, PLDH, and paclitaxel. Medical Subject Headings (MeSH) and text terms for ovarian cancer, topotecan, PLDH, and paclitaxel were taken from the search strategy presented in TA91, and text terms added for the interventions trabectedin and gemcitabine.

For the review of clinical effectiveness, only RCTs were considered for inclusion in the review. Systematic reviews and non-randomised studies were excluded, as were studies that considered drugs administered as ‘maintenance therapy’ following directly on from first-line therapy without evidence

of disease progression. No restrictions were imposed on language or date of publication. Reference lists of identified systematic reviews were used as a source of potential additional RCTs, as well as a resource to compare studies retrieved from the systematic literature search. Clinical experts were also used to identify any potentially missing studies.

Titles and abstracts returned by the search strategy were examined independently by two researchers and screened for possible inclusion. Disagreements were resolved by discussion or involvement of a third reviewer in cases where consensus could not be achieved. Full texts of potentially relevant studies were ordered. Full publications were assessed independently by two reviewers for inclusion or exclusion against pre-specified criteria, with disagreements resolved by discussion or input from a third reviewer when consensus could not be achieved. The quality of the clinical effectiveness data was assessed by two independent reviewers and checked for agreement. The study quality was assessed according to recommendations by the NHS Centre for Reviews and Dissemination and Cochrane Handbook for Systematic Reviews of Interventions and recorded using the Cochrane Risk of Bias Tool.

Evidence on the following outcome measures was considered: overall survival (OS); progression-free survival (PFS); overall response rate (ORR); health-related quality of life (HRQoL) and adverse effects of treatment. Treatment effects were analysed as hazard ratios (HRs) for time to event outcomes (i.e., OS and PFS) and as odds ratios (ORs) for dichotomous data (i.e., ORR and adverse events).

Extracted data and quality assessment for each study were presented in structured tables and as a narrative summary. Where sufficient comparable data were available for each outcome measure, network meta-analyses (NMAs) were performed using a Bayesian Markov Chain Monte Carlo (MCMC) simulation.

Following consultation with clinical experts, the TAG determined that it was appropriate to analyse patients with platinum-sensitive disease (PFI $\geq$6 months) and patients with platinum resistant/refractory disease (PFI <6 months or progression while on treatment) separately. Consequently, the TAG carried out a series of NMAs for platinum sensitive patients, and platinum resistant/refractory patients. Patients with platinum allergic disease were considered by the TAG to have the same probability of response to therapy as patients without and allergy for the same non-platinum-containing treatments, and therefore treatments for platinum allergic patients were not analysed separately.

1.3.2 Cost-effectiveness systematic review

For the cost-effectiveness review, the following databases were searched: MEDLINE (Ovid); EMBASE (Ovid); HTA database (HTA); NHS Economic Evaluations Database (NHS EED). In

addition, experts in the field were contacted with a request for details of relevant published and unpublished studies of which they may have knowledge, the NICE website was searched for any recently published Technology Appraisals in ovarian cancer that had not already been identified via the database searches, and reference lists of key identified studies were reviewed for any potentially relevant studies.

The search strategy for MEDLINE and EMBASE combined terms capturing the interventions and comparators of interest; ovarian cancer; and terms to capture all types of economic evaluations (cost-effectiveness, cost-benefit, cost-minimisation, cost-consequence). As this MTA is in part an update of TA91 in which a systematic review was carried out (search date of April 2004) to evaluate the cost-effectiveness of topotecan, PLDH, and paclitaxel; searches for these interventions were carried out with a date limit of 2004. Databases were searched from inception for gemcitabine and trabectedin. The search strategy for HTA and NHS EED combined terms for the target condition (ovarian cancer) with no further limits.

The searches were carried out in December 2012, and updated in May 2013. No restrictions on language or setting were applied to any of the searches. The titles and abstracts of papers identified through the searches were independently assessed for inclusion by two health economists. Results were described narratively, and quality assessed against the NICE reference case, and Philips checklist.

1.3.3 Review of manufacturer submissions

Two manufacturers (Eli Lilly and Company Limited [gemcitabine]; PharmaMar [trabectedin]) submitted evidence for consideration in this MTA. Of these, one manufacturer (PharmaMar) submitted cost-effectiveness evidence.

Clinical data presented that met the inclusion criteria, and had not been identified in another published source, were extracted and quality assessed in accordance with the procedures outlined in this protocol. The cost-effectiveness analyses reported in PharmaMar's submission to NICE were summarised and critically appraised using the NICE reference case and the Philips checklist.

1.3.4 TAG *de novo* cost-effectiveness analysis

The TAG developed a *de novo* economic model to address the decision problem outlined for this MTA from the perspective of the NHS and personal social services. Specifically, the TAG considered cost-effectiveness of topotecan, PLDH, paclitaxel, trabectedin and gemcitabine for the treatment of advanced, recurrent ovarian cancer.

The economic model was based upon the model structure utilised in TA91 in which three health states were modelled; stable disease, progressed disease and death. Within the TA91 model, the proportion

of patients within each health state were calculated from estimates of mean time to progression and mean time to death, available from the literature. The ERG for a subsequent technology appraisal in which the same model structure was applied, TA222, commented that this simplification made the incorporation of discounting difficult; this was because time was not explicitly modelled. Therefore, within the TAG analysis, the model was modified to incorporate PFS and OS over time in order to address this concern. The time horizon used for the analysis was 15 years; the TAG considers that this represents a life-time time horizon for the majority of patients within the model.

Effectiveness data required for the model were PFS and OS. These data were obtained from the clinical systematic review, and combined using network meta-analytical techniques.

The following costs were included in the model: treatment costs, administration costs, cost of adverse events, and health state costs.

Utility data associated with stable disease and progressed disease were obtained from TA222, following a systematic review of the HRQoL literature.

The results of the analyses were presented for people with platinum sensitive disease and people with platinum resistant/refractory disease separately, as probabilistic and deterministic estimates. The sensitivity of model parameters and assumptions were tested in probabilistic sensitivity analysis (PSA), one-way sensitivity analysis (OWSA), and through a series of scenario analyses.

1.4 Results

1.4.1 Clinical effectiveness systematic review

Sixteen randomised controlled trials (RCTs) reported in 28 publications were identified from the clinical effectiveness systematic review, including one RCT reported in TA91, the results of which have not been published in full elsewhere. Manufacturer submissions were reviewed for additional evidence; however, the relevant data within the manufacturer submissions was published in studies identified from the clinical review. The 16 RCTs identified evaluated 14 different comparisons. There were insufficient data for most comparisons to carry out a standard pair-wise meta-analysis. However, the TAG determined that the data identified were sufficiently homogenous to investigate comparative effectiveness of interventions via a network meta-analysis (NMA).

The trials identified in the clinical systematic review were unable to populate a single network for any of the outcomes assessed. A wider selection of treatments were assessed, as the systematic review was conducted in such a way as to identify all trials with at least one intervention of interest present, but unfortunately this did not uncover trials that could link the disconnected networks together. In

addition, the TAG's clinical advisors did not consider any of the suggested assumptions to link the disconnected networks together to have face validity.

Overall survival

For the subgroup of patients with platinum sensitive (relapse ≥ 6 months after last platinum-based chemotherapy) ovarian cancer, ten RCTs evaluating eight head-to-head comparisons of interventions and comparators were identified in which results were presented for OS. These data were combined via an NMA to inform the decision problem. Based on the trials identified, it was not possible to construct a complete network. Two discrete networks were generated, one evaluating platinum-based therapies and the second comparing non-platinum-based regimens.

In the network evaluating platinum-based chemotherapies (platinum sensitive network 1), PLDH plus platinum and paclitaxel plus platinum were found to significantly improve OS compared with platinum monotherapy, the NMA found no significant difference in OS between the remaining regimens in patients with platinum-sensitive disease.

Table 1. Estimates of relative overall survival from the Technology Assessment Group network meta-analysis for platinum sensitive network 1

Comparator	Paclitaxel plus platinum	Gemcitabine plus carboplatin	PLDH plus platinum	Platinum monotherapy
Paclitaxel plus platinum	–	1.247 (0.921 to 1.652)	1.023 (0.889 to1.172)	1.290 (1.096 to1.509)
Gemcitabine plus carboplatin	–	–	0.839 (0.602 to1.135)	1.051 (0.815 to1.335)
PLDH plus platinum	–	–	–	1.267 (1.030 to 1.545)

Comparator is listed in the left-hand side column. Results presented are HR and accompanying CrI. HR <1 favours the intervention (listed in the top table row) and HR >1 favours the comparator.

Abbreviations used in table: CrI, credible interval; HR, hazard ratio.

Analysis of non-platinum-based regimens (platinum sensitive network 2) indicates that PLDH monotherapy and trabectedin plus PLDH are both significantly more effective at prolonging OS than topotecan monotherapy. No other significant differences were identified.

Table 2. Estimates of relative overall survival from the Technology Assessment Group network meta-analysis for platinum sensitive network 2

Comparator	PLDH monotherapy	Trabectedin plus PLDH	Paclitaxel monotherapy	Topotecan monotherapy
PLDH monotherapy	–	0.835 (0.667 to 1.032)	1.219 (0.850 to 1.690)	1.367 (1.035 to 1.770)
Trabectedin plus PLDH	–	–	1.479 (0.962 to 2.176)	1.658 (1.157 to 2.307)
Paclitaxel monotherapy	–	–	–	1.145 (0.808 to 1.576)
Topotecan monotherapy	–	–	–	–

Comparator is listed in the left-hand side column. Results presented are HR and accompanying CrI. HR <1 favours the intervention (listed in the top table row) and HR >1 favours the comparator.

Abbreviations used in table: CrI, credible interval; HR, hazard ratio; PLDH, pegylated liposomal doxorubicin hydrochloride.

For the subgroup of patients with platinum resistant/refractory (relapse < 6 months after last platinum-based chemotherapy) ovarian cancer, five RCTs evaluating five head-to-head comparisons of interventions and comparators were identified in which results were presented for OS. Four of the five identified trials were included in the network. The results of the NMA are in alignment with the results of the individual trials, with no statistically significant differences in OS among the treatments evaluated.

Table 3. Estimates of relative overall survival from the Technology Assessment Group network meta-analysis for the platinum resistant/refractory network

	PLDH monotherapy	Paclitaxel monotherapy	Topotecan monotherapy	Topotecan monotherapy (Weekly)
PLDH monotherapy	–	1.053 (0.783 to 1.382)	0.973 (0.764 to 1.221)	1.026 (0.669 to 1.505)
Paclitaxel monotherapy	–	–	0.939 (0.694 to 1.244)	0.989 (0.619 to 1.499)
Topotecan monotherapy	–	–	–	1.054 (0.744 to 1.447)
Topotecan monotherapy (Weekly)	–	–	–	–

Comparator is listed in the left-hand side column. Results presented are HR and accompanying CrI. HR <1 favours the intervention (listed in the top table row) and HR >1 favours the comparator.

Abbreviations used in table: CrI, credible interval; HR, hazard ratio.

Progression free survival

Nine RCTs evaluating seven different head-to-head comparisons of interventions and comparators of interest reported on progression free survival (PFS) or time to progression (TTP). Results are presented for PFS or TTP, as reported in the trial. PFS and TTP are often used interchangeably and, for the purposes of the results presented here, TTP has been assumed approximate to PFS.

For the subgroup of patients with platinum sensitive (relapse ≥ 6 months after last platinum-based chemotherapy) ovarian cancer, it was not possible to construct a complete network. Again, two discrete networks were generated, one evaluating platinum-based therapies and the second comparing non-platinum-based regimens. It should be stressed that results from the two discrete networks are not directly comparable.

In the network evaluating platinum-based chemotherapies, all combination chemotherapy regimens significantly improved PFS compared with platinum monotherapy. In addition, PLDH plus platinum was found to be significantly more effective at prolonging PFS than paclitaxel plus platinum. No other statistically significant differences were identified between combination regimens.

Table 4. Estimates of relative progression free survival from the Technology Assessment Group network meta-analysis for platinum sensitive network 1

Comparator	Paclitaxel plus platinum	Gemcitabine plus carboplatin	PLDH plus platinum	Platinum monotherapy
Paclitaxel plus platinum	–	0.985 (0.748 to 1.273)	0.817 (0.717 to 0.927)	1.361 (1.182 to 1.559)
Gemcitabine plus carboplatin	–	–	0.845 (0.624 to 1.116)	1.400 (1.106 to 1.749)
PLDH plus platinum	–	–	–	1.672 (1.389 to 1.997)
Platinum monotherapy	–	–	–	–

Comparator is listed in the left-hand side column. Results presented are HR and accompanying CrI. HR <1 favours the intervention (listed in the top table row) and HR >1 favours the comparator.
Abbreviations used in table: CrI, credible interval; HR, hazard ratio.

Analysis of non-platinum-based regimens indicates that trabectedin plus PLDH statistically significantly improves PFS compared with PLDH, paclitaxel and topotecan when given as monotherapies. No statistically significant differences were identified among the monotherapies evaluated (PLDH, topotecan, and paclitaxel).

Table 5. Estimates of relative progression free survival from the Technology Assessment Group network meta-analysis for platinum sensitive network 2

Comparator	PLDH monotherapy	Trabectedin plus PLDH	Paclitaxel monotherapy	Topotecan monotherapy
PLDH monotherapy	–	0.736 (0.560 to 0.949)	1.615 (0.939 to 2.586)	1.298 (0.979 to 1.688)
Trabectedin plus PLDH	–	–	2.236 (1.209 to 3.795)	1.797 (1.207 to 2.578)
Paclitaxel monotherapy	–	–	–	0.842 (0.539 to 1.262)

Comparator is listed in the left-hand side column. Results presented are HR and accompanying CrI. HR <1 favours the intervention (listed in the top table row) and HR >1 favours the comparator.
Abbreviations used in table: CrI, credible interval; HR, hazard ratio; PLDH, pegylated liposomal doxorubicin hydrochloride.

For the subgroup of patients with platinum resistant/refractory (relapse < 6 months after last platinum-based chemotherapy) ovarian cancer, four RCTs reporting results for four different head-to-head comparisons involving PRR patients were identified. Two RCTs enrolled only patients with PRR, with the remaining two RCTs reporting results from a subgroup of patients within the trial. None of the trials identified a significant difference in PFS/TTP between the two treatment groups evaluated.

Three of the four identified trials were included in the network. The results of the NMA are in alignment with the results of the individual trials, with no statistically significant differences in PFS among PLDH, paclitaxel and topotecan monotherapy.

Table 6. Estimates of relative progression free survival from the Technology Assessment Group network meta-analysis for the platinum resistant/refractory network

Comparator	PLDH monotherapy	Paclitaxel monotherapy	Topotecan monotherapy	Topotecan monotherapy (weekly)
PLDH monotherapy	–	1.360 (0.817 to 2.123)	0.998 (0.767 to 1.277)	1.302 (0.859 to 1.894)
Paclitaxel monotherapy	–	–	0.765 (0.502 to 1.122)	0.999 (0.585 to 1.599)
Topotecan monotherapy	–	–	–	1.305 (0.951 to 1.744)

Comparator is listed in the left-hand side column. Results presented are HR and accompanying CrI. HR <1 favours the intervention (listed in the top table row) and HR >1 favours the comparator.
Abbreviations used in table: CrI, credible interval; HR, hazard ratio; PLDH, pegylated liposomal doxorubicin hydrochloride.

Overall response rate (ORR)

ORR has been defined as the number of patients achieving complete response (CR) or partial response (PR) as their best response. For the subgroup of patients with platinum-sensitive (relapse ≥ 6 months after last platinum-based chemotherapy) ovarian cancer, twelve RCTs evaluating eleven different head-to-head comparisons of interventions and comparators of interest reported on ORR. Of the eleven comparisons identified, only two trials reported a statistical significant difference in ORR. Based on the trials identified, it was not possible to construct a complete network. Again, two discrete networks were generated, one evaluating platinum-based therapies and the second comparing non-platinum-based regimens. It should be stressed that results from the two discrete networks are not directly comparable.

In the network evaluating platinum-based chemotherapies, paclitaxel plus platinum and gemcitabine plus carboplatin were found to have a significantly higher ORR than platinum monotherapy. There was no significant difference between PLDH plus platinum vs any of the chemotherapeutic treatments assessed.

Table 7. Estimates of relative overall response rate from the Technology Assessment Group network meta-analysis for platinum-based therapies

Comparator	Paclitaxel plus platinum	PLDH plus platinum	Platinum monotherapy	Gemcitabine plus carboplatin
Paclitaxel plus platinum	–	0.994 (0.574 to 1.609)	0.666 (0.474 to 0.908)	1.370 (0.765 to 2.261)
PLDH plus platinum	–	–	0.713 (0.386 to 1.208)	1.467 (0.672 to 2.793)
Platinum monotherapy	–	–	–	2.058 (1.305 to 3.108)

Comparator is listed in the left-hand side column. Results presented are OR and accompanying CrI. OR >1 favours the intervention (listed in the top table row) and OR <1 favours the comparator.
Abbreviations used in table: CrI, credible interval; HR, hazard ratio; PLDH, pegylated liposomal doxorubicin hydrochloride.

Analysis of non-platinum-based regimens indicates that trabectedin plus PLDH significantly improves ORR compared with PLDH, and oral topotecan. Compared with oral topotecan, intravenous topotecan was found to be associated with a significant increase in the proportion of patients achieving CR or PR. No other statistically significant differences were identified.

Table 8. Estimates of relative overall response rate from the Technology Assessment Group network meta-analysis for non-platinum based therapies

Comparator	PLDH	Trabectedin plus PLDH	Topotecan (IV)	Paclitaxel (every 3 weeks)	Topotecan (oral)	Paclitaxel (weekly)
PLDH	–	1.932 (1.231 to 2.905)	1.072 (0.565 to 1.858)	0.734 (0.207 to 1.871)	0.483 (0.145 to 1.169)	1.024 (0.204 to 3.097)
Trabectedin plus PLDH	–	–	0.582 (0.260 to 1.122)	0.399 (0.102 to 1.077)	0.262 (0.071 to 0.674)	0.556 (0.102 to 1.773)
Topotecan (IV)	–	–	–	0.683 (0.243 to 1.514)	0.451 (0.170 to 0.951)	0.953 (0.230 to 2.642)
Paclitaxel (every 3 weeks)	–	–	–	–	0.822 (0.191 to 2.337)	1.393 (0.578 to 2.852)
Topotecan (oral)	–	–	–	–	–	2.554 (0.431 to 8.493)

Comparator is listed in the left-hand side column. Results presented are OR and accompanying CrI. OR >1 favours the intervention (listed in the top table row) and OR <1 favours the comparator.

Abbreviations used in table: CrI, credible interval; IV, intravenous; OR, odds ratio; PLDH, pegylated liposomal doxorubicin hydrochloride.

For the subgroup of patients with platinum resistant/refractory (relapse < 6 months after last platinum-based chemotherapy) ovarian cancer, eight RCTs reporting results for eight different head-to-head comparisons involving PRR patients were identified. Two RCTs enrolled only patients with PRR, with the remaining six RCTs reporting results from a subgroup of patients within the trial. None of the trials identified a significant difference in ORR between the two treatment groups evaluated.

An NMA was carried out using five of the identified RCTs. PLDH was found to significantly increase ORR compared with paclitaxel (175 mg/m^2) every 21 days and with an alternative regimen in which paclitaxel was given weekly at a dose of 67 mg/m^2. PLDH monotherapy was also significantly more effective than an unconventional regimen of topotecan in which topotecan was administered weekly at a dose of 4 mg/m^2. No chemotherapeutic regimen was found to have a significantly higher ORR than PLDH monotherapy. No other comparison of chemotherapies was found to have a statistically significant difference.

Table 9. Estimates of relative overall response rate from the Technology Assessment Group network meta-analysis for resistant/refractory patients

Comparator	PLDH	Topotecan (IV, conventional)	Paclitaxel (every 3 weeks)	Topotecan (oral)	Paclitaxel (weekly)	Topotecan (un-conventional IV regimen)
PLDH	–	0.529 (0.184 to 1.166)	0.290 (0.040 to 0.982)	0.622 (0.098 to 2.116)	0.224 (0.022 to 0.884)	0.253 (0.051 to 0.761)
Topotecan (IV, conventional)	–	–	0.548 (0.111 to 1.553)	1.176 (0.283 to 3.283)	0.423 (0.059 to 1.470)	0.478 (0.154 to 1.086)
Paclitaxel (every 3 weeks)	–	–	–	3.387 (0.379 to 13.810)	0.771 (0.271 to 1.736)	1.383 (0.191 to 5.216)
Topotecan (oral)	–	–	–	–	0.530 (0.041 to 2.321)	0.601 (0.090 to 2.090)
Paclitaxel (weekly)	–	–	–	–	–	2.251 (0.215 to 9.439)
Topotecan (unconventional IV regimen)	–	–	–	–	–	–

Comparator is listed in the left-hand side column. Results presented are OR and accompanying CrI. OR >1 favours the intervention (listed in the top table row) and OR <1 favours the comparator.

Abbreviations used in table: CrI, credible interval; IV, intravenous; OR, odds ratio; PLDH, pegylated liposomal doxorubicin hydrochloride.

Health-related quality of life

Of the 16 RCTs identified, ten reported data on QoL. In addition, a systematic review of HRQoL reporting in ovarian cancer trials (identified in TAG's systematic review of HRQoL literature) acknowledged considerable disparity in the level of reporting of QoL results, the questionnaires used to evaluate QoL, and the time points for evaluation. Given the often palliative nature of second and subsequent line chemotherapeutic treatments for ovarian cancer, there has been a move to place greater emphasis on assessment of QoL in this condition.

The most commonly used scale in the identified trials is the EORTC QLQ-C30 questionnaire, which was developed to assess the QoL of cancer patients and can be supplemented with disease-specific modules for individual cancers, including ovarian cancer. Key findings from the identified trials are presented below.

For many comparisons, scores on QoL scales were comparable between treatments. Differences in QoL include:

- for PLDH plus platinum vs paclitaxel plus platinum, at 3 months, PLDH plus platinum was associated with a significant improvement in global health compared with paclitaxel plus platinum. However, this benefit was not maintained at 6 months;
- for paclitaxel plus platinum vs platinum-based therapy patients receiving platinum monotherapy scored significantly worse on the nausea and vomiting symptom scale than did the paclitaxel plus platinum-based chemotherapy group. However, this difference seemed to be transient and was observed for only the first 15 weeks after randomisation;
- for trabectedin plus PLDH vs PLDH in the subgroup of patients with partially platinum sensitive ovarian cancer, it is indicated that there exist a difference in global health status score among responding patients beyond cycle 5, with patients in the trabectedin plus PLDH group having a higher score than those receiving PLDH alone (higher score is favourable);
- for PLDH vs topotecan was associated with a significantly more favourable rating on the pain sub-scale of the EORTC QLQ-C30;
- for paclitaxel plus platinum vs paclitaxel patients receiving weekly paclitaxel plus platinum experienced improvements in constipation, abdominal/gastrointestinal symptoms, appetite loss, pain, and emotional functioning. Patients treated with weekly paclitaxel alone experienced improvements in attitude to disease and insomnia, but worsening of dyspnoea and peripheral neuropathy.
- for paclitaxel vs oxaliplatin, mean QoL score on the EORTC QLQ-C30 increased by more than 10 points between baseline and cycle 4 for patients in the paclitaxel group, irrespective of study withdrawal. By contrast, in the oxaliplatin group, the mean QoL score decreased through cycle 2, but by less than 10 points, after which most patients' mean scores returned to baseline levels.

Adverse events

Data for adverse effects for individual trials are reported in the main text. Within each trial, the most frequently reported adverse effects were as expected for the individual treatments based on the Summary of Product Characteristics (SmPC). Commonly occurring adverse effects were alopecia, nausea and vomiting, haematological toxicities (neutropenia, anaemia, thrombocytopenia, and leukopenia).

Based on expert clinical advice the TAG restricted its comparison of adverse events to those considered most problematic for patients or most likely to consume substantial health care resource. The potential for an NMA was, therefore, investigated for the following severe (grade 3-4) adverse events: allergic reaction, alopecia, anaemia, fatigue, febrile neutropenia, nausea and vomiting, and neuropathy. In many cases an NMA was not possible due to the lack of available data in the trials assessed. In these instances, the individual trial results are reported with the ORs and 95% confidence intervals calculated. The majority of results 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 plus platinum, PLDH plus 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 severe adverse events assessed.

1.4.2 Cost effectiveness systematic review

From the cost-effectiveness systematic review, the TAG identified 21 economic evaluations related to recurrent ovarian cancer. Of the 21 studies, 13 were cost-utility analyses of which eight related to either TA91 or TA222. All eight economic evaluations used the model structure constructed for TA91; a three state model (stable disease, progressed disease, and death) in which movements between health states were based upon mean time to progression (estimated using mean PFS) and mean time to death from progression (estimated using mean OS – mean PFS). Of the remaining five studies, one was an STA considering the cost-effectiveness of bevacizumab in recurrent ovarian cancer; the model developed by the manufacturer for this STA was a semi-Markov model based upon the model structure outlined in TA91. The remaining published cost-utility models also considered similar health states from the perspective of the US (Lesnock *et al*., Havrilesky *et al.*) and Korea (Lee *et al.*).

The majority of the published UK evidence, therefore, evaluated the cost-effectiveness of treatments in recurrent ovarian cancer based upon the model developed for TA91. However, based upon the results of the TAG systematic search of the cost-effectiveness literature in recurrent ovarian cancer, there is no published simultaneous comparison of all the interventions of interest for this MTA.

1.4.3 Manufacturer submissions

Two manufacturers (Eli Lilly and Company Limited [gemcitabine]; PharmaMar [trabectedin]) submitted clinical evidence for consideration for this MTA. Clinical data submitted that met the inclusion criteria were identified as part of the clinical review.

One manufacturer, PharmaMar, submitted cost-effectiveness evidence for consideration within this MTA for trabectedin. Trabectedin, in combination with PLDH, is indicated for the treatment of patients with relapsed platinum-sensitive (PFI $\geq$ 6 months) ovarian cancer. The patient population for whom the manufacturer is requesting consideration within this MTA comprises a subset of this indication, specifically: people who are not suitable for, or not best managed with, platinum-based chemotherapy because of an allergy, or intolerance due to residual toxicities; and people with partially platinum sensitive disease (PFI of 6 to 12 months).

PharmaMar developed an economic analysis based upon the model developed within TA91; i.e., based on mean estimates of PFS and OS. With this model, the manufacturer evaluated the cost-effectiveness of trabectedin (1.1 mg/m^2) in combination with PLDH (30 mg/m^2) administered every three weeks, vs PLDH monotherapy (50 mg/m^2) administered every four weeks, for the treatment of patients with relapsed platinum-sensitive ovarian cancer. The manufacturer did not compare the cost-

effectiveness of trabectedin in combination with PLDH versus any other comparator as listed within the NICE scope.

Effectiveness data for mean OS and mean PFS required for the model were obtained from the OVA-301 clinical trial; an RCT providing head-to-head data for trabectedin in combination with PLDH vs PLDH monotherapy in patients with relapsed ovarian cancer. The manufacturer fitted a variety of parametric curves (exponential, Weibull, Gompertz, log-logistic and log-normal) to OS and PFS Kaplan-Meier data from the clinical trial for patients with platinum sensitive disease. These curves were fitted separately by treatment arm and explanatory variables were considered to control for the baseline characteristics. In particular, the manufacturer controlled for PFI as a continuous variable after retrospectively identifying an imbalance in PFI at baseline between the treatment arms.

The manufacturer included the costs of drug, administration, medical management and adverse events within the model. Utility data for the stable and progressed disease health states were obtained from analysis of EQ-5D data from OVA-301, as reported in TA222.

Subsequent to initial submission, the manufacturer submitted a proposed patient access scheme (PAS) affecting the total chemotherapy costs associated with trabectedin in combination with PLDH. For the PAS, the manufacturer proposes that the NHS pays for the first 5 cycles of chemotherapy, after which acquisition costs would be met by the manufacturer. Without the PAS, the manufacturer estimated an incremental cost per additional QALY for trabectedin in combination with PLDH vs PLDH monotherapy to be £39,306 in the deterministic base case and £39,447 in the probabilistic base case. With the PAS, the manufacturer estimated an incremental cost per additional QALY for trabectedin in combination with PLDH vs PLDH monotherapy to be £27,573 in the deterministic base case and £27,761 in the probabilistic base case.

The manufacturer carried out a number of sensitivity analyses both deterministic (one-way sensitivity analysis, scenario analyses) and probabilistic for results with and without the PAS. The TAG considers that the sensitivity analyses presented by the manufacturer identified estimates of OS as the key driver of model results and the main accumulator of QALYs. In particular, through changes in the functional form, and through controlling for PFI in the extrapolated estimates of OS. According to the manufacturer's analysis, at a willingness-to-pay (WTP) threshold of £20,000, the probability that trabectedin in combination with PLDH is cost-effective vs PLDH monotherapy is 11% and 10% with and without the PAS, respectively. At a WTP threshold of £30,000, the probability of cost-effectiveness increases to 53% with the PAS and 20% without the PAS.

The main critique of the cost-effectiveness analysis submitted by PharmaMar by the TAG relates to the method of discounting used by the manufacturer within the TA91 model structure. The TAG

considers that, as a result of the discounting methodology used, the manufacturer may have overestimated the QALY gain. This is because, application of discounting to average estimates is unlikely to be as accurate as discounting based on monthly estimates, as the granularity of patient proportions, by health state, over time, is not captured.

1.4.4 Technology Assessment Group *de novo* cost-effectiveness analysis

As described above, following review of the available PFS and OS clinical data, a complete network incorporating all interventions and comparators of interest was not possible for patients with platinum sensitive disease; instead, two separate networks were constructed. For patients with platinum resistant/refractory disease, the TAG analysed a subset of the interventions and comparators listed within the scope, because data were not available for all treatments. Patients with platinum allergic disease were considered by the TAG 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 platinum allergic patients were not analysed separately. A summary of the results by network are presented in Table 10.

Table 10. Summary of key results from the Technology Assessment Group analyses, by network

Platinum sensitive network 1			
Treatment	**Incremental ICER probabilistic (deterministic)**	**Prob. cost-effective at threshold of:[a]**	
		£20,000	**£30,000**
Platinum	–	–	–
Gemcitabine plus carboplatin	Extendedly dominated		
Paclitaxel plus platinum	£24,539 (£24,361)	13%	78%
PLDH plus platinum	Strictly dominated		
Platinum sensitive network 2 (including platinum allergic patients)			
Treatment	**Incremental ICER probabilistic (deterministic)**	**Prob. cost-effective at threshold of:[a]**	
		£20,000	**£30,000**
Paclitaxel	–	–	–
PLDH	£25,931 (£23,733)	30%	59%
Topotecan	Strictly dominated		
Trabectedin plus PLDH	£81,353 (£85,212)	0%	0%
Platinum resistant/refractory (including platinum allergic patients)			
Treatment	**Incremental ICER probabilistic (deterministic)**	**Prob. cost-effective at threshold of:[a]**	
		£20,000	**£30,000**
PLDH	–	–	–
Paclitaxel	Strictly dominated		
Topotecan	£324,188 (£449,553)	0%	0%

[a] estimated probability that the comparison will be cost-effective at a willingness to pay threshold of £20,000 or £30,000 per additional quality-adjusted life-year

Abbreviations used in table: ICER, incremental cost-effectiveness ratio; PLDH, pegylated liposomal doxorubicin hydrochloride; prob, probability.

Platinum sensitive network 1 (platinum, paclitaxel plus platinum, PLDH plus platinum, gemcitabine plus platinum)

Of the treatments considered in platinum sensitive network 1 (platinum, gemcitabine plus carboplatin, paclitaxel plus platinum and PLDH plus platinum), base case probabilistic and deterministic analysis estimated that treatment with gemcitabine plus carboplatin was extendedly dominated by treatment with paclitaxel plus platinum. That is, for the additional costs associated with paclitaxel plus platinum, the additional benefit was such that paclitaxel plus platinum may be considered better value for money than treatment with gemcitabine plus carboplatin.

Probabilistic analysis of the addition of paclitaxel or PLDH to platinum therapy resulted in similar estimates of mean total costs and QALYs. However, on average treatment with paclitaxel plus platinum appeared to offer greater benefit than treatment with PLDH plus platinum. In addition, on average, treatment with PLDH plus platinum incurred higher costs than treatment with paclitaxel plus platinum; resulting in the dominance of PLDH plus platinum by paclitaxel plus platinum in probabilistic and deterministic analysis. The ICER associated with paclitaxel plus platinum vs platinum was estimated from probabilistic analysis as £24,539.

However, the TAG considers it important to note, that expert clinical advice highlighted that accumulated neurotoxicity as a result of prior taxane therapy means that not all patients may tolerate further treatment with paclitaxel. With this in mind, the TAG consider it important to note that the base case probabilistic ICER for the addition of PLDH to platinum therapy was £30,188, and PLDH plus platinum was associated with a 48% likelihood of being cost-effective vs platinum therapy at a WTP threshold of £30,000.

Platinum sensitive network 2 (paclitaxel, PLDH, trabectedin plus PLDH, topotecan)

For PS network 2, the TAG considers that the key comparisons within this network were PLDH vs paclitaxel, and trabectedin plus PLDH vs PLDH; topotecan was strictly dominated by paclitaxel. PLDH vs paclitaxel was estimated by the TAG to have a 59% probability of being considered cost-effective at a WTP threshold of £30,000 per additional QALY gained (probabilistic ICER: £25,931) with 15% of simulations resulted in PLDH being less effective and more costly (dominated). The results of this analysis were robust to changes in the majority of parameters with the notable exception of changes in the HR associated with OS for this comparison; use of the low value in OWSA resulted in PLDH becoming dominated by paclitaxel because the survival benefit associated with PLDH switched from increased survival compared with paclitaxel, to decreased survival.

Trabectedin plus PLDH vs PLDH was estimated by the TAG to have a probability of being considered cost-effective at a WTP threshold of £30,000 per additional QALY gained in 0% of simulations (probabilistic ICER: £81,353). The deterministic ICER was robust to the majority of

OWSA with the notable exception of changes in the HR associated with OS for this comparison; use of the low value resulted in a reduction of the ICER of over £40,000 because the relative survival benefit associated with trabectedin plus PLDH vs PLDH increased. Conversely, use of the high value of the OS HR resulted in trabectedin plus PLDH being dominated by PLDH; here, the survival benefit associated with trabectedin plus PLDH switched from increased survival compared with PLDH, to decreased survival. Additionally, in a scenario where the TAG considered only the head-to-head comparison of trabectedin plus PLDH versus PLDH monotherapy using survival data directly from the PharmaMar economic analysis (i.e. survival data with adjustments for baseline characteristics in each arm), the deterministic ICER reduced from £85,212 to £35,646. However, as efficacy data used in the TAG's base case model was unadjusted (to provide a consistent dataset), the TAG notes that the head-to-head ICER generated from using adjusted efficacy data is not comparable with ICERs estimated for other treatments in the TAG's base case analyses.

Platinum resistant/refractory (paclitaxel, PLDH, topotecan)

Following review of the probabilistic base case results, the TAG considers that the key comparison within this network was topotecan vs PLDH; paclitaxel was strictly dominated by PLDH.

The TAG estimated the probability of topotecan vs PLDH being considered cost-effective at a threshold of £20,000 or £30,000 per additional QALY to be 0% (probabilistic ICER: £324,188). The deterministic ICER was robust to the majority of OWSA with the notable exception of changes in the HR associated with OS for this comparison; use of the low value of the HR for OS for topotecan vs PLDH (greater benefit associated with topotecan vs PLDH) resulted in an ICER of £53,288, a reduction of nearly £400,000. In scenario analyses the ICER associated with topotecan vs PLDH did not fall below £370,000.

Furthermore, although on average paclitaxel was dominated by PLDH, the costs and QALYs associated with paclitaxel are similar to those associated with PLDH, with paclitaxel being dominated by PLDH in 39% of probabilistic simulations. As highlighted for patients with platinum sensitive disease, increased risk of neurotoxicity following prior taxane therapy means that not all patients may tolerate further treatment with paclitaxel.

1.5 Discussion

1.5.1 Strengths of the analysis

The systematic reviews and economic analyses were carried out by an independent research team using the latest evidence to a pre-specified protocol.

The evidence used to inform the decision problem that is the focus of this MTA has been identified following the general principles published by the Centre for Reviews and Dissemination (CRD).

Similarly, the methods used for the NMA followed the guidance described in the NICE Decisions Support Unit's (DSU's) Technical Support Documents (TSDs) for Evidence Synthesis.

Economic analyses have been carried out in accordance with NICE guide to methods of technology appraisal, ISPOR guidance and where possible, recommendations made by NICE DSU have been adhered to.

The economic model used to provide a framework for analysis has been widely used in the indication that is the focus of this MTA. In addition, amendments to the structure based on previous critiques have been made.

Expert clinical input has been sought and received throughout the project, in particular with respect to assumptions made in clinical and economic analyses and the face validity of final results and conclusions.

1.5.2 Weakness of the analysis and associated implications

The key weaknesses of the clinical and economic analyses are related to the limitations of the data available from the literature: the absence of clinical data; heterogeneity within and between included studies; use of unadjusted measures of treatment effect; and the assumption of proportional hazards.

Absence of data

The clinical and economic analyses have been carried out separately for patients with platinum sensitive (PFI $\geq$ 6 months) and platinum resistant/refractory (PFI < 6 months) disease. In addition, as a result of the limited clinical effectiveness data available, two separate networks, of interventions and comparators outlined in the scope of this MTA, have been constructed in patients with platinum sensitive disease. Consequently, clinical and cost-effectiveness is assessed for three networks of treatment, of which, two consider a population of patients with platinum sensitive disease and one considers a population of patients with platinum resistant/refractory disease.

For patients with platinum resistant/refractory disease, it was not possible to identify data for the full range of interventions and comparators outlined within the NICE scope.

For patients with platinum sensitive disease, the TAG was unable to identify a single platinum sensitive network in which clinical data were available for all the treatments and comparators of interest for this MTA. This absence of linking data means that the ICERs obtained for platinum sensitive network 1 and platinum sensitive network 2 cannot be compared. However, following consultation with clinical experts it is considered that, although a key limitation of the analysis, the disaggregation of relative efficacy for patients with platinum sensitive disease into the two networks described above is not entirely unreasonable.

According to clinical expert opinion, in practice, platinum sensitive patients that can be treated with platinum, generally would be treated with platinum in the first instance. For these patients, platinum sensitive network 1 provides the network of therapies most likely to be considered in practice. The treatments in platinum sensitive network 2, (PLDH, trabectedin plus PLDH, paclitaxel and topotecan) are therefore only likely to be considered in platinum sensitive patients who are unsuitable for platinum therapy. The TAG considers it important to note that the mean overall survival from the TAG analysis in platinum sensitive network 1 (i.e. platinum containing therapies) was estimated to range between 33.9 (platinum monotherapy) and 38.4 (paclitaxel plus platinum) months. In platinum sensitive network 2 (i.e. non-platinum containing therapies), the mean overall survival estimates from the TAG analysis ranged between 24.6 (topotecan) and 32.2 (trabectedin plus PLDH) months. These estimates cannot be directly compared without breaking randomisation; however, the TAG notes that these estimates may support the use of platinum-based chemotherapy rather than non-platinum-based chemotherapy in patients who can tolerate platinum.

Heterogeneity in included trials

It was not possible to assess the statistical homogeneity of the trials included within the TAG as a result of the low number of trials identified and the predominantly linear nature of the networks constructed; however, the homogeneity or otherwise, of the trials included in the TAG's NMAs was assessed from a clinical perspective.

Baseline characteristics were not presented for either the network of treatments identified for non-platinum based therapies for platinum sensitive patients, nor for the network of treatments identified for platinum resistant/refractory patients; consequently, assessment of clinical homogeneity was limited to the platinum sensitive network in which platinum-based therapies were identified. For this network, with the exception of baseline ECOG score in the trial carried out by Gonzalez-Martin et *al*., baseline characteristics were generally well balanced within trials. Gonzalez-Martin *et al*. compared paclitaxel plus platinum with platinum monotherapy in platinum sensitive patients. The TAG considers that it is likely that, as a result of the imbalance in ECOG status at baseline, the treatment effect associated with platinum has been understated, and therefore the relative treatment effect associated with paclitaxel plus platinum vs platinum, has been overstated.

In addition, whilst there exist differences in baseline characteristics between trials, in particular with respect to the length of the PFI and the method used to diagnose recurrence, the TAG considers that the magnitude of these differences is unlikely to affect estimates of the relative effect of treatment.

On balance, the TAG considers that, although differences in key prognostic factors across the trials have been identified, when considering the trials that would inform the NMA the TAG considers the

trials sufficiently clinically homogeneous to compare clinical effectiveness of treatments. That is, the impact of the identified heterogeneity is not expected to be large.

Unadjusted HRs

The TAG used unadjusted HRs for PFS and OS within the analysis. The TAG considers that this was appropriate. The TAG acknowledges 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 TAG did not consider it appropriate to analyse a blend of unadjusted and adjusted HRs. Moreover, although adjusted HRs were available for a small number of comparisons, the factors for which each HR was adjusted differed for each case.

The manufacturer of trabectedin, PharmaMar, submitted an analysis of the head-to-head comparison of trabectedin plus PLDH vs PLDH using PFS and OS data adjusted for baseline characteristics. Of particular importance within this analysis was the adjustment of PFS and OS data using PFI as a continuous variable. The TAG, following consultation with clinical experts, considers that this adjustment may be considered appropriate because, in clinical practice, platinum sensitivity is viewed along a continuum.

The TAG considered it inappropriate to use the adjusted HR estimated by the manufacturer within the economic model because no data with the same adjustment was available for any other intervention or comparator. Instead, as a sensitivity analysis, the TAG used head-to-head PFS and OS data estimated by the manufacturer within the TAG model to assess the resultant ICER. The ICER estimated by the TAG in this exploratory analysis was £35,646 per additional QALY. This figure compares with the manufacturer estimate of £27,573 for the same comparison. The difference in ICER estimated between the TAG model and the manufacturer's model was a result of a difference in estimated incremental QALYs, rather than the difference in incremental costs. The TAG believes that this may be due to the manufacturer's method of discounting future costs and benefits; an area in which the ERG for TA222 previously raised concerns.

Assumption of proportional hazards

The TAG did not have access to IPD for all the interventions and comparators of interest; therefore, summary measures of relative effect using the HR were applied within the model. The TAG therefore implicitly assumed that the relative treatment effect was constant over time. The TAG investigated this by plotting cumulative log-hazards where possible from digitised Kaplan-Meier data. These plots indicated that the assumption of proportional hazards did not hold generally, with many hazards decreasing over time, and in some cases the non-monotonic hazards being present. The impact of this across model results is unclear.

1.6 Conclusions

1.6.1 Main findings

In the network evaluating platinum-based chemotherapies, PLDH plus carboplatin and paclitaxel plus carboplatin were found to significantly improve OS compared with platinum monotherapy. However, no statistically significant differences in OS were identified between the remaining treatments considered in the network. When compared with platinum monotherapy, PFS was estimated to significantly improve in patients treated with paclitaxel plus carboplatin, gemcitabine plus carboplatin or PLDH plus carboplatin. In addition a statistically significant difference in PFS was estimated for paclitaxel plus carboplatin vs PLDH plus carboplatin.

The TAG considers that the comparison of paclitaxel plus platinum vs platinum is likely to be the most pertinent comparison for platinum sensitive network 1. On balance, this comparison may be considered cost-effective at a threshold of £30,000 per additional QALY; the TAG estimated that 78% of simulations resulted in an ICER at or below this threshold (probabilistic ICER: £24,539). The TAG notes that the ICER was most sensitive to changes in OS; the ICER increased by over £20,000 in OWSA when using the lowest credible interval value for the HR.

The TAG notes that clinical heterogeneity was identified for this comparison such that the TAG considers it likely that the relative efficacy of paclitaxel plus platinum have been overstated when compared with platinum. However, the TAG also notes that for this comparison, the assessment of proportional hazards indicates that the hazards are non-monotonic; that is the hazards initially increase and then decrease over time. Consequently, the TAG is unclear what impact the bias associated with the clinical heterogeneity and the bias associated with proportional hazards would have on model results overall.

However, the TAG considers it important to note, that expert clinical advice highlighted that accumulated neurotoxicity as a result of prior taxane therapy means that not all patients may tolerate further treatment with paclitaxel. With this in mind, the TAG consider it important to note that the addition of PLDH to platinum therapy was associated with a 48% likelihood of being cost-effective versus platinum therapy at a WTP threshold of £30,000 (probabilistic ICER: £30,188).

NMA of non-platinum based therapies indicated that PLDH monotherapy and trabectedin plus PLDH are both significantly more effective at prolonging OS than topotecan monotherapy. No other significant OS differences were identified. Analysis of non-platinum-based regimens indicates that trabectedin plus PLDH statistically significantly improves PFS compared with PLDH, paclitaxel and topotecan when given as monotherapies. No statistically significant differences were identified among the monotherapies evaluated (PLDH, topotecan, and paclitaxel).

The TAG considers that the comparisons of PLDH vs paclitaxel (probabilistic ICER: £25,931) and trabectedin plus PLDH vs PLDH (probabilistic ICER: £81,353) are likely to be the most pertinent comparisons for platinum sensitive network 2. On balance, the likely cost effectiveness of the comparison of PLDH vs paclitaxel at a threshold of £30,000 per additional QALY is unclear; the TAG estimated that 59% of simulations resulted in an ICER at or below £30,000, and 15% of simulations resulted in PLDH being less effective and more costly (dominated). As before, the ICER was most sensitive to changes in OS; PLDH was dominated by paclitaxel when the lowest credible interval value for the HR was used.

The TAG considers that, based upon the base case results, trabectedin plus PLDH vs PLDH is unlikely to be considered cost-effective. However, the TAG notes that in a scenario analysis in which the manufacturer estimates of PFS and OS (where survival was adjusted for baseline characteristics) were used within the TAG model, the ICER fell to £35,646. The TAG acknowledges that PFI is considered in clinical practice to be a continuous variable and notes that there was an imbalance at baseline in the head-to-head trial carried out by the manufacturer. However, the TAG notes that, given the data available, it is not possible to adjust survival for the remaining treatments in the network in a similar way, and therefore the results of the scenario analysis should be considered independently.

No statistically significant differences in OS or PFS were identified in NMA of treatment with paclitaxel, PLDH and topotecan. However, NMA of ORR estimated that PLDH significantly increased ORR compared with paclitaxel (175 mg/m^2) every 21 days and with an alternative regimen in which paclitaxel was given weekly at a dose of 67 mg/m^2. PLDH monotherapy was also significantly more effective than an unconventional regimen of topotecan in which topotecan was administered weekly at a dose of 4 mg/m^2.

The TAG considers the comparison of topotecan vs PLDH to be the most pertinent comparison for the platinum resistant/refractory network; paclitaxel was dominated by PLDH. The TAG considers it unlikely that topotecan is considered cost-effective at a threshold of £30,000 per additional QALY. 0% of simulations resulted in an ICER at or below £30,000 (probabilistic ICER: £324,188). However, the costs and QALYs associated with paclitaxel are similar to those associated with PLDH, with paclitaxel being dominated by PLDH in 39% of probabilistic simulations. As highlighted for patients with platinum sensitive disease, increased risk of neurotoxicity following prior taxane therapy means that not all patients may tolerate further treatment with paclitaxel

All model results have been shown to be sensitive to estimates of OS. The data used within the economic analysis for OS was based upon the best available evidence, using methods that ensured comparability of effect across treatments and allowed for use of summary statistics. However, as described above, OS data is subject to a number of limitations.

1.6.2 Suggested research priorities

- It was not possible to link platinum sensitive network 1 and platinum sensitive network 2; ideally an RCT should be carried out in which a link between these networks is established, but only if this was thought to be a potentially important research question by the wider clinical community. The TAG notes that, following review of clinical trial registries (Appendix 14), two RCTs are currently on-going for partially platinum sensitive patients (PFI 6 – 12 months) in which platinum-based therapies are compared with non-platinum based therapies, which may provide sufficient information for the wider clinical community;
- It was not possible to estimate the cost-effectiveness of paclitaxel plus platinum, or evaluate the comparators of etoposide (with and without platinum) and best supportive care, within the platinum resistant/refractory network. Ideally, an RCT should be carried out in which these interventions and comparators are assessed specifically in a platinum resistant/refractory population, but only if this was thought to be a potentially important research question by the wider clinical community;
- Given the palliative nature of second line or later treatment for recurrent ovarian cancer, particularly for patients with platinum resistant/refractory disease, a move to place greater emphasis on assessment of QoL in this condition may be warranted;
- Given the importance of platinum free interval on prognosis, further research and future consideration of PFI as a continuous variable may be warranted;
- The TAG considers that future research into the cost of best supportive care for women with ovarian cancer is warranted.

2 BACKGROUND

2.1 Description of health problem

Ovarian cancer is the fifth most common cancer in the UK, and is the fourth most common cause of cancer death.[1] Ovarian tumours are classified based on the cell type from which the tumour originates: surface epithelium; germ; or stroma. Most ovarian malignancies are epithelial in origin, accounting for 80–90% of ovarian cancers.[1] Today, it is widely accepted that fallopian tube carcinoma and primary peritoneal carcinoma are, in general, histologically serous, and are considered to arise from the same pathophysiology as epithelial ovarian cancer.[2] Epithelial tumours can be further divided based on their histology (high grade serous, low grade serous, mucinous, endometrioid, clear cell, and undifferentiated or unclassifiable). The most common type of ovarian cancer in the UK is high grade serous carcinoma. Other, rarer subtypes include germ cell tumours, which tend to occur in pre-menopausal women and are highly sensitive to chemotherapy (and therefore treatable), or borderline ovarian cancer.[1;3] Borderline ovarian cancers have low malignant potential and are usually considered separately as they do not usually require treatment with chemotherapy. It is thought that most histologies share common risk factors, with the probable exception of mucinous carcinomas.[1]

2.2 Epidemiology

2.2.1 Incidence and prevalence

Ovarian cancer is predominantly a disease of older, post-menopausal women, with over 80% of cases being diagnosed in women over 50 years of age.[1] The highest age-specific incidence rates are seen for women aged 80–84 years at diagnosis, with an incidence of 69 per 100,000, which drops to 64 per 100,000 in women aged 85 and over.[1] However, for women with *BRCA*-deficient tumours, the age of diagnosis can be about 10 years earlier.

In 2008, around 6,500 women were diagnosed with ovarian cancer in the UK, making it the second most common gynaecological cancer and the fifth most common cancer in women.[1] Focusing on England and Wales, in 2008, there were 5,304 new cases in England and 400 in Wales, giving age-standardised rates per 100,000 of 15.8 (95% Confidence Interval [CI] 15.4 to 16.2) and 19.6 (95% CI 17.7 to 21.5), respectively.[1] In 2010, 4,295 deaths were attributed to ovarian cancer, accounting for 5.7% of all female deaths from cancer.[1] It has been estimated that the lifetime risk (adjusting for multiple primaries) of developing ovarian cancer is 1 in 54 for women in the UK (based on data from 2008).[1]

2.2.2 Aetiology and pathology

Diagnosing ovarian cancer can be difficult. Patients typically present with subtle symptoms, such as difficulty eating, abdominal bloating and feeling "full" quickly, all of which are suggestive of other, more minor conditions. As a result, many people (~60%) are diagnosed with ovarian cancer when their disease is in an advanced stage.[4] Stage of ovarian cancer at diagnosis is based on the International Federation of Gynecology and Obstetrics (FIGO) classification system.[2] The FIGO system is a scale of I to IV, where Stage I represents early stage disease and Stages III and IV represent advanced disease (summarised in Table 11).

Table 11. FIGO stages for ovarian cancer[2]

Stage	Criteria
1	**Tumour confined to the ovaries**
1A	• Tumour limited to one ovary, and capsule intact; • No tumour on ovarian surface; • No malignant cells in ascites or peritoneal washings.
1B	As for 1A, but tumour limited to both ovaries
1C	Tumour limited to one or both ovaries, with any of the following: • Tumour on ovarian surface; • Ruptured capsule; • Malignant cells in ascites or peritoneal washings.
2	**Tumour involves one or both ovaries with pelvic extension**
2A	Extension and/or metastases in the uterus and/or fallopian tubes but with no malignant cells in ascites or peritoneal washings.
2B	Extension to other pelvic organs but with no malignant cells in ascites or peritoneal washings.
2C	Tumour staged either 2A or 2B with malignant cells in ascites or peritoneal washings.
3	**Tumour involves one or both ovaries with peritoneal metastasis outside the pelvis and/or regional lymph node metastasis** **Liver capsule metastasis equals Stage 3**
3A	Microscopic peritoneal metastasis beyond the pelvis.
3B	Macroscopic peritoneal metastasis beyond the pelvis, none of which exceed 2 cm in greatest dimension.
3C	Peritoneal metastasis beyond the pelvis, larger than 2 cm in greatest dimension and/or regional lymph node metastasis.
4	**Distant metastasis (beyond the peritoneal cavity)**
Abbreviation used in table: FIGO, International Federation of Gynecology and Obstetrics.	

The aetiology of ovarian cancer is not yet fully understood. Various factors have been linked with an increased risk of developing ovarian cancer, and, conversely, others have been proposed as having a "protective" effect and reducing ovarian cancer risk. The strongest known risk factors associated with a higher risk of ovarian cancer are increasing age and the presence of a mutation in the *BRCA1* and *BRCA2* genes, with the latter accounting for around 10% of cases.[1] The *BRCA1* and *BRCA2* genes are also associated with risk of breast cancer, and studies have shown a doubling in ovarian cancer risk for women with a previous breast cancer. Women who have a first-degree relative (i.e., parent,

sibling, or offspring) diagnosed with ovarian cancer have a 3–4-fold increased risk of developing the disease compared with women with no family history, although about only 10% of ovarian cancer cases occur in women with a family history.[1]

Ovarian cancer risk tends to be reduced by factors that interrupt ovulation, such as pregnancy (with a dose-response relationship between increasing risk and a lower number of children), breastfeeding, and oral contraceptive use.[1] Conversely, factors that prolong exposure to ovulation, such as nulliparity and infertility, increase risk.[1] It has been reported that 5 years' use of oestrogen-only hormone-replacement treatment (HRT) is associated with a 22% increase in the risk of ovarian cancer, which is considerably larger than the 10% risk increase identified with use of oestrogen–progestin HRT over the same time period.[1] It is estimated that about 50 cases of ovarian cancer in the UK in 2010 were linked with HRT, which is equivalent to about 1% of all ovarian cancers.[1] Past or short-term use of HRT is thought unlikely to increase the risk of ovarian cancer.

Risk of ovarian cancer seems to be higher in people who have some other gynaecological medical conditions. For example, studies have found that women with endometriosis have a 30–66% increased risk.[1] In addition, young women (15–29 years old) with ovarian cysts and functional cysts (harmless, short-lived cysts that are formed as a part of the menstrual cycle) have been found to have double the usual risk of ovarian cancer later in life, and women who had cysts surgically removed, or unilateral oophorectomy, have a 9-fold risk increase.[1] Hysterectomy may reduce ovarian cancer risk, with case-control studies reporting a 30–40% risk reduction regardless of age at time of surgery, and a 50% risk reduction for women whose hysterectomy was 15 or more years before the study.[1]

Lifestyle and environmental factors also affect risk of ovarian cancer, with both current and past smoking and high body mass index being linked with increased risk.[1]

2.2.3 Prognosis

Treatments for newly diagnosed ovarian cancer are given with curative intent. Primary treatment is determined by the stage and risk of disease at diagnosis.[1] Treatment options are surgery, or surgery followed by adjuvant chemotherapy (most likely platinum-based), or chemotherapy alone. Alternatively, if it is thought that removal of all the cancer during the initial surgery could be problematic because of tumour size, chemotherapy may be administered before surgery (neoadjuvant chemotherapy) to shrink the tumour, with additional adjuvant chemotherapy after surgery. Clinically complete remission is achieved in most newly diagnosed patients through a combination of cytoreductive surgery and chemotherapy.

Considering chemotherapy, up to 10% of patients might not respond to first-line chemotherapeutic treatment and, of those who do respond, between 55% and 75% of people will relapse within 2 years.[5] It is these latter populations, more specifically those people who have received prior

platinum-based treatment, that are the focus of this systematic review. Diagnosis of recurrent disease varies in UK clinical practice, with diagnosis based on clinical examination, biochemical markers (CA125), or radiological confirmation, or any combination of these three. Clinical expert advice is that, typically, a patient is diagnosed as relapsed if they have a serial rise in CA125 or have developed clinical signs, such as ascites. Diagnosis is typically confirmed with radiological scans. If a patient has no clinical symptoms but does have a rise in CA125, although possibly classified as relapse, the patient might not start a new chemotherapeutic regimen until they go on to develop symptoms. Date of relapse by CA125 is likely to be about 4 months earlier than date of relapse based on radiological scans. A patient is considered to have relapsed if they have progressed after achieving CR or PR, or after their disease has been stable for some time (typically, 8–12 weeks).

Prognostic factors thought to influence outcome (i.e., response to treatment and survival) are:

- the stage of the disease at diagnosis (FIGO stage);
- age;
- patient's general health (typically referred to as performance status) at the time of presentation;
- extent of residual disease after debulking surgery;
- tumour grade;
- tumour histology.

Of the prognostic factors listed, the stage of disease at diagnosis and extent of residual disease after debulking surgery are considered to be strong predictors of survival. Relative 5-year survival rate is more than 90% for early stage disease, but falls markedly to less than 10% for later stages.[1;3]

Based on age-standardised relative survival rates during 2005–2009 in England, data indicate that 72.3% of women are expected to survive for at least 1 year, falling to 42.9% surviving for 5 years or more, and to 35.4% surviving for 10 years or more.[1] Relative survival for ovarian cancer is higher in younger women, even after taking account of the higher background mortality in older people;[1] 5-year relative survival rates for ovarian cancer in England during 2005–2009 ranged from 87% in people aged 15–39 years to 16% in those aged 80–99 years. The higher survival rate in younger women is likely to be attributable to a combination of better general health, more effective response to treatment and earlier diagnosis in younger people.[1]

As with most cancers, relative survival for ovarian cancer is improving.[1] Much of the increase occurred during the 1980s and 1990s, and appears to be levelling off in the 2000s (Table 12).[1] Increased use of platinum-based chemotherapy, wider access to optimal primary treatment and greater determination to treat recurrent disease are all thought to have contributed to the observed improvements in overall survival (OS) at 1- and 5-years.[1]

Table 12. Relative 1- and 5-year survival rates for two time periods

Time period	1 year	5 years
1971–1975	42.0%	21.0%
2005–2009	72.3%	42.9%

2.2.4 Measurement of disease

Initially, an elevated level of CA125 (determined by a blood test) is used as an indicator in the diagnosis of ovarian cancer. About 90% of people who have later stages of ovarian cancer have an elevated CA125 level, whereas about 50% of people with early stage ovarian cancers have an elevated CA125 level; normal CA125 level is 0 to 35 U/ml.[6] However, CA125 is not specific to ovarian tumours, and other benign conditions of the womb and ovaries also result in elevated CA125 (e.g., endometriosis, fibroids, and pelvic inflammatory disease).[1] Other non-gynaecological conditions that are associated with increased CA125 are liver cirrhosis and pleural infusions. If a person is found to have ovarian cancer that produces CA125, this blood test can be used to monitor the clinical effectiveness of treatment.[1]

As CA125 elevation is not specific to ovarian cancer, it is recommended that diagnosis of ovarian cancer be confirmed by an ultrasound scan of the abdomen and pelvis.[3] If the ultrasound, serum CA125 and clinical status suggest ovarian cancer, a computed tomography (CT) scan of the pelvis and abdomen is carried out to establish the extent of disease. Expert advice is that the ratio of CA125 to carcinoembryonic antigen (CEA) may be a useful guide in assessing ovarian cancer. Research has suggested that a CA125:CEA ratio of <25 may be suggestive of a non-ovarian malignancy.[7]

2.3 Impact of health problem

2.3.1 Significance for patients in terms of ill-health (burden of disease)

As a result of the difficulties diagnosing ovarian cancer, many women present with advanced disease (e.g., 60% of women are diagnosed with stage III or IV disease), having had subtle symptoms for months before presentation.[1;3] Only around 29% of women are diagnosed at FIGO stage I, 4% at stage II and 6% are unstaged.[1]

Treatments for newly diagnosed ovarian cancer are given with curative intent; however, for women with advanced, recurrent disease, second and subsequent line chemotherapies are typically given with palliative rather than curative intent, with the aim of alleviating symptoms and prolonging survival. Thus, key considerations in the choice of treatment at these stages in the pathway are maintaining the patient's quality of life and adverse effects associated with the individual treatments.

A recent study by Hess *et al.*[8] investigated health-related quality of life for women with ovarian cancer before, during and after chemotherapy, via a systematic review. The review resulted in

identification of a total of 139 unique studies of patients with ovarian cancer in which quality of life data were collected. Within these studies, more than 90 different measures of quality of life were administered. The authors found that there was limited longitudinal data beyond the initial treatment and immediate follow-up which limited the understanding of the long-term impact upon quality of life for ovarian cancer survivors.

2.4 Significance for the NHS

Patients with ovarian cancer require significant amounts of hospital resources, including surgery and multiple courses of chemotherapy. In 2011–2012, ovarian cancer accounted for 36,690 finished consultant episodes, 34,376 admissions and totalling 66,003 bed days, in England alone.[9]

2.4.1 Current service provision

National Institute for Health and Care Excellence (NICE) guidance is available on the initial recognition and management of ovarian cancer,[3] first-line chemotherapeutic treatments for ovarian cancer,[5] and on the use of topotecan, paclitaxel, and PLDH as second-line or subsequent treatments of advanced ovarian cancer.[10]

2.4.1.1 Initial management of ovarian cancer

After confirmation of a diagnosis of ovarian cancer, primary treatment is determined by the patient's age and general health, in addition to the histology and grade of their cancer. Typically, surgery is the preferred initial treatment, the goal of which is to excise all macroscopic disease, irrespective of stage of disease.

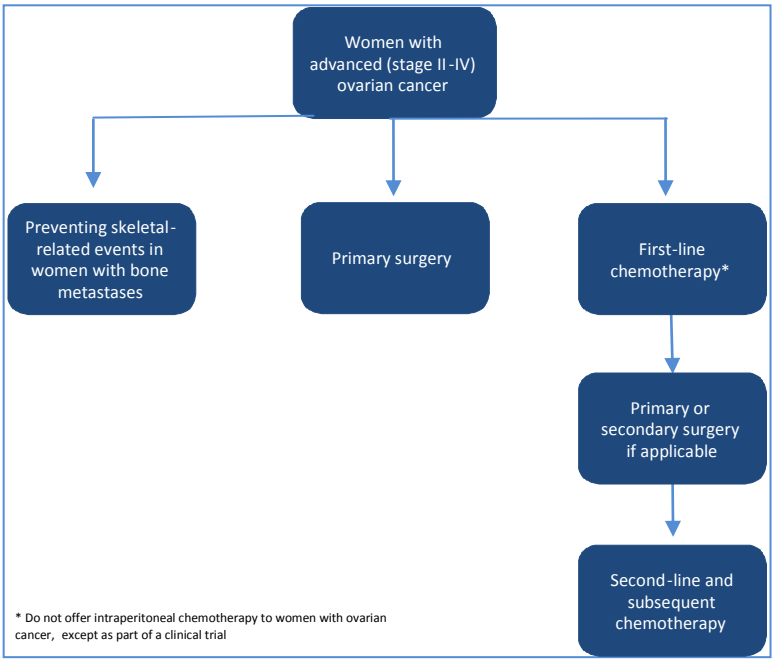
For suspected early (Stage I) ovarian cancer, NICE recommends optimal surgical staging, with no adjuvant chemotherapy for cancers identified as low risk disease (grade 1 or 2, stage Ia or Ib).[3] For suspected early stage disease that is considered high-risk (grade 3 or stage Ic), NICE recommends that surgery be followed by chemotherapy treatment comprising 6 cycles of carboplatin.[3]

As noted earlier, most people are diagnosed with ovarian cancer when their disease has reached an advanced stage (Stage II–IV). In such cases, complete excision of the tumour during surgery may be difficult and patients will typically require additional chemotherapeutic treatment. Chemotherapy may be administered prior to surgery (typically 3 cycles), with the objective of shrinking the tumour to facilitate excision and improve the probability of removal of all macroscopic disease. First-line chemotherapy is the first round of chemotherapeutic treatment a patient receives, whether it is as a neoadjuvant treatment before surgery, an adjuvant treatment to surgery or at some time in the longer term after surgery. Second and subsequent line treatment is for those who have either relapsed after first-line chemotherapeutic treatment or experienced progression of their disease while receiving chemotherapy.

Prior to offering cytotoxic chemotherapy to women with advanced ovarian cancer (Stage II–IV), NICE recommends confirmation of tissue diagnosis with histology (or by cytology if histology is not appropriate).[3] For first-line chemotherapy, NICE recommends paclitaxel in combination with a platinum-based compound or platinum-based therapy alone (cisplatin or carboplatin).[5] NICE does not recommend the use of bevacizumab in combination with paclitaxel and carboplatin as a first-line chemotherapeutic treatment.[11]

The NICE pathway for the management of advanced ovarian cancer is outlined in Figure 1.

Figure 1. Treatment pathway recommended by NICE for the management of patients with advanced (stage II–IV) ovarian cancer[12]



2.4.1.2 Second and subsequent-line chemotherapeutic treatment

Although first-line chemotherapeutic treatment achieves a response in approximately 70–80% of patients, most patients will eventually relapse and require second-line therapy.[13] Between 55% and 75% of those who respond to first-line therapy will relapse within two years of completing treatment. Second and subsequent line chemotherapies are typically given with palliative rather than curative intent, with the aim of alleviating symptoms and prolonging survival. Thus, key considerations in the choice of treatment at these stages in the pathway are maintaining the patient's quality of life and adverse effects associated with the individual treatments.

A patient's response to first-line platinum-based therapy is indicative of their response to second and subsequent lines of platinum-based treatment, with the length of the platinum-free interval (PFI) and the extent of relapse (site and number of tumours) particularly prognostic of response. However, most

patients will develop resistance to platinum-based therapy over time, with decreasing length of PFI with increasing rounds of treatment. Platinum-resistant ovarian cancer (defined in Table 13) has a particularly poor prognosis, with a reported median OS of less than 12 months.[14]

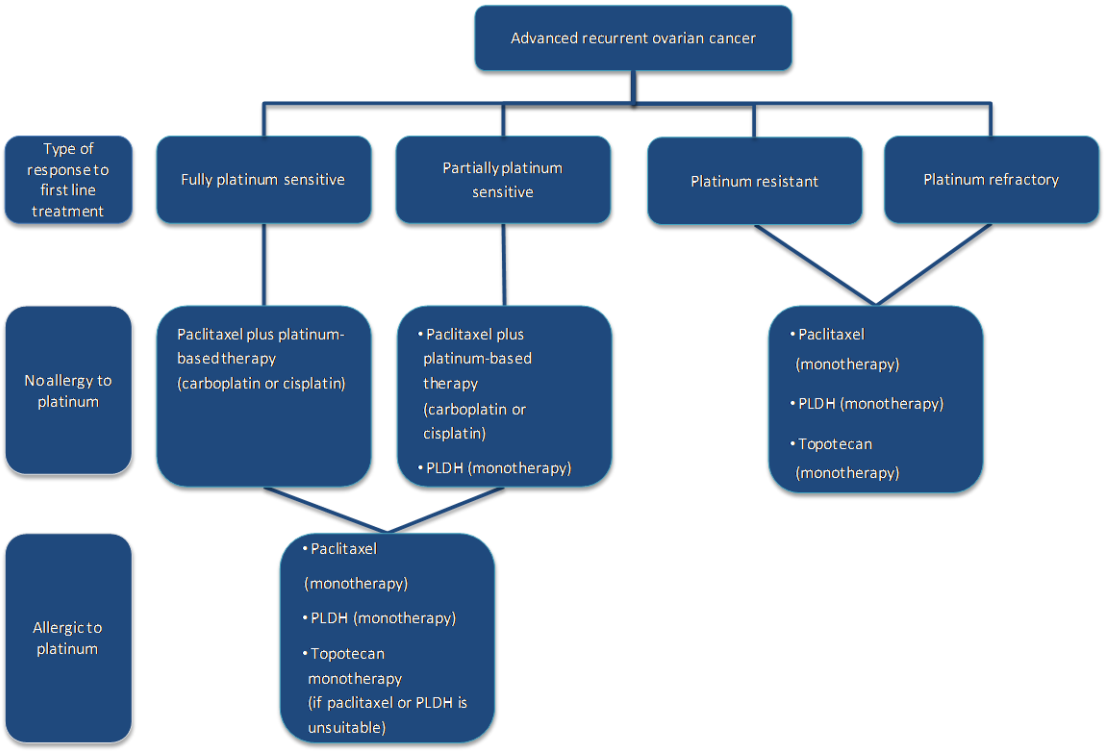
Table 13. Categorisations of platinum sensitivity used in choice of second and subsequent lines of treatment of ovarian cancer[10]

Categorisation	Definition
Platinum sensitive	Disease that responds to first-line platinum-based therapy but relapses 6 months or more after completion of initial platinum-based chemotherapy
Partially platinum-sensitive	Relapses between 6 and 12 months after completion of initial platinum-based chemotherapy
Fully platinum-sensitive	Relapses 12 months or more after completion of initial platinum-based chemotherapy
Platinum resistant	Disease that relapses within 6 months of completion of initial platinum-based chemotherapy
Platinum refractory	Disease that does not respond to initial platinum-based chemotherapy

The choice of second and subsequent line of treatment has long been based on a patient's PFI, that is, the period of time between the last treatment of one regimen and the first treatment of the next regimen. Current NICE guidance on second-line or subsequent treatment of advanced ovarian cancer is based on the duration of time since last platinum-based therapy, with treatment options of paclitaxel, either as a monotherapy or in combination with platinum-based (carboplatin or cisplatin) therapy, PLDH monotherapy and topotecan monotherapy.[10] Treatments options as recommended by NICE based on degree of platinum sensitivity are depicted in Figure 2. In recently completed Technology Appraisals, NICE did not recommend bevacizumab in combination with gemcitabine and carboplatin[15] or trabectedin plus PLDH[16] for the treatment of recurrent ovarian cancer.

An important consideration in the choice of second-line treatment is the adverse effect of neurotoxicity, which is commonly associated with paclitaxel and also with carboplatin. Neurotoxicity can persist for up to 2 years after the end of treatment.[17] Patients who relapse after first-line treatment with paclitaxel–platinum combination therapy and are subsequently re-challenged with the same regimen within 12 months (i.e., those who are partially platinum-sensitive) are at an increased risk of developing neurotoxicity.[18] However, despite the associated increased risk of neurotoxicity, paclitaxel plus carboplatin is generally the preferred second-line treatment in UK practice in recurrent platinum-sensitive cancer, particularly for patients who relapse >12 months after completion of first-line chemotherapy. Carboplatin is chosen over cisplatin because of its more favourable adverse effect profile.

Figure 2. Treatment options in relapsed ovarian cancer (figure based on NICE guidance[10] and adapted from TA222[19])



2.4.1.3 Current service cost

An analysis of Hospital Episode Statistics for 2006–08 of patients dying from prostate, breast, lung, upper gastrointestinal, colorectal, or ovarian cancer indicate that patients with ovarian cancer and in their last year of life required 53,700 elective bed days (at a cost of £14,274,623) and 216,723 emergency bed days (at a cost of £58,606,527).[20] On a per person basis, ovarian cancer had a longer elective stay and a longer emergency length of stay than the other cancers.[20] Ovarian cancer also had the highest overall cost at £8,000 per person.[20]

2.5 Description of technologies under assessment

2.5.1 Topotecan

Topotecan is a semi-synthetic, water-soluble derivative of camptothecin, a natural product isolated from the tree *Camptotheca acuminate*.[21] Topotecan elicits a chemotherapeutic effect through inhibition of the topoisomerase I enzyme, which has a crucial role in cell replication. Topoisomerase enzymes are involved in DNA replication, acting to relieve strain in the double-stranded DNA helix by "cutting" one strand to release tension followed by reconnection of the two separate strands. Topotecan binds to the topoisomerase I–DNA complex, thus blocking the action of topoisomerase I and preventing reformation of the DNA double helix.

Topotecan is licensed for the treatment of patients with metastatic carcinoma of the ovary after failure of at least one other treatment (i.e., topotecan is licensed as a second and subsequent line treatment).[22] The initial recommended dose of topotecan is 1.5 mg/m^2 of body surface area, to be administered by intravenous infusion over 30 minutes for 5 consecutive days, with a 3-week interval between the start of each course.[22] It is recommended that topotecan be given for a minimum of 4 cycles. If well tolerated, treatment can be continued until disease progression. Topotecan should be administered under the supervision of a clinician experienced in the use of chemotherapy. Topotecan has also been evaluated in randomised controlled trials (RCTs) at an intravenous dose of 4.0 mg/m^2 weekly[23] and as an oral treatment (dose of 2.3 mg/m^2/day).[24] A dose for oral administration of topotecan has not been recommended for ovarian cancer.

Topotecan is contraindicated in patients who:[22]

- have a history of severe hypersensitivity to the active substance or to any of the excipients;
- are breast feeding;
- already have severe bone marrow depression before starting first course, as evidenced by baseline neutrophils <1.5 x 109/L and/or a platelet count of <100 x 109/L.

Special warnings and precautions for use of topotecan include haematological toxicity, severe myelosuppression, topotecan-induced neutropenia, development of interstitial lung disease, and thrombocytopenia.[22]

The most common adverse events associated with topotecan (reported by at least 1 out of 10 patients) are: infection; febrile neutropenia; neutropenia; thrombocytopenia; anaemia; leucopoenia; anorexia (which may be severe); nausea; vomiting; diarrhoea; constipation; mucositis; abdominal pain; alopecia; pyrexia; asthenia; and fatigue.[22]

2.5.2 Pegylated liposomal doxorubicin hydrochloride (Caelyx®)

The active component in pegylated liposomal doxorubicin hydrochloride (PLDH) is doxorubicin hydrochloride, which is a member of the anthracycline class of antibiotics. Anthracyclines act by inhibiting synthesis, transcription and replication of DNA, and have potent antineoplastic (inhibits the growth and spread of cancerous cells) activity.[25] However, anthracyclines are also highly destructive to cellular membranes and are known to generate chemical species (oxygen-derived free radicals) that, as well as directly damaging DNA, are thought to damage the membranes of the heart, which may lead to congestive heart failure.[25] Cardiotoxic adverse effects of anthracyclines are irreversible and accumulative and limit the clinical usefulness of this class of antibiotics.

Liposomes are miniscule spheres comprising a lipid bilayer that can be used as vehicles for the administration of drugs. Coating the liposomes with methoxypolyethylene glycol (MPEG), a process

known as pegylation, protects the liposome from detection by the body's immune system. Encapsulation of doxorubicin hydrochloride in pegylated liposomes seems to increase the localisation and concentration of doxorubicin hydrochloride in cancerous cells while simultaneously reducing the toxicity of doxorubicin hydrochloride to non-cancer tissues and cells, and, thereby, reducing the risk of severe adverse effects.[26]

PLDH (2 mg doxorubicin hydrochloride in a pegylated liposomal formulation) is licensed for the treatment of advanced ovarian cancer in women who have failed a first-line platinum-based chemotherapy regimen.[27] The licensed dose of PLDH when given as a monotherapy is 50 mg/m^2 given intravenously once every 4 weeks for as long as disease does not progress and the patient continues to tolerate treatment;[27] clinical expert advice is that typical UK clinical practice is to administer PLDH at a dose of 40 mg/m^2. It should not be administered as a bolus injection or undiluted solution. PLDH should be given under the supervision of a clinician who is qualified in the use of cytotoxic medicines.[27] Importantly, PLDH cannot be interchanged with other medicines containing doxorubicin hydrochloride.

RCTs have also evaluated PLDH in combination with other agents, both platinum-based and non-platinum based.[28-31] No dose has been recommended for PLDH when used in combination treatment. Doses of PLDH evaluated in doublet-chemotherapy were 30 mg/m^2 in combination with trabectedin[30] and with carboplatin[28;31] and 45 mg/m^2 in combination with carboplatin.[29] In all RCTs, the interval between cycles was 4 weeks. Clinical experts fed back that PLDH would most likely be used at a dose of 30.0 mg in combination regimens.

PLDH is contraindicated in people with hypersensitivity to the active substance or to any of the excipients.[27] Special warnings and precautions for use of PLDH include cardiac toxicity, myelosuppression, and infusion-associated reactions.[27] It is recommended that all patients receiving PLDH routinely undergo frequent electrocardiogram monitoring.[27]

The most common undesirable adverse effect associated with PLDH (50 mg/m^2 every 4 weeks) treatment in breast cancer and ovarian cancer RCTs was palmar–plantar erythrodysesthesia (PPE), which is characterised by painful, macular reddening skin eruptions.[27] The overall incidence of PPE was 44.0%–46.1%.[27] These effects were reported to be predominantly mild, with severe (Grade III) cases reported in 17%–19.5% of patients.[27] The reported incidence of life-threatening (Grade IV) cases was <1%.[27]

In patients with ovarian cancer, the most common adverse effects (reported by at least 1 out of 10 patients) associated with PLDH treatment were: leucopoenia; anaemia; neutropenia; thrombocytopenia; anorexia; constipation; diarrhoea; nausea; stomatitis; vomiting; PPE; alopecia;

rash; asthenia; and mucous membrane disorder. Clinically significant laboratory abnormalities associated with PLDH included increases in total bilirubin (usually in patients with liver metastases) (5%) and serum creatinine levels (5%).[27]

2.5.3 Paclitaxel (Taxol®)

Paclitaxel is a taxane, a class of drugs that were isolated from the Pacific yew tree (*Taxus brevifolia*).[32] Paclitaxel targets a protein that is a key component of microtubules. Microtubules are important in various cellular processes, including the initiation of DNA synthesis. Unlike other taxanes, which inhibit microtubule assembly, paclitaxel stabilises the microtubule polymer, protecting the microtubule from disassembly and, therefore, further involvement in cellular processes.

In the UK, paclitaxel is licensed as first-line chemotherapy in combination with cisplatin or carboplatin for ovarian cancer patients with advanced carcinoma of the ovary or with residual disease (>1 cm) after initial laparotomy.[33] Paclitaxel is also licensed as a second-line chemotherapy for ovarian cancer after failure of standard, platinum-containing therapy.[33] The recommended dose for paclitaxel when used as a second and subsequent line treatment is 175 mg/m² administered over a period of 3 hours, followed by a platinum-based compound, with a 3-week interval between courses of treatment.[33] Prior to treatment with paclitaxel, patients should undergo pre-treatment with corticosteroids, antihistamines, and H_2-receptor antagonists.[33]

Paclitaxel is contraindicated during lactation and should not be used in patients with baseline neutrophil count of <1,500/mm³.[33] Special warnings and precautions for use of paclitaxel include hypersensitivity reactions, and bone marrow suppression (primarily neutropenia).[33] Patients with hepatic impairment may be at increased risk of toxicity, particularly Grade 3–4 myelosuppression.[33]

The most common adverse effects associated with paclitaxel (reported by at least 1 out of 10 patients) are: infection (mainly urinary tract and upper respiratory tract infections); myelosuppression; neutropenia; anaemia; thrombocytopenia; leucopoenia; bleeding; minor hypersensitivity reactions (mainly flushing and rash); neurotoxicity (mainly peripheral neuropathy); hypotension; diarrhoea; vomiting; nausea; mucosal inflammation; alopecia; arthralgia; and myalgia.[33]

2.5.4 Trabectedin (Yondelis®; PharmaMar)

Trabectedin is a synthetic antineoplastic drug, the structure of which is derived from a natural product originally extracted from the marine Caribbean tunicate ('sea squirt'; a marine animal) *Ecteinascidia turbinata*.[34] Trabectedin binds to the minor groove of DNA, a process that triggers various events that affect multiple transcription factors, DNA binding proteins and DNA repair pathways, and ultimately results in disruption of the cell cycle.

Trabectedin in combination PLDH is licensed for the treatment of patients with relapsed platinum-sensitive ovarian cancer.[35] PLDH is administered first at a dose of 30 mg/m^2 immediately followed by administration of trabectedin as a 3-hour infusion at a dose of 1.1 mg/m^2. The recommended interval between treatment cycles is 3 weeks. To minimize the risk of PLDH infusion reactions, the initial dose of PLDH is administered at a rate no greater than 1 mg/minute.[35] If no infusion reaction is observed, subsequent PLDH infusions may be administered over a 1-hour period.

All patients should be treated with corticosteroids 30 minutes before administration of PLDH (in combination therapy) or trabectedin (when used as a monotherapy).[35] Corticosteroids not only act as anti-emetic prophylaxis, but also seem to afford hepatoprotective effects.[35]

Trabectedin is contraindicated in:[35]

- people who are hypersensitive to trabectedin or to any of the excipients;
- people who have concurrent serious or uncontrolled infection;
- people who are breast-feeding;
- concomitant combination with yellow fever vaccine.

Patients must meet specific criteria on hepatic function parameters before treatment (or re-treatment) with trabectedin can commence.[35] If patients do not meet the criteria listed below, treatment must be delayed for up to 3 weeks until the required levels are reached. Patients must have:

- absolute neutrophil count ≥1,500/mm3;
- platelet count ≥100,000/mm3;
- bilirubin ≤upper limit of normal (ULN);
- alkaline phosphatase ≤2.5 x ULN;
- albumin ≥5 g/L;
- alanine aminotransferase and aspartate aminotransferase ≤2.5 x ULN;
- creatinine clearance ≥30 ml/min (monotherapy), serum creatinine ≤1.5 mg/dL (≤132.6 µmol/L) or creatinine clearance ≥60 ml/min (combination therapy);
- creatine phosphokinase ≤2.5 x ULN;
- haemoglobin ≥9 g/dL.

Additional special warnings and precautions for use of trabectedin include: hepatic impairment; renal impairment; neutropenia; thrombocytopenia; nausea; vomiting; rhabdomyolysis; severe creatine phosphokinase elevations (>5 x ULN); liver function test abnormalities; and injection site reactions.[35]

The most common adverse effects associated with trabectedin (reported by at least 1 out of 10 patients) are: neutropenia; leucopoenia; anaemia; thrombocytopenia; anorexia; nausea; vomiting;

constipation; stomatitis; diarrhoea; hyperbilirubinaemia; increase in alanine aminotransferase; increase in aspartate aminotransferase; increase in blood alkaline phosphatase; PPE syndrome; alopecia; fatigue; asthenia; mucosal inflammation; and pyrexia.[35]

2.5.5 Gemcitabine (Gemzar®; Eli Lilly and Company Limited)

Gemcitabine is an analogue of the nucleoside deoxycytidine; in cells, nucleosides are modified enzymatically to produce nucleotides, which are the building blocks of RNA and DNA. As a nucleoside analogue, gemcitabine is a prodrug and, as such, once transported into a cell undergoes modification to produce the active form.[36] The activated form of gemcitabine replaces one of the nucleosides essential for DNA replication. Incorporation of the modified form of gemcitabine onto the growing DNA strand blocks further DNA synthesis and leads to apoptosis (cell death).[36]

Gemcitabine is licensed for the treatment of patients with locally advanced or metastatic epithelial ovarian carcinoma, in combination with carboplatin, in patients with relapsed disease after a recurrence-free interval of at least 6 months after platinum-based, first-line therapy.[37] Gemcitabine in combination with carboplatin for the treatment of recurrent ovarian cancer has not as yet been evaluated by NICE as part of the Single Technology Appraisal (STA) process. When used as a treatment for recurrent ovarian cancer, it is recommended that gemcitabine be administered at a dose of 1,000 mg/m^2 as a 30-minute intravenous infusion on days 1 and 8 of each 21-day cycle.[37] Carboplatin should be administered after gemcitabine on day 1 of the cycle, and at a dose consistent with a target area under curve (AUC) of 4.0 mg/ml/min. Dosage reduction with each cycle or within a cycle may be applied based on the grade of toxicity experienced by the patient.[37]

Gemcitabine is contraindicated in people who are hypersensitive to the active substance or to any of the excipients and in those who are breast feeding.[37] Prolongation of the infusion time of gemcitabine and increased dosing frequency have been shown to increase toxicity.[37] Additional special warnings and precautions for use of gemcitabine include haematological toxicity, hepatic insufficiency, concomitant radiotherapy, use with concomitant live vaccinations (e.g., yellow fever), risk of cardiac and/or vascular disorders, pulmonary effects, renal effects, and effects on sodium levels.

The most common adverse effects (reported by at least 1 out of 10 patients) associated with gemcitabine treatment are: leucopoenia; bone-marrow suppression (typically mild to moderate); thrombocytopenia; anaemia; dyspnoea (usually mild and passes rapidly without treatment); vomiting; nausea; elevation of liver transaminases and alkaline phosphatase; allergic skin rash; haematuria; mild proteinuria; influenza-like symptoms; and oedema/peripheral oedema.[37]

3 DEFINITION OF THE DECISION PROBLEM

3.1 Decision problem

3.1.1 Population including subgroups

The population of interest is people with ovarian cancer that has recurred after first-line (or subsequent) platinum-based chemotherapy or that is refractory to platinum-based chemotherapy.

Subgroups of particular interest are:

- people with platinum-sensitive recurrent ovarian cancer (i.e., relapse at 6 months or more after completion of initial platinum-based chemotherapy), which will be divided further, evidence permitting, into those with partial (i.e., relapse within 6–12 months) and those with full platinum sensitivity (i.e., relapse at 12 months of more);
- people with platinum-resistant (i.e., relapse within 6 months of completion of initial platinum-based chemotherapy) or platinum-refractory (i.e., disease that does not respond to initial platinum-based chemotherapy) recurrent ovarian cancer;
- those who are allergic to platinum-based treatment.

3.1.2 Interventions

The technology assessment report considers five interventions used within their licensed indication:

- paclitaxel alone or in combination with platinum chemotherapy;
- pegylated liposomal doxorubicin hydrochloride (PLDH) alone or in combination with platinum chemotherapy;
- gemcitabine in combination with carboplatin;
- trabectedin in combination with PLDH;
- topotecan.

As per the final protocol,[38] the clinical and cost-effectiveness of the five interventions of interest have been evaluated in the pre-specified subgroups listed in Section 3.1.1. Interventions of interest for the individual subgroups are presented in Table 14.

Table 14. Interventions of interest by population

Population	Interventions of interest
Platinum-sensitive	• Paclitaxel alone or in combination with platinum chemotherapy; • PLDH alone or in combination with platinum chemotherapy; • Gemcitabine in combination with carboplatin; • Trabectedin in combination with PLDH; • Topotecan.
Platinum-resistant or platinum refractory	• Paclitaxel alone or in combination with platinum chemotherapy; • PLDH; • Topotecan.
People who are allergic to platinum-based compounds	• Paclitaxel; • PLDH; • Trabectedin in combination with PLDH; • Topotecan.
Abbreviation used in table: PLDH, pegylated liposomal doxorubicin hydrochloride.	

3.1.3 Relevant comparators

As per the final protocol,[38] the relevant comparators have been evaluated based on the pre-specified subgroups listed in Section 3.1.1 Comparators of interest listed by individual subgroup are presented in Table 15.

Table 15. Comparators of interest by population

Population	Comparators of interest
Platinum-sensitive	• Interventions listed in Section 3.1.2 in comparison with each other; • Single-agent platinum chemotherapy.
Platinum-resistant or platinum refractory	• Interventions listed in Section 3.1.2 in comparison with each other; • Etoposide alone or in combination with platinum chemotherapy; • Best supportive care
People who are allergic to platinum-based compounds	• Interventions listed in Section 3.1.2 in comparison with each other; • Etoposide; • Best supportive care.

In the final protocol, bevacizumab in platinum-containing chemotherapy was listed as a potential comparator of interest for platinum-sensitive patients subject to appraisal by the National Institute for Health and Care Excellence (NICE).[38] Subsequent to finalisation of the protocol, the outcome of the NICE Single Technology Appraisal (STA) was not to recommend bevacizumab in combination with

gemcitabine and carboplatin for the treatment of first recurrence of platinum-sensitive ovarian cancer.[15] Therefore, bevacizumab in platinum-containing chemotherapy has not been evaluated as a comparator in this group of patients.

3.1.4 Outcomes

The outcomes of interest considered for this review included:

- overall survival (OS);
- progression-free survival (PFS);
- overall response rate (ORR);
- adverse effects of treatment;
- health-related quality of life (HRQoL).

In addition to PFS, although not listed in the final protocol, time to progression (TTP) was also analysed in the evaluation of clinical effectiveness.

3.2 Overall aims and objectives of assessment

The purpose of this report is to assess the clinical and cost-effectiveness of paclitaxel (monotherapy or in combination with platinum-based chemotherapy), PLDH (monotherapy or in combination with platinum-based chemotherapy), gemcitabine in combination with carboplatin, trabectedin in combination with PLDH, and topotecan as a monotherapy within their licensed indications for the treatment of advanced ovarian cancer that has relapsed after first-line treatment with a platinum-based regimen.

4 ASSESSMENT OF CLINICAL EFFECTIVENESS

4.1 Methods for reviewing effectiveness

Evidence for the clinical effectiveness of topotecan, pegylated liposomal doxorubicin hydrochloride (PLDH), paclitaxel, trabectedin and gemcitabine was assessed by conducting a systematic review of published research evidence. The review was undertaken following the general principles published by the Centre for Reviews and Dissemination (CRD).[39]

4.1.1 Identification of studies

The literature search for this review was designed to update and expand the systematic search carried out in Technology Appraisal 91 (TA91), which evaluated the clinical and cost effectiveness of topotecan, PLDH, and paclitaxel.[13] Medical Subject Headings (MeSH) and text terms for ovarian cancer, topotecan, PLDH, and paclitaxel were taken from the search strategy presented in TA91, and text terms added for the interventions trabectedin and gemcitabine. To ensure capture of all potentially relevant studies to inform a network meta-analysis (NMA), the decision was taken not to restrict the start date of the update search to the end date of the search (2004) reported in TA91.

As a result of the large number of studies retrieved from the scoping search, the decision was taken to implement search filters for randomised controlled trials (RCTs). Filters developed and validated by Scottish Intercollegiate Guidelines Network were used.[40] The identified RCTs facilitated construction of three distinct networks for the outcomes of overall survival (OS) and progression-free survival (PFS) for both the platinum-sensitive (two networks) and platinum-resistant/refractory (1 network) subgroups. In an attempt to identify a study to link the discrete networks for the platinum-sensitive subgroup, the retrieved abstracts were re-examined to consider interventions outside the scope of this review. Due to time constraints, the decision was taken not to search for non-randomised trials. Bibliographies of previous reviews and retrieved articles were searched for additional studies. Clinical trial registries were also searched to identify planned, ongoing and finalised clinical trials of interest. In addition, clinical experts were contacted with a request for information on any additional studies of which they had knowledge. The manufacturers' submissions (MSs) were assessed for unpublished data. Although the protocol stipulates that the Index to Scientific and Technical Proceedings would be searched to identify relevant conference proceedings, due to time constraints this was not undertaken. However, based on the conference abstracts retrieved from the search of the pre-specified electronic databases, the Technology Assessment Group (TAG) considers it likely that the key conference abstracts have been identified. Conference abstracts that were reviewed and found not to report additional results to those presented in the relevant full publication were excluded.

Electronic databases were initially searched on 18 January 2013 and results uploaded into Reference Manager Version 11.0 and deduplicated. An update search was carried out on 23 May 2013. No papers or abstracts published after this date were included in the review. Full details of the strategies are presented in Appendix 1.

Titles and abstracts returned by the search strategy were examined independently by two researchers (SB and TK) and screened for possible inclusion. Disagreements were resolved by discussion, or involvement of a third reviewer (SJE) in cases where consensus could not be achieved. Full texts of potentially relevant studies were ordered. Full publications were assessed independently by two reviewers (SB and TK/AS) for inclusion or exclusion against prespecified criteria, with disagreements resolved by discussion or input from a third reviewer when consensus could not be achieved.

4.1.2 Inclusion and exclusion criteria

For the review of clinical effectiveness, only RCTs were considered for inclusion in the review. Systematic reviews and non-randomised studies were excluded, as were studies that considered drugs administered as 'maintenance therapy' following directly on from first-line therapy without evidence of disease progression. Inclusion criteria were based on the decision problem outlined in Section 3.1 (presented as a whole in Table 16). No restrictions were imposed on language or date of publication. Reference lists of identified systematic reviews were used as a source of potential additional RCTs, as well as a resource to compare studies retrieved from the systematic literature search.

As in TA91,[13] second-line chemotherapy was defined as the second chemotherapy regimen administered either as a result of relapse after first-line therapy or immediately following on from first-line therapy in patients with progressive or stable disease. The definition applied in cases where the second-line regimen comprised the same treatments as the first-line regimen.

For the purposes of this review, based on expert opinion, supportive care was defined as treatment for recurrent ovarian cancer that does not have anti-tumour mode of action.

Table 16. Inclusion criteria (based on the decision problem) for studies evaluating clinical effectiveness

	Inclusion criteria
Study design	Randomised controlled trials
Population	People with ovarian cancer that has recurred after first-line (or subsequent) platinum-based chemotherapy or is refractory to platinum-based chemotherapy
Interventions	For people with platinum-sensitive ovarian cancer: • paclitaxel as monotherapy or in combination with platinum-based chemotherapy; • PLDH as monotherapy or in combination with platinum-based chemotherapy;

	• gemcitabine in combination with carboplatin; • trabectedin in combination with PLDH; • topotecan monotherapy. For people with platinum-resistant or platinum-refractory ovarian cancer: • paclitaxel as monotherapy or in combination with platinum-based chemotherapy; • PLDH monotherapy; • topotecan monotherapy. For people with ovarian cancer who are allergic to platinum-based chemotherapy: • paclitaxel monotherapy; • PLDH monotherapy; • trabectedin in combination with PLDH; • topotecan monotherapy.
Comparators	For people with platinum-sensitive ovarian cancer: • the interventions listed above in comparison with each other; • bevacizumab in combination with platinum-containing chemotherapy (subject to NICE appraisal); • single-agent platinum chemotherapy. For people with platinum-resistant or platinum-refractory ovarian cancer: • the interventions listed above in comparison with each other; • etoposide as monotherapy or in combination with platinum-based chemotherapy; • best supportive care. For people with ovarian cancer who are allergic to platinum-based chemotherapy: • the interventions listed above in comparison with each other; • etoposide monotherapy; • best supportive care.
Abbreviations used in table: NICE, National Institute for Health and Clinical Excellence; PLDH, pegylated liposomal doxorubicin hydrochloride.	

4.1.3 Data abstraction strategy

Data pertaining to study design, methodology, baseline characteristics, and clinical outcomes efficacy were extracted by two reviewers (TK/AS) into a standardised data extraction form and validated by a second (SB). Discrepancies were resolved by discussion when necessary. Authors of reports published as meeting abstracts only, where insufficient methodological details were reported to allow critical appraisal of study quality were contacted with a request for additional information. If no additional information was obtained, the studies were excluded. Data extraction forms for the included studies are provided in Appendix 2.

4.1.4 Critical appraisal strategy

The quality of the clinical effectiveness data was assessed by two independent reviewers (TK and SB) and checked for agreement. The study quality was assessed according to recommendations by the

NHS Centre for Reviews and Dissemination[39] and Cochrane Handbook for Systematic Reviews of Interventions[41] and recorded using the Cochrane Risk of Bias Tool.[41]

4.1.5 Methods of data synthesis

Details of results on clinical effectiveness and quality assessment for each included study are presented in structured tables and as a narrative summary. The possible effects of study quality on the clinical effectiveness data and review findings are discussed. The 16 RCTs identified evaluated 14 different pair-wise comparisons. Therefore, there were insufficient data for most comparisons to carry out a standard pair-wise meta-analysis. However, the Technology Assessment Group (TAG) determined that the data identified were sufficiently homogenous to investigate comparative effectiveness of interventions via a network meta-analysis (NMA). The methods used for the NMA followed the guidance described in the NICE Decisions Support Unit's (DSU's) Technical Support Documents (TSDs) for Evidence Synthesis. In essence, an NMA assumes that each trial included in the network could have potentially included all treatments of interest but that some of these treatments are missing completely at random (MCAR). To illustrate this further, in a simple indirect comparison of three treatments A, B and C, the trials of A versus B and of B versus C are assumed to have been potentially trials of A versus B versus C but where one arm from each trial is MCAR. In this example, an estimate of the relative treatment effect of A versus C can be inferred using treatment B as a common comparator.

The TAG conducted an NMA for each network using a Bayesian Markov Chain Monte Carlo (MCMC) simulation in WinBUGS. The following were implemented for each analysis:

- Uniform priors (also called "flat" priors) were used;
- All outcomes were considered independent. For example, while OS and PFS might be correlated in advanced ovarian cancer, the degree of correlation is unlikely to be derived from summary trial estimates provided in published papers.[42] As such, in the absence of individual patient data (IPD), the TAG took the pragmatic approach of assuming all efficacy and safety outcomes were independent;
- Results for all efficacy outcomes analysed were based on 50,000 iterations after a "burn in" of 30,000 iterations. For safety outcomes all analyses had a "burn in" of 30,000 iterations, with results based on 100,000 iterations;
- Summary effect estimates for OS and PFS were HRs, while ORR and all safety outcomes used ORs as summary effect estimates;
- As a result of disparity in HRs reported in the identified trials, in terms of unadjusted HRs versus adjusted HRs, together with variation in adjustment factors, for consistency the TAG used only unadjusted HRs in the NMA;
- Any results taken forward into the economic model (Section 5.2.7) used the posterior sampling to retain the correlation between parameter estimates caused by their joint estimation from a single dataset.[43]

However, the ability of the TAG to conduct NMAs was limited by the low number of trials identified (typically only one trial per treatment comparison). The constraints imposed by the limited number of trials available for analysis were:

- Implementation of a fixed effects model for all analyses. While it was planned that fixed and random effects models would be explored and the model with the lowest deviance information criterion (DIC) selected as the preferred dataset the sparse number of trials available necessitated the use of a fixed effects model. Using an uninformed prior for the between trial heterogeneity in a random effects model "overwhelmed" the influence of the available data for analysis with the posterior estimation of tau approximating the prior value used. Identification of an alternative source for the prior, e.g. from an existing systematic review, was explored but no suitable review was identified.[43] As such, despite the potential clinical heterogeneity from two studies. which are discussed in detail later (Section 4.2.1.4), the TAG made the pragmatic decision to use a fixed effects model in the absence of any reliable estimate available;
- Disconnected networks identified for each outcome assessed. The trials identified in the clinical systematic review were unable to populate a single network for any of the outcomes assessed. A wider selection of treatments were assessed, as the systematic review was conducted in such a way as to identify all trials with at least one intervention of interest present, but unfortunately this did not uncover trials that could link the disconnected networks together.[44] In addition, the TAG's clinical advisors did not consider any of the suggested assumptions to link the disconnected networks together to have face validity;
- Heterogeneity and inconsistency. The networks constructed, typically "linear" in nature, and the sparse number of trials available, typically on one per pairwise comparison, prevented the TAG from exploring any potential heterogeneity or inconsistency in each analysis.

The potential impact of these limitations is discussed where the results are reported.

4.1.6 Manufacturer's submissions

All data submitted by the manufacturers were assessed. Data presented that met the inclusion criteria, and had not been identified in another published source, were extracted and quality assessed in accordance with the procedures outlined in this protocol. Economic evaluation included in the manufacturer(s)'s submission(s) that complied with NICE's advice on presentation, was assessed for clinical validity, reasonableness of assumptions and appropriateness of the data used in the economic model (Section 5.1.3).

4.1.7 Interpreting the results from the clinical trials

4.1.7.1 Clinical effectiveness

For the outcomes of OS and PFS/TTP, which are time to event outcomes, most trials identified evaluated comparative clinical effectiveness using a hazard ratio (HR), which is the ratio of the hazard (e.g., death or progression) rate between two groups. Typically, a reported HR of <1 indicates that the event of interest is occurring more slowly in the experimental group compared with the control group. In some trials identified, HR >1 (i.e., event occurs more frequently in the experimental group) is reported to favour a treatment. In these instances, the event recorded is not the hazard but the opposite

event, that is, survival or no progression over time. For the purposes of this review, PFS and TTP have been reported and evaluated under the outcome heading of PFS. Many trials identified also assess the extent to which a tumour shrinks compared with initial size, which is the response rate. Response rate is a dichotomous event (i.e., patients either respond or do not respond) and is reported as the proportion of patients achieving a response according to prespecified criteria.

4.1.7.2 Adverse effects

Many trials evaluating chemotherapeutic treatments categorise the severity of adverse effects based on criteria developed by the National Cancer Institute (NCI), one aim of which was to standardise reporting of adverse effects.[45] According to the NCI-Common Toxicity Criteria (CTC), adverse effects are graded from 0 to 5, with increasing grade indicating more severe adverse effect (Table 17). The NCI-CTC also provides a detailed list of adverse effects commonly occurring in oncology trials, together with clinical descriptions on grade of severity that are specific for each adverse reaction.

Table 17. National Cancer Institute-Common Toxicity Criteria for adverse effects

Grade	Degree of severity
1	Mild, with no or mild symptoms; no interventions required
2	Moderate; minimal intervention indicated; some limitation of activities
3	Severe but not life-threatening; hospitalization required; limitation of patient's ability to care for him/herself
4	Life-threatening; urgent intervention required
5	Death related to adverse event

4.2 Results

The RCTs meeting the inclusion criteria are discussed in the sections that follow. Initially, a summary of the quantity and quality of the evidence is provided, together with a table presenting an overview of the included trials. Additionally, a more detailed narrative description, together with an overview of trial quality, for each included trial is presented, including those trials previously identified in TA91.[13] A narrative description of population baseline characteristics and potential imbalances are discussed for each trial. Due to the number of trials identified, baseline characteristics are not tabulated within the main body of the report but are provided within the data abstraction forms in Appendix 2. Instead, baseline characteristics for key prognostic factors in recurrent ovarian cancer (age, number of prior lines of chemotherapy, interval since last chemotherapy, and performance score) are presented for included trials in a summary table (Table 20).

Clinical effectiveness results are reported by outcome (OS, PFS, ORR, quality of life [QoL], and adverse effects). Within the efficacy outcomes of OS, PFS, and ORR, results are presented separately based on platinum-sensitivity. Results by population are ordered: platinum sensitive, which is broken down further to fully platinum-sensitive (FPS) and partially platinum-sensitive (PPS), where data are

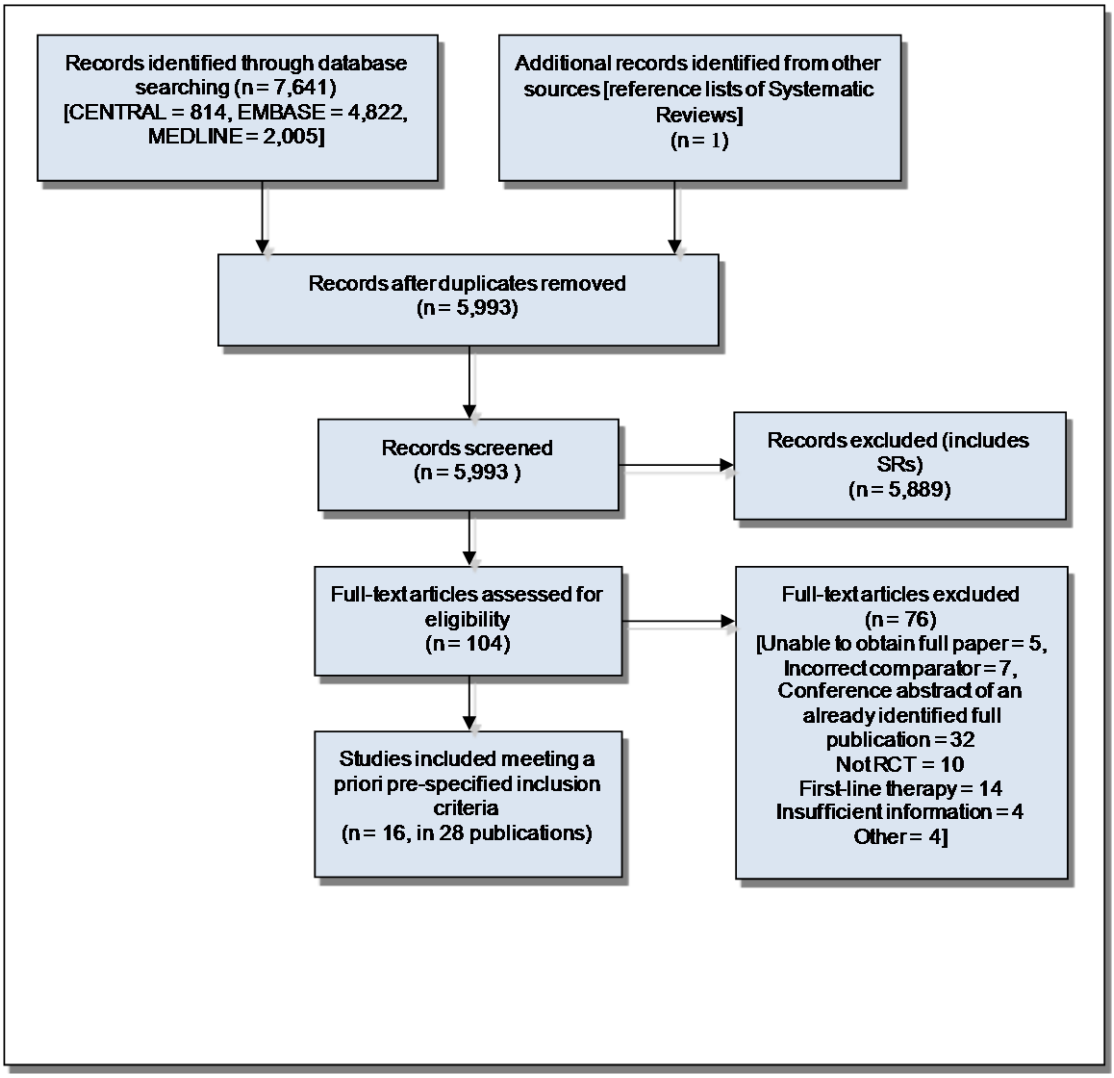
available; platinum resistant/refractory (PRR); and the overall population (where trial includes patients with platinum-sensitive or PRR disease). Results for QoL and adverse effects are presented for the overall population, irrespective of sensitivity to platinum. Within the outcome, results are initially presented separately for each trial reporting data, and are supplemented with the findings from the network-meta analysis (NMA), including a description of assumptions made and potential bias across the trials included in the network.

4.2.1 Quantity and quality of research available

The searches retrieved a total of 5,993 records (post deduplication) that were of possible relevance to the review (Figure 3). These were screened and 104 full references were ordered. Of these 5 had to be cancelled because they were unobtainable. Of the full references evaluated, 28 papers describing 16 studies were included in the review.

The full list of studies included in the review is given in Table 18, while a list of the papers screened but subsequently excluded (with reasons for exclusion) from the review is presented in Appendix 3.

Figure 3. PRISMA flow diagram for studies included and excluded from the clinical effectiveness review



4.2.1.1 Included studies

Sixteen randomised controlled trials (RCTs) reported in 15 primary publications, with 13 accompanying publications, were included in the review. One RCT from TA91[13] was included that was identified in the literature search as only an abstract and the results of which have not been published in full elsewhere (referred to hereafter as trial 30–57).[46] An overview of the identified trials is provided in Table 18. Of the 16 RCTs identified, 5 evaluated the intervention and comparator within their licensed indication, and dose and route of administration.[13;21;47-49] The remaining 11 RCTs evaluated the intervention or comparator outside the parameters specified in the licence, in terms of, for example, dose or route of administration. No RCT identified evaluated interventions specifically in a population who were allergic or intolerant to platinum-based treatments. Of the 9 RCTs identified in TA91, only one RCT (Cantu *et al.*[50]) has been excluded from this update. Cantu *et al.*[50] evaluated paclitaxel alone versus a combination of cyclophosphamide, doxorubicin and cisplatin (CAP). Doxorubicin administered in the trial is the non-pegylated formulation and is outside the scope of this review, which specifies PLDH as the intervention of interest.

Two manufacturers (Eli Lilly and Company Limited [gemcitabine]; PharmaMar [trabectedin]) submitted clinical evidence for consideration for this MTA.

Eli Lilly (gemcitabine) did not carry out a systematic review of the literature; instead, the manufacturer reported clinical data from three studies:

- a phase III study comparing gemcitabine plus carboplatin with carboplatin monotherapy in patients with platinum sensitive, recurrent ovarian cancer (study "JHQJ");
- a single arm, phase II study of gemcitabine plus carboplatin in platinum sensitive, recurrent ovarian cancer (study "JHRW");
- a single arm, phase I/II dose finding study of gemcitabine plus carboplatin in platinum sensitive, recurrent ovarian cancer (study "SO026").

The data provided by the manufacturer for JHQJ, the phase III study comparing gemcitabine plus carboplatin with carboplatin monotherapy, are reported in the full publication of the trial (Pfisterer *et al.*[49]), which was identified and included as part of the systematic review of the literature on clinical effectiveness (Section 4.2).

The two additional studies (JHRW and SO026) are single arm trials and as such do not meet the criteria for inclusion in the review (Section 4.1.2).

PharmaMar (trabectedin) carried out a systematic search of the literature. Specifically, the manufacturer updated the review carried out for the Single Technology Appraisal (STA) TA222,[19] which evaluated the use of trabectedin plus PLDH in the treatment of platinum-sensitive ovarian cancer. The manufacturer searched the following databases: EMBASE; MEDLINE; MEDLINE (R) In-Process; and the Cochrane Library. Studies were included if:

- the study type was an RCT;
- the population of interest was relapsed platinum-sensitive ovarian cancer;
- outcome data for PFS, OS or adverse events were included;
- the interventions and comparators of interest included at least one of trabectedin, PLDH, paclitaxel, topotecan, etoposide, or best supportive care.

The manufacturer limited the comparators within search to the comparators outlined in the NICE pathway for patients who are unsuitable for platinum-based chemotherapy; this represents the target population for the manufacturer's submission.

The manufacturer identified two additional relevant studies relating to OVA-301,[30] which were identified as part of the review of the clinical effectiveness literature and are discussed in a subsequent section (Section 4.2.1.1).

Table 18. Summary of studies included in the review of the clinical effectiveness literature

Study and principal citation	Trial design	Population (N)	Platinum-free interval	Randomised treatments		Supplementary publications
				Intervention	Comparator	
Both intervention and comparator used within licensed indication and at licensed dose						
ten Bokkel Huinink *et al*. (1997)[21]	Phase III, multicentre, open label RCT	235	Disease that recurred or progressed after first-line platinum based therapy (no minimum PFI specified)	Topotecan (1.5 mg/m^2 as a 30 min IV infusion) for 5 consecutive days every 21 days	Paclitaxel (175 mg/m^2 as a 3 hr IV infusion) every 21 days	ten Bokkel Huinink *et al*. (2004)[51] Gore *et al*.[52]
Gordon *et al*. (2001)[48]	Phase III RCT, multicentre, open label	474	Disease that recurred after or failed first-line platinum-based chemotherapy (no minimum PFI specified)	PLDH (50 mg/m^2 as a 1 hr IV infusion) every 28 days	Topotecan (1.5 mg/m^2 as a 30 min infusion) for 5 consecutive days every 21 days	Gordon *et al*. (2004)[53]
Trial 30–57 Data taken from TA91[13]	Phase III, multicentre, open-label RCT	216	Disease that recurred after or failed one platinum-based first-line regimen (no minimum PFI specified)	PLDH (50 mg/m^2) every 28 days	Paclitaxel (175 mg/m^2) every 21 days	One conference abstract (O'Byrne *et al*.[46])
Gonzalez Martin *et al*.[47]	Phase II, 'pick the winner' design, multicentre RCT Level of masking unclear	81	Progression >6 months after completion of platinum-based chemotherapy	Paclitaxel (175 mg/m^2 as a 3 hr IV infusion) plus carboplatin (AUC 5) every 3 weeks	Carboplatin alone (AUC 5) every three weeks	None identified
Pfisterer *et al*.[49]	Phase III, multicentre, international, open label RCT	356	Disease recurrence at least 6 months after completion of first-line, platinum-based therapy	Gemcitabine (1,000 mg/m^2) plus carboplatin (AUC 4) every 21 days	Carboplatin alone (AUC 5) every 21 days	None identified
Intervention or comparator used outside licensed indication or dose						
Gore *et al*.[24]	Multicentre, open label RCT (phase not clear)	266	Disease progression on first-line platinum-based chemotherapy or relapse within 12 months of completion of first-line platinum-based treatment	Oral topotecan (2.3 mg/m^2) given daily	Intravenous topotecan (1.5 mg/m^2) for 5 consecutive days every 21 days	None identified

Sehouli *et al*.[23]	Phase II, multicentre RCT	194	Disease that had recurred after radical surgery and at least one platinum-based chemotherapy with recurrence <6 months after cessation of platinum-based treatment	Topotecan (4.0 mg/m^2 as a 30 min IV infusion on days 1, 8, and 15) weekly every 28 days	Topotecan (1.25 mg/m^2 as a 30 min IV infusion) for 5 consecutive days every 21 days	None identified
Alberts *et al*.[28]	Phase II RCT Level of masking unclear	61	Disease that recurred within 6–24 months of completing platinum-based chemotherapy	PLDH (30 mg/m^2 as a 1 hr IV infusion) plus carboplatin (AUC 5) every 4 weeks	Carboplatin alone (AUC 5) every 4 weeks	Markman *et al*.[54]
Bafaloukos *et al*.[29]	Phase II RCT Level of masking unclear	204	Recurrence >6 months after completion of platinum-based chemotherapy	PLDH (45 mg/m^2 as a 90 min IV infusion) plus carboplatin (AUC 5) every 4 weeks	Paclitaxel (175 mg/m^2 as a 3 hr IV infusion) plus carboplatin (AUC 5) every 21 days	None identified
CALYPSO Pujade-Lauraine *et al*.[31]	Phase III, non-inferiority, multicentre, international, open label RCT	976	Disease that had recurred/progressed longer than 6 months after first- or second-line platinum-based chemotherapy	PLDH (30 mg/m^2 as an IV infusion) plus carboplatin (AUC 5) every 28 days	Paclitaxel (175 mg/m^2 as an IV infusion) plus carboplatin (AUC 5) every 21 days	Wagner *et al*.[55] Gladieff *et al*.[56] Kurtz *et al*. 2011[57] Brundage *et al*.[58]
Rosenberg *et al*. [59]	Multicentre RCT (phase not clear)	208	Disease that recurred or progressed after first-line platinum-based therapy (no minimum PFI specified)	Paclitaxel (67 mg/m^2) weekly	Paclitaxel (200 mg/m^2) every 21 days	None identified
ICON4/AGO-OVAR-2.2 Parmar *et al*.[60]	Phase III, multicentre, international RCT (3 parallel RCTs, each with its own protocol)	802	Disease that had been treatment free for >6 months	Paclitaxel (175 or 185 mg/m^2) plus carboplatin or cisplatin every 21 days	Carboplatin or cisplatin alone every 21 days	None identified
CARTAXHY Lortholary *et al*.[61]	Phase II, multicentre, open-label 3-armed RCT[a]	165	Disease progression during or relapse within 6 months of completing platinum-based chemotherapy	Paclitaxel (80 mg/m^2 on days 1, 8, and 15) weekly plus carboplatin (AUC 5) every 28 days	Paclitaxel (80 mg/m^2 on days 1, 8, and 15) weekly every 28 days	None identified

Piccart *et al*.[62]	Phase II, open label, multicentre RCT	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 hr infusion) every 21 days	Oxaliplatin (130 mg/m^2 as a 2 hr infusion) every 21 days	None identified
OVA-301 Monk *et al*. (2010)[30]	Phase III, open label, multicentre, international RCT	672	Disease that was persistent, recurrent or progressing on current treatment	Trabectedin (1.1 mg/m^2 as a 3 hr infusion) plus PLDH (30 mg/m^2 as a 90 min infusion) every 21 days	PLDH (50 mg/m^2 as a 90 min infusion) every 28 days	Monk *et al*. (2012)[63] Poveda *et al*.[64] Kaye *et al*. Krasner *et al*.[65]
Omura *et al*.[66]	Phase III, multicentre RCT	372	Histologically confirmed ovarian cancer treated with no more than one prior platinum-based regimen and no prior taxane	Paclitaxel 250 mg/m^2 (24 hour infusion) every 21 days (patients in this group also randomized to filgrastim 5 or 10 µg/kg subcutaneously)	Paclitaxel 175 mg/m^2 (24 hour infusion) every 21 days	None identified

[a] The third arm of the trial evaluated paclitaxel weekly in combination with topotecan. Based on the definitions set out in the systematic review, patients included in the trial are classed as refractory or resistant to platinum. As per the protocol, topotecan in combination with another chemotherapeutic agent is neither an intervention nor a comparator of interest for this group of patients. The regimen and results for this group are not discussed in detail.

Abbreviations used in table: AUC, area under curve; IV, intravenous; PLDH, pegylated liposomal doxorubicin hydrochloride; RCT, randomised controlled trial.

4.2.1.2 Study characteristics

Pegylated liposomal doxorubicin hydrochloride plus carboplatin versus paclitaxel plus carboplatin

Two RCTs (Bafaloukos *et al*.[29] and Pujade-Lauraine *et al*.[31]) were identified for this comparison. The RCTs were of similar design, but one was a phase II RCT (Bafaloukos *et al*.[29]) and one a phase III RCT (Pujade-Lauraine *et al*.[31]). In addition, the dose of PLDH evaluated differed between the trials, with 45 mg/m^2 and 30 mg/m^2 used by Bafaloukos *et al*.[29] and Pujade-Lauraine *et al*.[31], respectively. The licence for PLDH does not recommend a dose of PLDH for use in combination with platinum-based chemotherapy. Bafaloukos *et al*.[29] note in the discussion that, at the time of initiation of the trial, limited information was available on the optimal dose for PLDH in combination with carboplatin. As highlighted by Bafaloukos *et al*.[29], retrospective analyses suggest that lower dose intensities of PLDH (30–40 mg/m^2) are as clinically effective but with improved tolerance. Clinical experts have fed back that, in UK clinical practice, PLDH would most likely be used at a dose of 30 mg/m^2 when combined with carboplatin.

Bafaloukos *et al*.[29] report the results of a randomised study in which 204 patients with histologically confirmed recurrent ovarian cancer were randomised to either PLDH (45 mg/m^2) plus carboplatin (AUC 5) every 28 days or paclitaxel (175 mg/m^2) plus carboplatin (AUC 5) every 21 days. Patients recruited had disease that had recurred at least 6 months after platinum-based chemotherapy, that is, women with platinum-sensitive disease. Women with only elevated CA125 (≥twice the upper limit of normal) as an indicator of disease were also included.

The primary aim of the study was to evaluate the comparative clinical effectiveness of the two treatment regimens in terms of response rate and toxicity in women with platinum-sensitive ovarian cancer relapsing after first-line platinum-based therapy. OS and time-to-progression (TTP) were analysed as secondary outcomes. Subsequent to randomisation, 15 patients were found to be ineligible (reasons provided). Therefore, analyses presented are based on data from 189 eligible patients (96 in the paclitaxel plus carboplatin group vs 93 in the PLDH plus carboplatin group). The reported power calculation indicates that 201 patients were needed to identify a 20% difference in response rate between the groups. The study might have been underpowered to detect a difference between groups in response rate.

Randomisation (1:1) was performed at the central HeCOG Data Office in Athens, but details on the method of randomisation were not reported. Stratification criteria were not applied at randomisation. Tumour response was evaluated using World Health Organization (WHO) criteria for patients with measurable disease and CA125 based on Rustin's criteria or patients without measurable disease. Median duration of follow-up was reported as 43.6 months (95% CI 0.1 to 74.8 months), but the range of follow-up was not reported either for the full trial population or the individual treatment groups.

All patients received standard premedication of dexamethasone, diphenhydramine and ranitidine prior to paclitaxel. In the group receiving paclitaxel, premedication was administered twice, orally 12 hours before and again intravenously 30 min before paclitaxel infusion. In the group receiving PLDH, premedication was administered only intravenously prior to PLDH infusion. Six cycles of chemotherapy were administered, unless disease progression or unacceptable toxicity occurred. A maximum of 2 weeks delay was allowed for toxicity and treatment was discontinued if longer toxicity-related delays occurred. For grade 3 and 4 thrombocytopenia, a 25% and a 50% dose reduction, respectively, was recommended for all drugs.

A median of 6 cycles of paclitaxel plus carboplatin (range 1–9) and 6 cycles of PLDH plus carboplatin were administered. Most patients in each group completed the planned treatment (68% in paclitaxel plus carboplatin and 70% in PLDH plus carboplatin).

In the second RCT identified for this comparison, Pujade-Lauraine *et al*.[31] report the results of a randomised international, multicentre, open-label phase III non-inferiority trial (CALYPSO) in which 976 patients with platinum-sensitive (disease progression longer than 6 months after prior treatment) relapsed/recurrent ovarian cancer received a combination of PLDH plus carboplatin (N = 467) or carboplatin plus paclitaxel (N = 509). Prior treatment must have included a taxane and no more than two previous platinum-based regimens (i.e., patients had failed first or second-line treatment). Patients with measurable (according to RECIST criteria) and CA125 assessable (according to GCIG) criteria were eligible.

The primary publication presents results on PFS. Accompanying publications were identified that present results on mature OS data,[55] clinical effectiveness results in the subgroup of patients with PPS ovarian cancer (relapse between 6 and 12 months since receipt of last cycle of chemotherapy),[56] and QoL.[58]

The trial was of a non-inferiority design with the aim of determining whether PLDH (30 mg/m^2) plus carboplatin (AUC 5) every 4 weeks was non-inferior to the standard treatment of paclitaxel (175 mg/m^2) plus carboplatin every 3 weeks.[31] The goal was to evaluate the comparative effectiveness of the treatments in terms of efficacy and toxicity. The primary outcome of the trial was PFS, with OS, QoL and toxicity as prespecified secondary outcome measures. Determination of disease progression was based on RECIST and GCIG criteria modifications and included any of the following: occurrence (clinically or by imaging) of any new lesion; increase in measurable and/or non-measurable tumour defined by RECIST; CA125 elevation defined by GCIG criteria; health status deterioration attributable to disease; and death from any cause before progression was diagnosed. Assessments were independently reviewed. All patients were observed for at least 5 years from random assignment to assess OS.

Randomisation was in permuted blocks of 6 in a 1:1 ratio, and patients were stratified based on therapy-free interval from last chemotherapy (6–12 vs 12 months), measurable disease (yes vs no) and centre. Despite randomisation, an imbalance in treatment allocation was noted (467 randomised to PLDH plus carboplatin vs 509 randomised to paclitaxel plus carboplatin).

All patients received antiemetics, including a serotonin antagonist and corticosteroid. Patients randomly assigned to paclitaxel plus carboplatin received premedication to prevent hypersensitivity reactions. Dose delay and dose reduction were allowed for haematological and non-haematological toxicity. In the absence of unacceptable toxicity or disease progression, patients were treated for a total of 6 courses of therapy; if stable disease or partial response was achieved after 6 courses of therapy, patients were allowed to remain on therapy until progression.

To assert non-inferiority of PLDH plus carboplatin, it was estimated that a sample size of 898 evaluable patients (estimate of 745 progression) would be required.[31] The calculation was based on non-inferiority margin with an HR of 1.23 at 15 months or a 7.9% absolute difference at 12 months (90% power and a one-sided CI of 95%).

Median follow-up was 22 months; median follow-up in the individual treatment groups not reported.[31] The median number of cycles was 6 in each treatment group, with a range of cycles from 1 to 14 in the PLDH plus carboplatin and 1 to 12 in the paclitaxel plus carboplatin group. A significantly larger proportion of patients in the PLDH plus carboplatin group completed at least 6 cycles of treatment (85% vs 77%; $p < 0.001$).

Pegylated liposomal doxorubicin hydrochloride plus carboplatin versus carboplatin alone

Alberts *et al*.[28] reported the results of a randomised study in which 61 patients from the USA with recurrent stage III or IV epithelial or peritoneal ovarian carcinoma were randomised to pegylated liposomal doxorubicin hydrochloride (PLDH) (IV infusion of 30 mg/m^2) plus carboplatin (AUC 5) once every 4 weeks (31 patients) or carboplatin (AUC 5) alone once every 4 weeks (30 patients). A follow-up study reporting final OS results was also identified.[54]

To be eligible for enrolment, patients had to have histologically diagnosed Stage III or IV disease that was determined to be progressive based on RECIST or GCIG CA-125 criteria. Patients also had to have a progression-free and platinum-free interval of 6–24 months after first-line platinum-based chemotherapy, which indicates that the study focused on women with platinum-sensitive disease. Patients were excluded if Zubrod performance status was >1. Prior treatment with up to 12 courses of a non-platinum containing consolidation treatment during the 6–24 month platinum-free interval (PFI) was allowed on the proviso that treatment had been completed at least 28 days prior to registration.

The primary aim of the study was to evaluate the comparative clinical effectiveness of the two treatment regimens in terms of OS in women with platinum-sensitive ovarian cancer. PFS, confirmed complete response rate, and time to treatment failure were analysed as secondary outcomes. Objective response and disease progression were defined according to standard RECIST criteria.[67] GCIG CA125 progression criteria were also implemented in defining disease progression.[68]

Details on the method of randomisation were not reported, but randomisation was 1:1 to each group and was reported to be equal between the groups. Randomisation was stratified by disease measurability, number of disease sites, and serous histology. The power calculation reported indicates that the study had initially planned to recruit 900 patients over a period of 4.5 years. However, as a result of slow patient accrual, the study closed early with only 61 patients enrolled. Initially designed as a phase III RCT, results were reported as for a phase II RCT. Median duration of follow-up was reported as 22.4 months, but the range of follow-up was not reported either for the full trial population or the individual treatment groups. Markman *et al*.[54] reported a longer follow-up of the same trial. However, the duration of follow-up in this study is unclear.

Each treatment was given until progression, intolerable toxicity, or a request from either the clinician or the patient to be removed from the study. Dose modifications were allowed based on toxicity to PLDH. The maximum cumulative dose of PLDH was 600 mg/m^2. Any patient with a compromised left ventricular ejection fraction (<45% or decreases by a relative 20% from baseline) was removed from PLDH and continued on the carboplatin treatment. Carboplatin dose modifications were allowed for gastrointestinal and neurological toxicity. Patients with persistently greater than equal to grade 2 peripheral neuropathy, despite dose reduction, were permanently taken off carboplatin treatments. The median number of treatment cycles given was 7 (range 1–18) for patients in the PLDH plus carboplatin group and 6 (range 2–16) for those in the carboplatin alone group. No major protocol violations were reported.

Trabectedin plus PLDH versus PLDH alone

Monk *et al*. (2010)[30] report the results of an open-label, randomised multicentre (124 centres in 21 countries) phase III trial involving 672 women with recurrent ovarian cancer after failure of first-line platinum-based chemotherapy (OVA-301). Patients with platinum-resistant (PFI <6 months) or platinum-sensitive (PFI ≥6 months) ovarian cancer were eligible, but those who experienced progression during first-line therapy (platinum-refractory) were excluded. Measurable disease by RECIST criteria was also an inclusion criterion. Related publications identified were a follow-up study reporting mature OS analysis,[63] clinical efficacy results for the subgroup of patients with PPS,[64] and full results for QoL.[65]

The aim of OVA-301 was to compare the efficacy and safety of PLDH (30 mg/m^2) plus trabectedin (1.1 mg/m^2) every 21 days (N = 337) versus PLDH (50 mg/m^2) alone every 28 days (N = 335). The primary outcome was PFS, which was defined as time from randomisation to disease progression or death. Primary analysis of PFS was based on independent radiology review (radiological evaluation alone) by radiologists who were masked to treatment allocation. Secondary end points included OS, ORR (response maintained ≥4 weeks by RECIST), and duration of response (calculated from date of first documentation of response to date of PD or death from PD). QoL was a tertiary outcome and was evaluated using the EORTC QLQ-C30 and ovarian cancer-specific QLQ-OV28. All efficacy analyses were based on the ITT principle.

Randomisation was by a permuted block method (1:1 ratio) and patients were stratified by performance status (ECOG score 0 or 1 vs 2) and platinum sensitivity (sensitive vs resistant). After enrolment of 440 patients, and before central radiology review, the study was amended, changing the two primary efficacy end points, OS and PFS, to a single primary end point, PFS. OS became a secondary end point; the sample size remained unchanged. The sample size calculation indicated that 415 PFS events were required to test statistical difference between treatment groups with at least 90% power; it is reported that approximately 650 patients were to be randomised over 2 years.

Treatment was continued until disease progression or confirmation of CR and could be continued for two or more cycles beyond confirmed CR. A maximum of two dose reductions for each drug was allowed (in the trabectedin plus PLDH group, trabectedin could be reduced to 0.9 mg/m^2, and subsequently to 0.75 mg/m^2 and PLDH to 25 mg/m^2, then to 20 mg/m^2; in the PLDH group, PLDH could be reduced to 37.5 mg/m^2, and then to 28 mg/m^2). Median cumulative trabectedin dose was 5.6 mg/m^2 (range 1 to 23 mg/m^2). For PLDH, median cumulative PLDH dose was 154.4 mg/m^2 (range 15 to 630 mg/m^2) and 216 mg/m^2 (range 3 to 1,061 mg/m^2) when administered in combination with trabectedin and as a monotherapy, respectively. Incidence of dose reductions was similar between groups, whereas cycle delays were less frequent with PLDH alone than trabectedin plus PLDH.

Median duration of follow-up in the initial publication was not reported,[30] but median follow-up in the longer-term study was 47 months.[63]

The authors report that, despite stratification before randomisation, there was an imbalance between groups in mean baseline PFI that favoured PLDH alone (13.3 months with PLDH alone vs 10.6 months with trabectedin plus PLDH; p = 0.009). *Post hoc* hypothesis-generating analyses on the influence of PFI on OS were carried out (discussed in Section 4.2.2).

It should be noted that use of trabectedin plus PLDH as an intervention in patients with PRR is not covered by the scope of this review. Clinical effectiveness data for only platinum-sensitive patients are presented.

Pegylated liposomal doxorubicin hydrochloride versus topotecan

Gordon *et al*. (2001)[48] report the results of a phase III randomised study comparing PLDH versus topotecan in 474 women with histologically proven recurrent epithelial ovarian carcinoma that recurred after or did not respond to first-line platinum-based chemotherapy. The RCT was open-label in design and was carried out at multiple centres (104 sites) in the USA and Europe. Patients with either measurable or assessable disease were included, where measurable disease was defined as presence of bidimensionally measurable lesions with clearly defined margins based on imaging scans and assessable disease was defined as unidimensionally measurable lesions by imaging scan in conjunction with serum CA125 levels greater than 100 U/ml. A follow-up publication reported data on more mature OS, together with subgroup analyses based on platinum sensitivity.[53]

Patients were randomised to receive either PLDH 50 mg/m^2 as a 1-hour infusion every 28 days (239 patients) or topotecan 1.5 mg/m^2 daily for 5 consecutive days every 21 days (235 patients).[48] In the absence of disease progression, treatment in each group could be continued for up to 1 year. Treatment could also continue if the patient demonstrated sustained clinical benefit. Patients who discontinued treatment after 6 months (six cycles of PLDH, or eight cycles of topotecan) were considered protocol completed.

The study was described as randomised, but details on the method of randomisation were not reported. Patients were stratified for platinum sensitivity and for the presence or absence of bulky disease (tumour mass >5 cm). Patients were classified as platinum sensitive if they had a PFI of greater than 6 months after first-line platinum based chemotherapy and platinum refractory if they had stable disease, progressed during initial platinum-based therapy or relapsed within 6 months after completion of therapy. In the subsequent publication,[53] analyses for OS and PFS for the subgroups of patients with partially (PPS; PFI >6–≤12 months) and fully platinum sensitive (FPS; PFI >12 months) disease are presented. The authors report that the main outcome measures of efficacy were PFS and OS. Overall response rate (confirmed CR plus PR), time to response, duration of response, quality of life and safety and toxicity were also assessed. The study was designed with 80% power to demonstrate statistical equivalence between the two treatment groups. The initial sample size calculation found that a total of 350 assessable patients, 175 patients in each treatment group, would need to be randomised. To accommodate two interim analyses (necessitating 5% more patients) and anticipated loss of 20% of randomised patients who might not be assessable for efficacy end points, the sample size was increased to 460.

Protocol deviations included: (1) failure to meet entry criteria (7 patients receiving PLDH, 2 patients receiving topotecan); (2) patients who continued on study after first clinically significant change in LVEF (13 patients receiving PLDH); (3) patients who continued treatment after documented disease progression (40 patients receiving PLDH, 42 patients receiving topotecan); and (4) patients who completed fewer than 8 cycles of treatment but were deemed protocol-completed by the investigator (20 patients receiving topotecan).

Dose modifications were permitted. Reasons for reduction in PLDH dose included PPE, hematologic toxicity, elevated bilirubin, stomatitis, or all other Grade 3 and 4 events until resolution to Grade 2 or lower. In the event of severe neutropenia during any cycle with topotecan, the dose was reduced by 0.25 mg/m^2 for subsequent courses. Treatment with either drug was temporarily suspended or discontinued in cases of: disease progression; serious or intolerable adverse events precluding further treatment; inability to tolerate study drug despite dose modification; LVEF less than 45% or a 20% decrease from baseline; and patient's decision to withdraw participation or patients requiring radiation.

Median duration of follow up was not reported in either publication.[48;53] In addition, information on mean or median number of cycles received in each treatment group was not provided. However, the mean cycle dose and cycle length for each treatment group were reported to be close to those specified in the protocol, indicating good compliance in following the dosing guidelines.

Pegylated liposomal doxorubicin hydrochloride versus paclitaxel

In a publication available as only a conference abstract, O'Byrne *et al*.[46] provided a brief overview of a trial comparing PLDH versus paclitaxel. The search did not retrieve a full publication of this study. However, as part of TA91,[13] the manufacturer of PLDH (Schering–Plough) provided a full trial report as part of the industry submission.[69] The description of trial methodology and results for OS and adverse effects have been adapted from TA91.

The trial by Schering–Plough was a phase III, randomised, open-label study involving 216 women with epithelial ovarian carcinoma after failure of first-line platinum-based chemotherapy. Additionally, to be eligible, women had to have measurable disease and be taxane-naïve. The trial was designed to compare the clinical effectiveness and safety PLDH (50 mg/m^2) every 28 days versus paclitaxel (175 mg/m^2) every 21 days.

Randomisation was carried out in a 1:1 ratio, with patient stratification by platinum-sensitivity and bulky disease. No details on the method of randomisation are reported.

TA91 reports that the planned enrolment was for 438 patients, but only 216 were randomised (108 in each treatment arm), with the trial closing early due to poor accrual. It is thought that poor accrual

was associated with the approval of Taxol® for use in combination with platinum-based therapy for the first-line treatment of ovarian cancer by the European Agency for the Evaluation of Medicinal Products.

Patients were assessed weekly for haematological toxicities, and radiologic imaging was repeated every 7–8 weeks to assess disease status. Patients achieving either a CR or PR re-evaluated 4 weeks later to confirm the initial observation of response. All participants were to have been followed for a minimum of 1 year for survival and disease progression

At baseline, the two treatment groups were balanced in terms of age, treatment-free interval, disease bulk, the number of previous chemotherapy regimens, the type of previous chemotherapy agents received, histology and performance status.

As a result of the low recruitment rate, efficacy analysis in TA91 was limited to OS. Adverse events were also described.

Topotecan versus paclitaxel

ten Bokkel Huinink *et al*. (1997)[21] report the results of an open-label phase III randomised study involving 235 patients with Stage III/IV ovarian cancer, who had progressed during or after treatment with one platinum-based chemotherapy. The study was designed to compare the effectiveness and toxicity of topotecan (1.5 mg/m^2) for 5 consecutive days every 21 days versus paclitaxel (175 mg/m^2) every 21 days. Enrolled patients had at least one bidimensionally measurable lesion as evidenced by CT or MRI scan, ultrasound or physical examination. Patients who had received more than one prior chemotherapy, or been previously treated with topotecan or paclitaxel were ineligible. A second publication reporting more mature OS data was also identified.[51] A related study reports results from an analysis of patients who received third-line treatment during the trial, and specifically cross-over therapy with the treatment received in the other group.[52]

The primary outcome measures were response rate, duration of response and TTP. Response rate included CR or PR as a best response as determined by WHO criteria, with all responses independently reviewed by a radiologist who was masked to treatment allocation. Secondary outcome measures were time to response and OS. Of the 235 patients randomised, 9 patients did not receive treatment and were excluded from analyses. An additional 24 patients were not evaluated for response, but were included in the calculation of response rate.

Randomisation was reported to be carried out by telephone, but details on the method of randomisation were not available. Patients were stratified by age (<65 vs ≥65 years), ascites (present vs absent) and prior response to platinum-based therapy (resistant vs early vs interim vs late response). Resistant disease was defined as no response to initial chemotherapy or having an initial

PR or CR with subsequent progression while still receiving treatment. Early, interim and late response were defined as initial CR or PR with subsequent relapse within 3 months (early), 3–6 months (interim), or more than 6 months (late) after cessation of chemotherapy.

Patients with a CR or PR continued treatment until either progression or 6 months past the maximal response; those who progressed were removed from the study. Those whose best response was stable disease after 6 cycles could be removed from the study or switched to the alternative regimen.

Patients on paclitaxel received premedication with dexamethasone and H_1 and H_2 receptor antagonists to prevent hypersensitivity. No premedication was initially given to those on topotecan but was allowed in subsequent cycles if nausea or vomiting occurred. Dose reductions in each group were permitted for toxicity. The minimum dose allowed was 1.0 mg/m^2 per day for topotecan and 135 mg/m^2 for paclitaxel; the dose of topotecan could also be escalated to a maximum of 2 mg/m^2 per day. Patients were withdrawn from treatment if there was a greater than 2 week delay in treatment at the minimum dose of either medication because of toxicity. The target dose was achieved in 90% of cycles of topotecan and 98% of cycles of paclitaxel. Median number of cycles received was 5 in each group, with patients treated with topotecan receiving between 1 and 17 cycles compared with between 1 and 12 cycles for patients treated with paclitaxel.

A sample size calculation was not reported. Median duration of follow up at the time of the first publication was unclear.[21] Median follow up at the time of the publication reporting more mature OS data was reported in TA91 to be 58.5 weeks in the topotecan group (0–86 weeks) and 52.6 weeks in the paclitaxel group (0–117 weeks).[13]

Gemcitabine plus carboplatin versus carboplatin alone

Pfisterer *et al*.[49] report the results of a phase III international, open-label randomised study assessing the comparative clinical effectiveness of gemcitabine (1,000 mg/m^2) plus carboplatin (AUC 4) (N = 178) versus carboplatin alone (AUC 5; N = 178) in patients with platinum-sensitive recurrent ovarian cancer, with recurrence occurring at least 6 months after completion of first-line platinum-based therapy. Patients were enrolled with measurable or assessable lesions according to Southwest Oncology Group (SWOG) criteria. Exclusion criteria included ECOG score >2, inadequate bone marrow or kidney function or serious concomitant conditions, or life expectancy <12 weeks.

The primary outcome of the trial was PFS, with OS, response rate, duration of response, quality of life and toxicity measured as secondary outcomes. It should be noted that the study was not powered to detect a difference between treatments in OS. Randomisation was carried out through the central AGO-OVAR office (method of randomisation not reported), with patients randomised at a 1:1 ratio.

Patients were stratified by PFI (6–12 months vs ≥12 months), first-line therapy (platinum plus paclitaxel vs other platinum-based therapy), and bidimensionally measurable disease (yes vs no).

Median duration of follow-up was reported as 17 months, but the range of follow-up was not reported either for the full trial population or the individual treatment groups. Treatment cycles in each group were repeated every 21 days for 6 cycles, in the absence of progressive disease or unacceptable toxicity. At the investigator's discretion, benefiting patients could receive a maximum of 10 cycles of therapy. The median number of cycles administered was 6 cycles in each group. Cycles could be postponed up to 2 weeks due to toxicity, and longer toxicity-related delays led to treatment discontinuation. For Grade 3 non-haematological toxicities (excluding nausea/vomiting), dose modifications and/or study discontinuation were at the investigator's discretion. Patients in the gemcitabine plus carboplatin arm received 75.6% of the planned mean dose of gemcitabine (92.8% on day 1 and 63.4% on day 8) and 96.2% of the planned dose of carboplatin. Patients in the carboplatin arm received 98.2% of the planned dose.

Paclitaxel plus carboplatin versus platinum-based therapy alone

Two RCTs were identified for this comparison.[47;60] One RCT was a collaboration between the International Collaborative Ovarian Neoplasm (ICON) group and the Arbeitsgemeinschaft Gynaekologische Onkologie (AGO) group and hereafter is referred to as ICON4/AGO-OVAR 2.2 (Parmar *et al*.[60]). The RCTs identified were of similar design, but one was a phase II RCT (Gonzalez-Martin *et al*.[47]) and one a phase III RCT (ICON4/AGO-OVAR 2.2[60]).

The ICON4/AGO-OVAR 2.2 trial comprised results from two randomised trials that were run in parallel.[60] ICON4/AGO-OVAR 2.2 was an international multicentre trial enrolling 802 patients in 119 hospitals across 5 countries. ICON4 was co-ordinated by the Istituto Mario Negri (IRFMN), and the Medical Research Council's Clinical Trials Unit (MRC CTU), and AGO-OVAR 2.2 was co-ordinated by AGO. Each co-ordinating unit had its own protocol, with minor differences in eligibility criteria.

All centres enrolled patients with relapsed epithelial ovarian cancer who had previously received 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. The IRFMN and AGO-OVAR 2.2 protocols specified that women were to have received only one prior chemotherapy treatment to be eligible for enrolment, whereas the MRC-CTU protocol permitted women to have received more than one previous line of chemotherapy. Measurable disease at baseline was an entry criteria for patients randomised in centres co-ordinated by the IRFMN, but not MRC CTU or AGO co-ordinated centres. The IRFMN and MRC CTU protocols required that patients have had previous platinum-based chemotherapy, with or without paclitaxel. By contrast, the AGO protocol specified

that patients must have previously received cisplatin plus paclitaxel or carboplatin plus paclitaxel. Patients with concomitant or previous malignant disease were ineligible.

The trial compared the clinical effectiveness of paclitaxel plus platinum-based chemotherapy versus platinum-based chemotherapy alone. Patients were randomised to receive paclitaxel (175 [ICON4] or 185 [AGO-OVAR 2.2] mg/m^2 as a 3 hour infusion) plus platinum chemotherapy (392 patients) or conventional platinum-based therapy (410 patients). Platinum-based therapy comprised carboplatin (AUC 5) or cisplatin (minimum 75 mg/m^2 as monotherapy or 50 mg/m^2 in combination therapy). In all protocols, cycles were administered every 21 days.

The aim of the study was to evaluate whether paclitaxel should be given in addition to platinum-based chemotherapy in patients with platinum-sensitive disease and who would otherwise be treated with conventional platinum-containing regimens. Randomisation used a computer minimisation method (1:1 ratio) and patients were stratified by multiple factors that were determined by the protocol of the assigned centre. In ICON4 protocols, patients were stratified by age, centre, last chemotherapy received, time since last chemotherapy completed, intended platinum treatment. In AGO/OVAR 2.2, patients were stratified by whether the patient had undergone secondary debulking surgery and time since completion of last chemotherapy.

The primary outcome measure of all protocols was OS; secondary outcomes were PFS and quality of life. Progression required clinical or radiological evidence of disease (not only raised CA125). The sample size calculation found that 800 patients would be sufficient to detect an 11% difference between the groups if the control group survival was 50% at a power of 90% and a 5% significance level.

Median follow-up was 42 months. Of the full trial population, 72% of patients received a minimum of 6 cycles of assigned chemotherapy; reasons for not completing 6 cycles included disease progression or death, toxicity or patient preference.

Gonzalez-Martin *et al*.[47] reported the results of a phase II study, in which 81 patients with platinum-sensitive recurrent ovarian cancer, who had received no more than two previous chemotherapy lines, were randomised to receive carboplatin alone (AUC 5; 40 patients) every 21 days or paclitaxel (125 mg/m^2 over 3 hours) plus carboplatin (AUC 5; 41 patients) every 21 days. Patients had to have measurable disease as measured by computed tomography (CT) or clinically evident but non-measurable disease that was evaluable by CA125 based on Rustin's criteria. Patients who had an ECOG performance status >2, life expectancy <12 weeks or inadequate bone marrow, liver or kidney function were ineligible.

The primary outcome measure was ORR (CR or PR), which was evaluated using WHO criteria in those with measurable disease, or by CA125 according to Rustin's criteria in those without measurable disease. OS, TTP and quality of life were reported as secondary outcome measures.

Both treatments were administered for a minimum of 6 cycles unless there was progression, unacceptable toxicity or a patient refused treatment. After 6 cycles, patients could continue for 3 further cycles if clinical benefit could be expected. All patients randomised to receive paclitaxel were treated with standard premedication 30 minutes before infusion, which comprised dexamethasone, diphenhydramine and ranitidine. In cases of grade 4 neutropenia or thrombocytopenia, doses were reduced to carboplatin AUC 4 (both groups) and paclitaxel 150 mg/m^2.

Randomisation was reported to have been carried out by a central data centre (no further details reported). Patients were stratified by PFI (6–12 months [partially platinum sensitive] versus >12 months [fully platinum sensitive]) and number of previous chemotherapy lines (one versus two). The trial was an unusual "pick up the winner" design. The authors of the trial comment that this type of design has a "90% chance of selecting the better treatment if the difference is at least 15% and the smaller response rate is assumed to be 30%". A sample size calculation is not presented, but the authors state that the trial was not designed or powered to detect differences in survival. The authors go on to comment that "no formal statistical comparison between the two arms was planned", but a selection of statistical comparisons are reported "for exploratory purposes only".

Patients in both treatment groups received a median of 6 cycles of treatment, with between 2 and 9 cycles of carboplatin alone administered and between 1 and 8 cycles of paclitaxel plus carboplatin administered. Three patients in the paclitaxel plus carboplatin arm did not receive one cycle of treatment. The proportion of patients requiring a dose reduction was small and was similar between the groups (4.7% with carboplatin alone vs 6.6% with paclitaxel plus carboplatin). By contrast, a significantly larger proportion of patients required a dose delay in the carboplatin alone group (34.4%) compared with the paclitaxel plus carboplatin group (21%; p value for difference: p <0.006). The difference was attributed to the absence of haematological recovery by day 21 in the group receiving carboplatin alone.

The three patients who received no treatment in the paclitaxel plus carboplatin group were included in the ITT analysis of overall response, but were excluded from other analyses. Median duration of follow up was 67.7 weeks. At this time point, 32 patients had died and median OS has not been reached in the paclitaxel plus carboplatin group. The range of follow-up was not reported either for the full trial population or the individual treatment groups.

Paclitaxel plus carboplatin versus paclitaxel alone

Lortholary *et al*.[61] reported the results of a phase II, multicentre, open-label, 3-armed randomised trial (CARTAXHY) in patients with platinum resistant or refractory recurrent ovarian cancer. Eligible patients were those who had received at least one prior therapy, with the most recent regimen combining platinum with a taxane agent. In addition, patients were required to have either measurable (according to RECIST criteria) or CA125 assessable disease, an Eastern Cooperative Oncology Group (ECOG) performance status of ≤2 and a life expectancy of > 12 weeks. Patients with measurable disease (according to RECIST criteria) or evaluable disease (CA125) were enrolled. Patients who previously been treated with weekly paclitaxel were excluded.

In total, 165 patients were randomised (1:1:1 ratio) to treatment with weekly paclitaxel (80 mg/m^2 administered on days 1, 8 and 15 of a 4-week cycle; 57 patients), weekly paclitaxel plus carboplatin (AUC 5 administered on day 1 of a 4-week cycle; 51 patients) or weekly paclitaxel plus weekly topotecan (3 mg/m^2 administered on days 1, 8 and 15 of a 4-week cycle; 57 patients). The combination of paclitaxel plus topotecan in the treatment of patients with PRR ovarian cancer is not covered by the scope of this review and the efficacy results for this group are not presented.

The primary outcome was PFS. Secondary end points were response rate, OS, quality of life and toxicity. Quality of life was assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ) and toxicity was assessed according to National Cancer Institute Common Toxicity Criteria. The efficacy analyses were based on the ITT principle.

Randomisation was carried out at the GINECO data centre but details on the method of randomisation are not available. Patients were stratified according to centre, treatment-free intervals (progression during treatment vs relapse between 0 and 3 months vs relapse >3 months and ≤6 months), and presence of a measurable lesion at baseline.

Treatments were administered for six to nine cycles or until progression or unacceptable toxicity. On progression, patients treated with weekly paclitaxel or weekly paclitaxel plus weekly topotecan received carboplatin (AUC 5) and patients treated with weekly paclitaxel plus carboplatin went on to receive treatment of physician's choice. One patient in the weekly paclitaxel group did not receive any treatment. Patients received a median three cycles in each group.

Dose reductions for toxicity of one level were to paclitaxel 65 mg/m^2, carboplatin AUC 4 mg/ml/min, and topotecan 2.4 mg/m^2. Dose reductions of two levels were to paclitaxel 5 mg/m^2, carboplatin AUC 3.5 mg/ml/min, and topotecan 2 mg/m^2. In cases where there was a treatment delay >2 weeks, patients were discontinued from the study.

The sample size calculation was indicated that 165 patients would be required for adequate power to detect a difference among groups with 80% power. Median duration of follow-up was 15 months.

Paclitaxel versus oxaliplatin

Piccart *et al*.[62] report the results of a multicentre (17 European centres across 6 countries), open-label, randomised, phase II study. Patients were enrolled who had histologically or cytologically proven advanced ovarian cancer that had progressed or stabilised after prior treatment, with relapse occurring within 12 months of the last platinum-based chemotherapy regimen. No more than two prior cisplatin- and/or carboplatin-containing chemotherapy regimens were permitted. Patients were also ineligible if they had had prior treatment with platinum derivatives other than cisplatin and carboplatin or with paclitaxel, docetaxel, or high-dose chemotherapy with hematopoietic stem cell support.

The primary aim of the trial was to evaluate the clinical effectiveness of oxaliplatin (130 mg/m^2 over 2) hours every 21 days (N = 45) compared with paclitaxel (175 mg/m^2 over 3 hours) every 21 days (N = 41).

Patients were assigned to their study group by the EORTC. No details on the method of randomisation are reported in the full publication. Patients were stratified by centre, performance status (0 vs 1 vs 2), platinum-free interval (0–6 months vs 6–12 months), and number of prior platinum-based regimens (1 vs 2). The primary outcome measure was the objective confirmed response rate, which was assigned as per WHO criteria and verified by two independent radiologists. Secondary outcome measures TTP, OS, time to treatment failure, and QoL.

For patients randomised to receive paclitaxel infusion, premedication included oral dexamethasone (20 mg) 12 and 6 hours before infusion, and diphenhydramine (50 mg intravenously) plus cimetidine (300 mg) or ranitidine (50 mg intravenously) 30 minutes before the infusion. Antiemetic therapy before oxaliplatin infusion was a serotonin antagonist (5-HT$_3$), with a single dose of corticosteroid (e.g., dexamethasone 20 mg).

Treatment in each group was continued until disease progression, unacceptable toxicity, or patient refusal. The initial paclitaxel and oxaliplatin doses could be reduced in subsequent cycles, or the cycles could be delayed by 1 or 2 weeks, depending on toxicity. Doses reduction below 90 mg/m^2 for paclitaxel and 75 mg/m^2 oxaliplatin per cycle were not permitted, and patients requiring these or lower doses went off study. Median number of cycles of treatment was 6 (range 1 to 8) in the paclitaxel group and 4 (range 1 to 8) in the oxaliplatin group. Most patients had a delivered relative dose-intensity of at least 95%.

Median duration of follow-up was not reported. A total of five patients were not assessable for response (two in the paclitaxel arm and three in the oxaliplatin arm): four were ineligible because of eligibility deviations and one died 6 days after the first oxaliplatin cycle, as a result of a massive pulmonary thromboembolism (unrelated to treatment).

A sample size calculation was not reported. The authors comment that, despite the use of several centres, as a result of wider use of paclitaxel as a first-line treatment at the time the trial was initiated, accrual of paclitaxel-naïve patients became slow in the later stages of the trial. It is unclear whether the trial was adequately powered to detect a difference between treatments.

Topotecan oral versus topotecan intravenous

Gore *et al.*[24] report the results of a multicentre, international (Europe, South Africa, and North America) randomised trial of open-label design that compared topotecan administered orally (2.3 mg/m^2 daily for 5 consecutive days; N = 135) versus intravenously (1.5 mg/m^2 daily for 5 consecutive days; N = 131). Both treatment regimens were given on a 21 day cycle. Patients were enrolled who had relapsed epithelial ovarian cancer (histological diagnosis) that was measurable at baseline and was of FIGO Stage III or IV (266 patients randomised). To be eligible, patients were also required to have an ECOG score of ≤2. Patients had either progressed during or relapsed within 12 months of completing first-line chemotherapy, and only one prior chemotherapy regimen was permitted. Initial treatment must have been platinum-based and could have been given in conjunction with a taxane.

The aim of the study was to compare the efficacy, safety, and tolerability of oral topotecan versus standard intravenous topotecan in patients with relapsed ovarian cancer. Randomisation (1:1 ratio) was carried out by telephone (no further details reported) and stratified by prior taxane exposure, interval from previous platinum therapy and tumour diameter (< vs ≥5 cm). Three categorisations of response to first-line chemotherapy were defined: platinum-refractory (progressive or stable disease during initial chemotherapy); platinum resistant (initial response followed by relapse within 6 months); and platinum sensitive (initial response with subsequent relapse at >6 months).

Outcomes assessed included response rate (as per WHO criteria), time to response, time to progression, survival and toxicity. Median follow-up was not stated. Although open-label in design, all claimed confirmed and partial responses were subject to independent, blinded radiological review. The only outcome evaluated for the subgroups categorised by extent of sensitivity to platinum was response rate.

Duration of treatment with topotecan was determined by response to therapy and was at the discretion of the clinician. It was recommended that patients with stable disease receive a minimum of 4 cycles of treatment and that patients responding to treatment receive at least 2 cycles of treatment beyond

response. Patients assigned to oral topotecan received a median of 4 (range 1–23) cycles and those assigned intravenous topotecan received a median of 6 (range 1–26) cycles. Dose reductions were permitted for Grade 3 or 4 adverse events, with about 10% of patients in each group requiring a reduction in dose.

Topotecan administered on 5 consecutive days (conventional regimen) versus topotecan administered weekly

Sehouli *et al*.[23] report the results of a randomised multicentre phase II trial in Germany involving 194 patients with platinum-resistant recurrent epithelial ovarian or primary peritoneal cancer after radical surgery and at least one platinum-containing chemotherapy. Patients with measurable disease by CT or MRI or evaluable disease by CA125 according to GCIG criteria were eligible. Platinum resistance was defined as clinical disease progression after a treatment-free interval of <6 months after a platinum-based regimen. Inclusion criteria with regards to number of previous lines of chemotherapy were not specified.

The primary goal of the trial was to compare weekly administration of topotecan at a dose of 4.0 mg/m^2 each week applied on days 1, 8, and 15 of a 28-day cycle (N = 97) versus the conventional regimen of 1.25 mg/m^2 for 5 consecutive days (N = 97). The rationale for the trial was that weekly administration of topotecan is considered to be less toxic and is widely used in clinical practice, despite the lack of an evidence base of effectiveness. It should be noted that the dose used in the "conventional" 5-day regimen is lower than the dose recommended in the Summary of Product Characteristics for topotecan (1.5 mg/m^2).

Randomisation was central with permutated blocks in a 1:1 ratio and was carried out by phone and facsimile. However, the level of masking in the trial is unclear. The primary outcome evaluated was the clinical benefit rate, which was defined as the composite of CR, PR and stable disease (SD). Response was determined according to Response Criteria in Solid Tumors (RECIST) for measurable disease or GCIG criteria for serum CA125 levels. Use of CA125 or scans to evaluate response was at investigators' discretion, with all responses confirmed by a second examination. Secondary end points were toxicity, PFS, and OS; quality of life was also explored. All analyses were based on the ITT principle. No sample size calculation was reported but it is stated that the study was not powered for a direct comparison between the dosing schedules or to reveal differences in response rates.

Treatment in each group was continued until intolerable toxicity or disease progression or until the patient refused further therapy, with maximum treatment duration of 12 months. Dose of topotecan could be reduced by 25% for any Grade 3 or 4 adverse effects according to the National Cancer Institute Common Toxicity Criteria (NCICTC).

Median follow-up was 23.4 months (range 12.7 to 41.4 months). Patients in the weekly topotecan group received statistically significantly fewer cycles of chemotherapy compared with the group receiving topotecan at the conventional dosing regimen (3.5 with weekly topotecan vs 4.8 with conventional topotecan; p = 0.002).

Paclitaxel high dose (250 mg/m^2) versus paclitaxel standard dose (175 mg/m^2)

Omura *et al*.[66] conducted a phase III randomised, multicentre trial comparing two doses of paclitaxel (250 mg/m^2 versus 175 mg/m^2) involving patients with recurrent or persistent histologically confirmed epithelial ovarian cancer despite prior platinum therapy. A third group, paclitaxel 135 mg/m^2, was closed early because of inadequate patient accrual. Eligible patients had received not more than one prior platinum-based regimen, had adequate bone marrow, kidney and liver function; and a Gynecologic Oncology Group performance status of 0, 1 or 2.

The aim of the trial was to evaluate whether increasing dose of paclitaxel was associated with an increase in response. The primary outcome measures were PFS and OS. Objective response (CR or PR) rates were recorded in patients with measurable disease (pleural effusion or elevated CA125 were not regarded as measurable disease). The study also assessed whether prophylactic filgrastim 10 μg/kg was more effective than filgrastim 5 μg/kg at reducing the incidence of febrile neutropenia in patients receiving paclitaxel 250 mg/m^2. The TAG considers that the administration of filgrastim is unlikely to influence comparative clinical effectiveness.

Sequential, permuted block randomisation was used to assign patients to paclitaxel 175 mg/m^2 or 250 mg/m^2 by 24-hour intravenous infusion every 3 weeks. Both treatments were administered for a minimum of 6 cycles. Patients could continue treatment indefinitely if there was no clinical progression or excessive toxicity after 6 cycles. Paclitaxel dose intensity could be reduced for some grade 3 or greater toxicities (not otherwise specified). Patients experiencing neutropenic fever while receiving paclitaxel 175 mg/m^2 were allowed filgrastim during subsequent therapy cycles.

Based on the sample size calculation, it was estimated that 540 patients, followed until approximately 80% had died, would provide an 80% chance of detecting a true hazard ratio of 1.4 between paclitaxel 135 mg/m^2 and either of the more intense regimens (type I error p = 0.025 for one-tail test). However, the study failed to enrol sufficient patients in the paclitaxel 135 mg/m^2 arm and a decision was made to 'allocate all of the type I error to the comparison of the two higher-dose regimens'. Initially designed to evaluate effects of the two paclitaxel regimens in platinum-resistant clinically measurable disease, due to slow accrual, after commencement of the trial the eligibility criteria were expanded to include patients with platinum-sensitive disease and without clinically measurable disease.

Of the 184 women randomly assigned to paclitaxel 175 mg/m^2 and the 188 to paclitaxel 250 mg/m^2, 164 (89%) and 166 (88%), respectively, were eligible. Ten eligible women (three in the paclitaxel 175 mg/m^2 group and seven in the paclitaxel 250 mg/m^2 group) were not assessed for tumour response because of death, toxicity or withdrawal, but were classified as not responding for an ITT analysis among eligible patients. The primary survival outcomes were restricted to eligible patients.

Median duration of follow-up is not reported. The proportion of women receiving six or more cycles of therapy was similar between the two groups, with 58% and 55% of patients in the paclitaxel 175 mg/m^2 and paclitaxel 250 mg/m^2 group, respectively, receiving six or more cycles. One patient refused to take any dose of the allocated treatment.

Paclitaxel weekly versus paclitaxel every 3 weeks

Rosenberg *et al.*[59] report the results of a randomised bifactorial multicentre study carried out at sites in Sweden and Finland. The aim of the study was to assess the efficacy and toxicity of paclitaxel given at the same dose intensity administered either weekly or every 21 days. Patients were randomised to paclitaxel 67 mg/m^2 every 7 days or paclitaxel 200 mg/m^2 every 21 days. Enrolled patients (N = 208) had advanced ovarian cancer (histologically proven) that had progressed during or relapsed after administration of a platinum-based regimen. To be eligible, patients had to have measurable disease that had been documented clinically and/or radiologically. Only one prior platinum-containing regimen was permitted. In addition, all patients were taxane-naïve.

The RCT was of a bifactorial design. In addition to randomisation to either paclitaxel weekly or every 21 days, patients were also randomised to oral dexamethasone (20 mg) taken 12 hours and 6 hours before paclitaxel infusion or administration of intravenous dexamethasone (20 mg) 30 minutes before paclitaxel infusion. Results in the full publication cited here focus on treatment with paclitaxel. Premedication with clemastine 2 mg and cimetidine 300 mg (or ranitidine 50 mg) was given intravenously to all patients 30 minutes prior to paclitaxel infusion.

The primary endpoint of the study was clinical response rate as per WHO criteria, with TTP and OS evaluated as secondary outcomes. Randomisation was reported to have been carried out at the Bristol-Myers-Squibb office in Stockholm and patients were randomised in a 1:1 ratio. Patients were stratified by platinum resistance, with a differentiation at 6 months (randomisation strata: relapse ≤6 months vs >6 months after primary platinum-based treatment). No further on the method of randomisation are reported. The level of masking in the trial is unclear.

Median duration of follow up was 27 months (range 7 to over 47 months). Patients to whom paclitaxel was administered weekly at a dose of 67 mg/m^2 received a median of 5.7 courses of treatment (range 1–16) compared with a median of 7 courses in the group receiving paclitaxel 200

mg/m^2 every 21 days (range 1–17). More patients in the paclitaxel weekly arm (32 vs 20) were taken off the study early (within 9 weeks) due to either early progression or for administrative reasons. The difference in early progressions could be because of a low initial weekly dose or some patients may have had a more aggressive tumour biology.

The sample size calculation estimated that 318 patients would be required to detect the prespecified relative difference between groups of 54% with 80% power. To ensure a sufficient number of evaluable patients, it had been planned to recruit a total of 350 patients. Owing to slow recruitment of taxane-naïve patients with recurrent disease, the study closed early after inclusion of 208 patients. The study may therefore have been underpowered to detect a difference between the two regimens.

4.2.1.3 Quality assessment of studies included in clinical effectiveness review

Pegylated liposomal doxorubicin hydrochloride plus carboplatin versus paclitaxel plus carboplatin

The trial carried out by Bafaloukos *et al*.[29] is generally well-designed with the primary analysis based on the ITT population. However, limited details on trial methodology are provided in the full publication. Randomisation is reported to have been carried out at the central HeCOG Data office in Athens but a description of the method of randomisation is not reported. The level of masking within the trial is unclear. The primary outcome is response rate, which is determined by radiological scan or CA125 level. Assessment of response is associated with disparity in interpretation of scan results, both across different assessors and within categorisation (CR or PR) by an individual assessor. It is unclear whether radiological scans were evaluated by an independent review panel. In addition, 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. The evaluation of the quality of the trial is presented in Table 19.

CALYPSO (Pujade-Lauraine *et al*.[31]) is a well-designed and well-conducted trial. Progression and response were reviewed independently. Although the methods indicate that analyses are based on the ITT principle, 3 randomised patients (1 in the PLDH plus carboplatin group and 2 in the paclitaxel plus carboplatin group) were judged to be ineligible because of absence of evidence of ovarian cancer post randomisation and were excluded from analyses of clinical effectiveness. Thus, the analyses are not strict ITT analyses. The evaluation of the quality of the trial is presented in Table 19.

Pegylated liposomal doxorubicin hydrochloride plus carboplatin versus carboplatin alone

Alberts *et al*.[28] seems to be generally well-designed, although limited details on the methodology of the trial are provided in the full publication. The method of randomisation and level of masking are unclear. As the primary outcome is OS, masking, or lack of masking, is unlikely to introduce bias into the evaluation of treatment effect. The key issue associated with trial design is that the study is 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). The authors identify several factors that could have contributed to slow accrual, including dissolution of the SWOG Gynecological Cancer Committee after initiation of the trial, and publication of results from the larger ICON4/AGO-OVAR 2.2 trial.[60] The evaluation of the quality of the trial is presented in Table 19.

Trabectedin plus PLDH versus PLDH alone

OVA-301 (Monk *et al*. [2010][30]) was a well-conducted trial. Methodologically, the design of the trial was robust, with clinical effectiveness analyses based on the ITT population and progression and response reviewed by an independent radiologist who was masked to treatment allocation. A secondary analysis of the primary outcome of PFS was carried out based on review by an independent oncologist (radiologic assessment in conjunction with prespecified clinical data) who was also masked to treatment allocation. The methods of the trial are well reported. As noted in the Final Appraisal Determination (FAD) for the assessment of trabectedin plus PLDH as part of the Technology Appraisal process (TA222),[70] one potential area that affects the external validity of the trial is the omission of a platinum-based chemotherapy 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. The evaluation of the quality of the trial is presented in Table 19.

Pegylated liposomal doxorubicin hydrochloride versus topotecan

The trial carried out by Gordon *et al*. (2001)[48] was generally a well-designed trial. Although open-label in design, scans for assessment of disease response and progression underwent independent radiological review. Although the methods state that analyses are based on the ITT principle, in the first publication, results are based on patients who received at least a partial dose of study drug (474 patients out of 481 randomised), which is a modified ITT analysis. However, in the publication describing longer-term follow-up of OS, analysis of OS is based on the "all randomised" population and as such is a true ITT analysis. The evaluation of the quality of the trial is presented in Table 19.

Pegylated liposomal doxorubicin hydrochloride versus paclitaxel

TA91 reports that the study carried out by Schering–Plough (trial 30–57) was a reasonably good quality randomised open-label comparative trial.[13] The key issue noted was that approximately 50% of the planned number of patients was recruited (216 recruited out of planned 438 patients). It is therefore likely that the trial is underpowered to detect a difference between PLDH and paclitaxel in treatment effect. TA91 also notes that the results of the trial "are likely to be preliminary and the longer term implications of any differences observed in the treatment effect at the time of data analysis are unclear". The evaluation of the quality of the trial is presented in Table 19.

Topotecan versus paclitaxel

A key strength of the trial evaluating topotecan versus paclitaxel (ten Bokkel Huinink *et al*. (1997)[21]) is that, for the primary outcome of response rate, all claimed responses were evaluated by an independent radiologist who was masked to treatment allocation. As a sample size calculation was not reported there is uncertainty as to whether the trial was adequately powered to detect a difference between treatments. Furthermore, results are not based on the ITT principle, with only patients who received at least one dose of study drug being included in the final analysis. The trial design allowed patients to cross-over to the alternative treatment should they fail to respond to their allocated treatment. The switch in treatment during the trial generates confounding in the final analysis of OS. The evaluation of the quality of the trial is presented in Table 19.

Gemcitabine plus carboplatin versus carboplatin alone

The trial carried out by Pfisterer *et al*.[49] is generally a well-designed and well-conducted trial, with efficacy analyses were based on the ITT principle. With PFS as a primary outcome and an open-label design, there is potential for bias. It is unclear from the full publication whether radiological assessment of progression was reviewed by an independent panel. The evaluation of the quality of the trial is presented in Table 19.

Paclitaxel plus carboplatin versus platinum-based therapy alone

ICON4/AGO-OVAR 2.2 are well-conducted parallel trials.[60] Comprehensive details on most aspects of trial methodology are provided in the full publication.[60] The level of masking is unclear but OS is the primary outcome and therefore awareness of treatment allocation is unlikely to influence results of this outcome. Analyses of clinical effectiveness are based on the ITT population. The evaluation of the quality of the trial is presented in Table 19.

The trial carried out by Gonzalez-Martin *et al*.[47] was a phase II trial of a "pick the winner" design, which the authors state has a "90% chance of selecting the better treatment if the difference is at least 15% and the smaller response rate is assumed to be 30%". Therefore, no sample size calculation was carried out. A "pick the winner" trial is designed as a screening trial to facilitate a selection between promising experimental regimens in a phase II setting, and as such do not typically include the standard of care. Trials with a "pick the winner" design are underpowered for hypothesis testing or comparisons of treatment effect on the outcomes of interest, such as survival.[71] Therefore, as the authors comment, all reported statistical analyses are exploratory and reported p values should be interpreted with caution. Limited details on trial methodology are reported and the level of masking in the trial is unclear. Although it is reported that randomisation was carried out in a central data centre, the method of randomisation is not described. The evaluation of the quality of the trial is presented in Table 19.

Paclitaxel plus carboplatin versus paclitaxel alone

Limited details of the methodology of the CARTAHXY trial (Lortholary *et al*.[61]) are available in the publication presenting the results of the trial. A key strength of the trial is that clinical efficacy analyses were based on the ITT principle. Although it is stated that the study is randomised, details on the method of randomisation are not reported. As an open-label trial, there is potential for bias in the assessment of progression and response. It is unclear whether radiological scans underwent independent radiological review. The evaluation of the quality of the trial is presented in Table 19.

Paclitaxel versus oxaliplatin

The trial reported by Piccart *et al*.[62] is generally a well-designed trial. The primary outcome was objective confirmed response. As an open-label design, the outcome of confirmed response could potentially be open to bias. The descriptions of the methods states that response verified by two independent radiologists. However, it is unclear whether the independent radiologists were truly independent and masked to treatment allocation. Although limited details are reported on the method of randomisation, it is reported that the treatment allocation was assigned by the EORTC. The key issue associated with the trial is the uncertainty around the power of the trial. The evaluation of the quality of the trial is presented in Table 19.

Topotecan oral versus topotecan intravenous

The trial reported by Gore *et al*.[24] is generally well designed, with analysis based on the ITT population. In addition, although open-label in design claimed confirmed and partial responses were validated by masked independent radiological review. It is stated that randomisation was carried out by telephone but no details on the method of randomisation are reported. No power calculation is reported and thus it is unclear whether the study is adequately powered. The population is clinically homogenous in that all patients randomised had measurable disease at baseline and also had received only one prior chemotherapeutic treatment. The evaluation of the quality of the trial is presented in Table 19.

Topotecan administered on 5 consecutive days (conventional regimen) versus topotecan administered weekly

There are several factors that impact on the quality of the design and conduct of the trial carried out by Sehouli *et al*.[23] Although it is stated that all analyses are carried out based on the ITT principle, the analysis of clinical benefit does not include all patients randomised. There is no discussion of the omission of patients from this analysis. The dose used for the "conventional" regimen for topotecan is lower than that recommended in the SmPC. The authors comment that the reduced dose is widely accepted by many international cancer societies but go on to highlight that there are no RCTs evaluating the comparative effectiveness of 1.25 mg/m^2 versus 1.5 mg/m^2 of topotecan. In addition, use of radiological scans or CA125 to determine response was at the discretion of the investigator. It

is widely accepted that CA125 level is not sufficient to confirm response to treatment. Examination of the results for response indicates that a large proportion of patients were evaluated by CA125 alone (80.1%). Moreover, it is unclear whether the investigator was masked to treatment allocation. Although responses had to be confirmed by a second examination, it is unclear whether response was confirmed by the same investigator or by independent review. The trial was not adequately powered to detect a difference between groups. These factors potentially limit the comparison of the results from this trial with similar trials in ovarian cancer. The evaluation of the quality of the trial is presented in Table 19.

Paclitaxel high dose (250 mg/m^2) versus paclitaxel standard dose (175 mg/m^2)

Limited methodological details were reported in Omura *et al*.[66] Method of randomisation was robust, with treatment regimens sequentially assigned from stratified, permuted blocks. The level of masking in the trial is unclear. Although the methods state that the analyses are based on the ITT principle, patients identified post-randomisation to be ineligible for participation in the trial were excluded from all analyses, and, therefore, analyses are not based on the ITT population. A key issue with the trial is the sample size, with only 265 patients recruited from a planned 540, even after expansion of the protocol to include platinum-sensitive patients and those with measurable disease. Thus, the study is likely to be underpowered to detect a true difference between the treatment regimens for which results are reported.

Paclitaxel weekly versus paclitaxel every 3 weeks

The trial carried out by Rosenberg *et al.*[59] is of reasonable quality. Efficacy analyses are based on the ITT principle. Limited details are reported on trial methodology in terms of method of randomisation and level of masking. The key issue with the trial is that it is potentially underpowered to detect a difference in the primary outcome of response rate between the paclitaxel regimens evaluated. The evaluation of the quality of the trial is presented in Table 19.

Table 19. Summary of quality assessments of studies included in review of clinical effectiveness

Study	Potential bias affecting trial methodology												Potential bias affecting outcome								
	Random sequence generation			Allocation concealment			Selective reporting			Other bias			Masking of personnel			Masking of outcome assessment			Incomplete outcome data		
	Low	Unclear	High	Low	Unclear	High	Low	Unclear	High	Low	Unclear	High	Low	Unclear	High	Low	Unclear	High	Low	Unclear	High
Bafaloukos *et al.*[29]		✓			✓		✓				✓										
OS														✓		✓			✓		
TTP														✓			✓		✓		
Response rate														✓			✓		✓		
Adverse events														✓			✓		✓		
CALYPSO Pujade-Lauraine *et al.*[31]	✓				✓		✓				✓										
OS															✓	✓			✓		
PFS															✓	✓			✓		
Response rate															✓	✓			✓		
Adverse events															✓		✓		✓		
Alberts *et al.* 2008[28]		✓			✓		✓				✓										
OS														✓		✓			✓		
PFS														✓			✓		✓		
Response rate														✓			✓		✓		
Adverse events														✓			✓		✓		
OVA-301 Monk *et al.* (2010)[30]	✓				✓		✓				✓										

OS														✓	✓			✓			
PFS														✓	✓			✓			
Response rate														✓	✓			✓			
Quality of life														✓		✓			✓		
Adverse events														✓		✓		✓			
Gordon *et al*. (2001)[48]		✓			✓		✓				✓										
OS														✓	✓			✓			
PFS														✓		✓		✓			
Response rate														✓		✓		✓			
Quality of life														✓		✓			✓		
Adverse events														✓		✓		✓			
Trial 30–57 Data taken from TA91[13]	✓			✓				✓			✓										
OS														✓	✓			✓			
Adverse events														✓		✓		✓			
ten Bokkel Huinink *et al*. (1997)[21]		✓			✓		✓				✓										
OS														✓	✓			✓			
TTP														✓	✓			✓			
Response rate														✓	✓			✓			
Quality of life														✓		✓			✓		
Adverse events														✓		✓		✓			
Pfisterer *et al*.[49]		✓			✓		✓				✓										

OS														✓	✓			✓		
PFS														✓		✓		✓		
Response rate														✓		✓		✓		
Quality of life														✓		✓			✓	
Adverse events														✓		✓		✓		
ICON4/AGO-OVAR-2.2 Parmar *et al.*[60]	✓				✓		✓				✓									
OS														✓		✓		✓		
PFS														✓			✓	✓		
Response rate														✓			✓		✓	
Quality of life														✓			✓		✓	
Adverse events														✓			✓	✓		
Gonzalez Martin *et al.*[47]		✓			✓		✓				✓									
OS														✓		✓		✓		
PFS														✓			✓	✓		
Response rate														✓			✓	✓		
Quality of life														✓			✓		✓	
Adverse events														✓			✓	✓		
CARTAXHY Lortholary *et al.*[61]		✓			✓		✓				✓									
OS														✓	✓			✓		
PFS														✓		✓		✓		
Response														✓		✓		✓		

rate																				
Quality of life														✓		✓			✓	
Adverse events														✓		✓		✓		
Piccart *et al.*[62]		✓			✓		✓				✓									
OS														✓	✓			✓		
PFS														✓		✓		✓		
Response rate														✓		✓		✓		
Quality of life														✓		✓			✓	
Adverse events														✓		✓		✓		
Gore *et al.*[24]		✓			✓		✓				✓									
OS														✓	✓			✓		
TTP														✓	✓			✓		
Response rate														✓	✓			✓		
Adverse events														✓		✓		✓		
Sehouli *et al.*[23]	✓				✓		✓				✓									
OS														✓		✓			✓	
PFS														✓					✓	
Response rate														✓					✓	
Quality of life														✓					✓	
Adverse events														✓				✓		
Omura *et al.*[66]	✓				✓			✓			✓									
OS														✓		✓			✓	
PFS														✓						✓
Response														✓						✓

rate																				
Adverse events													✓			✓				✓
Rosenberg *et al.*[59]		✓			✓		✓				✓									
OS													✓		✓			✓		
TTP													✓			✓		✓		
Response rate													✓			✓		✓		
Adverse events													✓			✓		✓		
Additional details are provided in the full quality assessment forms presented in Appendix 13. Abbreviations used in table: PFS, progression-free survival; OS, overall survival; TTP, time to progression.																				

4.2.1.4 Comparability of baseline characteristics

Within most of the trials identified, the treatment groups were well matched in terms of population baseline characteristics, including age, treatment-free interval, the number of previous chemotherapy agents received, disease measurability (for those trials including patients with measurable and non-measurable disease), and performance status. Differences between groups that were reported to be significant are described below; imbalances that were reported to be non-significant or for which the significance of the difference was not assessed in the trial are not discussed. Detailed baseline characteristics of the individual trials are available in the data abstraction forms presented in Appendix 2.

An unanticipated imbalance in PFI was noted in a retrospective analysis of OVA-301 (Monk *et al*. [2010][30]). Patients in the PLDH monotherapy group had a significantly longer mean PFI than patients in the trabectedin plus PLDH group (mean PFI: 13.3 months with PLDH alone vs 10.6 months with trabectedin plus PLDH; p = 0.009). Longer PFI is correlated with increased likelihood of response to treatment. Therefore, the potential direction of bias in analysis of treatment effect is against trabectedin plus PLDH. To account for this imbalance, the authors carried out additional exploratory analyses based on PFI as a continuous covariate (discussed in Section 5.1.3.1). The analyses were not prespecified and as such were hypothesis generating.

Baseline characteristics of key prognostic factors (based on expert advice) are summarised in Table 20. Also, based on expert advice, the TAG has focused on the subgroups of platinum-sensitive and PRR ovarian cancer rather than the full trial population. Baseline characteristics are considered in terms of comparability within platinum-sensitive and PRR patients.

Considering patients with platinum-sensitive disease, a potential source of heterogeneity within the trials is the proportion of patients with FPS (relapse >12 months after last platinum-based treatment) versus PPS (relapse ≥6–12 months after last platinum-based treatment) at baseline. The greater the duration of PFI, the more favourable the prognosis. In trials involving patients with only platinum-sensitive disease,[28;29;31;47;49;60] the proportion of patients with PPS ovarian cancer ranges from 28.6% to 43.0%. Considering the large trial ICON4/AGO-OVAR2.2, the proportion of patients with PPS versus FPS is 74.7% and 25.3%, respectively. ICON4/AGO-OVAR2.2 has been reported to have longer median PFS and OS for both groups compared with other trials involving platinum-sensitive patients, which is thought to be attributable to the comparatively larger proportion of patients with FPS who have an improved prognosis compared with those who are PPS.[60] Given that the NMA is based on relative treatment effects (HR), and that most trials are well balanced between groups in FPS versus PPS, the TAG considered the trials sufficiently clinically homogeneous to compare treatments in an NMA.

Number of prior lines of chemotherapy is another source of potential heterogeneity. Increasing number of previous chemotherapy regimens is associated with a decrease in response to treatment. Of the 16 trials identified, seven included patients who had received two or more prior lines of chemotherapeutic treatment. In trials involving only patients with platinum-sensitive disease, the proportion of patients with more than one line of prior chemotherapy in each trial is generally small, ranging from 4% to 15.5%. By contrast, as could be expected, in trial involving patients with PRR, the proportion of patients with two or more chemotherapy regimens is larger, at about 30% in all trials. In all trials, the number of patients with multiple lines of prior chemotherapy is well balanced within the trial. It is possible that inclusion of trials in which patients received two or more chemotherapy regimens is likely to underestimate the effects of the evaluated treatments in patients with first recurrence of disease, and thus potentially bias the results of an indirect comparison towards treatments that are given as second-line. Again, as the HR used in the NMA is a relative treatment effect, the impact of these trials on the overall result could be minimal.

Scales evaluating performance status are used to assess disease progression and how a patient's daily living abilities are affected by their disease. On the ECOG scoring system (also referred to as the Zubrod or WHO score), the lower a patient's performance score, the greater their capacity for physical activity; a score of 0 or 1 indicates that the patient is ambulatory. In the Karnofsky scale, which scores from 100 to 0, higher performance score is favourable; a score >80 indicates that a patient is able to carry on normal activity and to work with no special care required. Good performance status has been shown to be an important prognostic factor in several types of cancer.[72]

In the identified trials, the proportion of patients with unfavourable baseline performance score (ECOG/Zubrod/WHO, ≥2; Karnofsky <80) is small, ranging from 0% to 16% across the trials. Including patients with less favourable performance scores is likely to underestimate the effect of the treatments. For example, in Gonzalez-Martin *et al*.[47], the 12.3% increase in ECOG score 2 in the platinum treatment group may limit the benefit received by people receiving platinum monotherapy when compared with paclitaxel plus platinum (i.e., paclitaxel plus platinum may have less benefit over platinum monotherapy). In addition, in Rosenberg *et al*.[59] the 9% increase in WHO score 2 in the three-weekly paclitaxel group may limit the benefit received by three-weekly paclitaxel monotherapy compared with weekly paclitaxel monotherapy (i.e., the benefit of paclitaxel weekly may have less benefit over three-weekly paclitaxel). However, in those trials that include patients with a less favourable performance score, the proportion of patients in each treatment group is well-balanced and thus the impact on the overall result could be minimal.

Diagnosis of recurrent disease based on raised CA125 levels alone has been found to predate evidence of disease progression from clinical examinations or radiological scans by a median of 4 months in 70% of patients with ovarian cancer.[73] Thus, there is uncertainty as to whether patients diagnosed as having recurrent disease by only CA125 level would have the same diagnosis on radiological scan. In

addition, it is also possible that the degree of sensitivity to platinum could differ. For example, based on CA125 alone, a patient could be categorised as partially platinum-sensitive at baseline but as fully platinum-sensitive 4 months later with radiological confirmation. Of the trials identified, 7 RCTs reported that patients with only CA125 as an indicator of recurrent disease were enrolled.[23;28;29;31;47;61;66] In trials in patients with platinum-sensitive disease, there was considerable variation across the trials in the proportion of patients with non-measurable disease at baseline, ranging from 8.5% to 38.2%. In some trials, patients with non-measurable disease were not included in analyses of response rate. Despite the identified disparity in methods used to diagnose recurrent disease at baseline, as the proportion of patients in each group within the individual trials was well-balanced, the TAG considered that the heterogeneity could have a minimal impact on the NMA.

Considering heterogeneity among treatments evaluated, it is important to note that ICON4 evaluated the efficacy of adding paclitaxel to "conventional" platinum-based chemotherapy versus platinum-based therapy alone. A large proportion of patients in each treatment group received carboplatin as the platinum component of their regimen (80% in the paclitaxel plus platinum-based therapy group vs 29% in the platinum-based chemotherapy alone group). Of the remaining 20% of patients in the paclitaxel plus platinum group, 10% were administered cisplatin, and 5% received paclitaxel plus carboplatin or cisplatin, switching between the two platinum monotherapies. In the conventional platinum-based monotherapy group, 4% of patients received cisplatin alone, and a further 2% received either carboplatin or cisplatin monotherapy, switching between the two platinum monotherapies. Moreover, 17% of patients in the conventional chemotherapy group received the triple therapy of cyclophosphamide, doxorubicin, and cisplatin, which the ICON investigators had compared against carboplatin in an earlier trial and found no statistically significant difference between the treatments in effect on OS.[60] Although a small proportion of patients received platinum-treatment other than carboplatin, there is evidence that the regimens received have similar efficacy.

Although differences in key prognostic factors across the trials have been identified, when considering the trials that would inform the NMA for platinum-sensitive and for PRR disease, the TAG considers the trials sufficiently clinically homogeneous to compare clinical effectiveness of treatments.

Table 20. Population baseline characteristics of the included trials

Trial name	Intervention	Age (median, years)	Performance score	Proportion of patients with two or more lines of previous chemotherapy	Platinum sensitivity (interval since last chemotherapy)	Measure of ovarian cancer at baseline
Bafaloukos et al.[29]	PLDH plus carboplatin	62 (38–89)	ECOG 0: 55/93 (59%) ECOG 1: 30/93 (32%) ECOG 2: 1/93 (1%)	4/93 (4%)	6–12 months: 22/93 (23%) 12.1–24 months: 38/93 (41%) >24 months: 29/93 (31%)	Elevated CA125 only: 9/93 (10%)
	Paclitaxel plus carboplatin	63 (37–81)	ECOG 0: 62/96 (65%) ECOG 1: 27/96 (28%) ECOG 2: 0/96 (0%)	4/96 (4%)	6–12 months: 32/96 (33%) 12.1–24 months: 32/96 (33%) >24 months: 23/96 (24%)	Elevated CA125 only: 7/96 (7%)
CALYPSO (Pujade-Lauraine et al.[31]*)*	PLDH plus carboplatin	60.5 (24–82)	ECOG 0: 286/466 (61.4%) ECOG 1: 158/466 (33.9%) ECOG 2: 13/466 (2.8)	58/466 (12.4%)	6–12 months: 161/466 (35.0%) >12 months: 305/466 (65.0%)	Measurable disease: 281/466 (60.3%)
	Paclitaxel plus carboplatin	61 (27–82)	ECOG 0: 317/466 (62.5%) ECOG 1: 164/466 (32.3%) ECOG 2: 15/466 (3.0)	88/466 (17.3%)	6–12 months: 183/466 (36.1%) >12 months: 324/466 (63.9%)	Measurable disease: 321/466 (63.3%)
Alberts et al.[28]	PLDH plus carboplatin	66.9 (43–87)	Zubrod 0: 20/31 (65%) Zubrod 1: 11/31 (35%)	0/31 (0%)	6–12 months: 13/31 (43%) 12–24 months: 18/31 (57%)	Measurable disease: 19 (61%) Elevated CA125: 4 (13%) Other non-measurable disease: 8 (26%)
	Carboplatin alone	62.5 (31–80)	Zubrod 0: 16/30 (53%) Zubrod 1: 14/30 (47%)	0/30 (0%)	6–12 months: 13/30 (43%) 12–24 months: 17/30 (57%)	Measurable disease: 20 (67%) Elevated CA125: 2 (7%) Other non-measurable disease: 8 (27%)
OVA-301 (Monk et al. *[2010]*[30]*)*	Trabectedin plus PLDH	56.0 (26–82)	ECOG 0: 230/337 (68%) ECOG 1: 98/337 (29%) ECOG 2: 9/337 (3%)	0/337 (0%)	<6 months: 115/333 (35%) 6–12 months: 123/333 (37%) >12 months: 95/333 (28%)	All patients had measurable disease at baseline
	PLDH alone	58.0 (27–87)	ECOG 0: 192/335 (57%) ECOG 1: 132/335 (39%) ECOG 2: 11/335 (3%)	0/335 (0%)	<6 months: 117/330 (35%) 6–12 months: 91/330 (28%) >12 months: 122/330 (37%)	All patients had measurable disease at baseline

Gordon et al. *(2001)*[48]	PLDH	60 (27–87)	Karnofsky <80: 39/239 (16.3%) Karnofsky ≥80: 199/239 (83.3%)	0/239 (0%)	<6 months: 130/239 (54.4%) ≥6 months: 109/239 (45.6%)	Not reported
	Topotecan	60 (25–85)	Karnofsky <80: 37/235 (15.7%) Karnofsky ≥80: 195/235 (83.0%)	0/235 (0%)	<6 months: 130/239 (54.4%) ≥6 months: 109/239 (45.6%)	Not reported
Trial 30-57[13]	PLDH	60.5 (27-80)	Karnofsky <80: 11/108 (10.2%) Karnofsky ≥80: 95/108 (88%) Not available: 2/108 (1.9%)	0/108 (0%)	Not reported	All patients had measurable disease at baseline
	Paclitaxel	61.0 (20-78)	Karnofsky <80: 12/108 (11.1%) Karnofsky ≥80: 90/108 (83.3%) Not available: 6/108 (5.6%)	0/108 (0%)	<6 months: 67/108 (62%) ≥6 months: 41/108 (38%)	All patients had measurable disease at baseline
ten Bokkel Huinink et al. *(1997)*[21]	Topotecan	Mean: 59.2 (29–85)	ECOG 0: 41 (36.6%) ECOG 1: 51 (45.5%) ECOG 2: 20 (17.9%)	0/117 (0%)	<6 months: 52/112 (46.4%) ≥6 months: 60/112 (53.6%)	All patients had measurable disease at baseline
	Paclitaxel	Mean: 58.3 (29–79)	ECOG 0: 42 (36.8%) ECOG 1: 53 (46.5%) ECOG 2: 17 (14.9%)	0/118 (0%)	<6 months: 55/114 (48.4%) ≥6 months: 59/114 (51.8%)	All patients had measurable disease at baseline

Pfisterer et al.[49]	Gemcitabine plus carboplatin	59 (36–78)	ECOG 0: 83/178 (46.6%) ECOG 1: 79/178 (44.3%) ECOG 2: 11/178 (6.2%)	0/178 (0%)	6–12 months: 71/178 (39.9%) >12 months: 106/178 (59.6%)	Not reported
	Carboplatin alone	58 (21–81)	ECOG 0: 93/178 (52.2%) ECOG 1: 72/178 (40.4%) ECOG 2: 9/178 (5.1%)	0/178 (0%)	6–12 months: 71/178 (39.9%) >12 months: 107/178 (60.1%)	Not reported
ICON4/AGO-OVAR 2.2 (*Parmar* et al.[60]	Paclitaxel plus platinum	60.0	WHO 0: 246/392 (62.8%) WHO 1: 121/392 (30.9%) WHO 2–3: 25/392 (6.4%)	37/392 (9.4%)	6–12 months: 92/392 (35.0%) >12 months: 300/392 (65.0%)	Not reported
	Platinum monotherapy	59.2	WHO 0: 262/410 (63.9%) WHO 1: 122/410 (29.7%) WHO 2–3: 26/410 (6.3%)	30/410 (7.3%)	6–12 months: 111/410 (27.1%) >12 months: 299/410 (72.9%)	Not reported
Gonzalez-Martin et al.[47]	Paclitaxel plus carboplatin	59 (40–77)	ECOG 0: 17/41 (47.2%) ECOG 1: 17/41 (47.2%) ECOG 2: 2/41 (5.6%)	7/41 (18.4%)	6–12 months: 17/41 (45%) >12 months: 21/41 (55%)	WHO criteria: 27 (71%) CA125 criteria: 11 (28.9%)
	Carboplatin alone	61 (35–77)	ECOG 0: 14/40 (35.9%) ECOG 1: 18/40 (46.2%) ECOG 2: 7/40 (17.9%)	5/40 (12.5%)	6–12 months: 16/40 (40%) >12 months: 24/40 (60%)	WHO criteria: 25 (62.5%) CA125 criteria: 15 (37.5%)
CARTAXHY (*Lortholary* et al.[61])	Weekly paclitaxel plus carboplatin	60 (43–77)	0–1: 47/51 (92%) 2: 4/51 (8%)	15/51 (29%)	All patients platinum-resistant	Measureable (RECIST): 35/51 (68%) Elevated CA125 only: 14/51 (28%)
	Weekly paclitaxel	60 (30–80)	0–1: 54/57 (95%) 2: 3/57 (5%)	15/57 (26%)	All patients platinum-resistant	Measureable (RECIST): 32/57 (57%) Elevated CA125 only: 21/57 (37%)
Piccart et al.[62]	Paclitaxel	62 (37–81)	WHO 0–1: 35/41 (85%) WHO 2: 6/41 (15%)	11/41 (27%)	<6 months: 31/41 (76%) 6–12 months: 10/41 (24%)	Not reported
	Oxaliplatin	59 (28–71)	WHO 0–1: 38/45 (84%) WHO 2: 7/45 (16%)	16/45 (36%)	<6 months: 32/45 (71%) 6–12 months: 13/45 (29%)	Not reported

Gore et al.[24]	Oral topotecan	60 (23–80)	ECOG 0: 59/135 (45%) ECOG 1: 60/135 (46%) ECOG 2: 12/135 (9%)	0/135 (0%)	Platinum sensitive: 58 (43%) Platinum resistant: 37 (27%) Platinum refractory: 40 (30%)	All patients had measurable disease at baseline
	Intravenous topotecan	60 (27–80)	ECOG 0: 47/131 (35%) ECOG 1: 77/131 (57%) ECOG 2: 11/131 (8%)	0/131 (0%)	Platinum sensitive: 56 (43%) Platinum resistant: 36 (27%) Platinum refractory: 39 (30%)	All patients had measurable disease at baseline
Sehouli et al.[23]	Weekly topotecan	65 (41–82)	ECOG 0: 33/97 (34%) ECOG 1: 48/97 (49%) ECOG 2: 12/97 (12%)	28/97 (29%)	All patients platinum-resistant	Measurable disease: 86/97 (89%)
	Conventional topotecan	65 (36–85)	ECOG 0: 34/97 (35%) ECOG 1: 50/97 (52%) ECOG 2: 11/97 (11%)	31/97 (32%)	All patients platinum-resistant	Measurable disease: 90/97 (93%)
Omura et al.[66]	Paclitaxel 250 mg/m^2	62 (24–80)	GOG 0: 88/166 (53%) GOG 1: 63/166 (38%) GOG 2: 15/166 (9%)	0/166 (0%)	<6 months: 132/166 (79%) >6 months: 34/166 (21%)	134/166 (81%)
	Paclitaxel 175 mg/m^2	60 (23–88)	GOG 0: 89/164 (54%) GOG 1: 65/164 (40%) GOG 2: 10/164 (6%)	0/164 (0%)	<6 months: 125/164 (76%) >6 months: 39/164 (24%)	131/164 (80%)
Rosenberg et al.[59]	Weekly paclitaxel	59 (37–74)	WHO 0: 57/105 (54%) WHO 1: 40/105 (38%) WHO 2: 8/105 (7%)	0/105 (0%)	<6 months: 57/105 (54%) >6 months: 48/105 (46%)	All patients had measurable disease at baseline
	Three-weekly paclitaxel	60 (40–76)	WHO 0: 56/103 (54%) WHO 1: 33/103 (32%) WHO 2: 14/103 (16%)	0/103 (0%)	<6 months: 51/103 (50%) >6 months: 52/103 (50%)	All patients had measurable disease at baseline
Abbreviations used in table: GOG, Gynecologic Oncology Group; PLDH, pegylated liposomal doxorubicin hydrochloride; WHO, World Health Organisation.						

4.2.2 Assessment of effectiveness

Based on clinical expert advice, the Technology Assessment Group (TAG) has focused on the clinical effectiveness of interventions in populations defined by degree of platinum-sensitivity (i.e., platinum-sensitive [i.e., recurrence ≥6 months after last platinum-based treatment] and platinum resistant [i.e., recurrence <6 months after last platinum-based treatment] or refractory [progression during platinum-based treatment]). Where it was not possible to extract data for the pre-specified populations, for completeness, the TAG presents data for the full population of the study.

4.2.2.1 Overall survival

OS is universally accepted as a measure of benefit in trials evaluating treatments for cancer, and is generally considered to be the most reliable endpoint.[74] However, the large number of patients required to ensure adequate power to detect a difference between treatments and long follow-up periods can hinder the collection and analysis of survival data. The FDA and other regulatory authorities define OS as the time from randomisation until death from any cause.[74] It should be noted that some of the trials reported here define OS as the time from administration of first cycle of study drug until death from any cause. As the event recorded is all-cause mortality, there is no bias associated with measurement of the endpoint.

A potential area of confounding with measurement of OS derives from the use of post-progression therapies. It has been proposed that subsequent lines of therapy are likely to be more effective in the less clinically effective group than in the treatment group, and is more likely to be considered when there is no significant difference in OS between the treatment and the control. Confounding from post-progression therapy is most likely to be an issue in trials in which most patients cross over to the alternative group after progression or in trials in which the "new" therapy is available as a post-progression treatment in the control group.[75]

Summary of results for OS

Most trials identified reported results for the outcome of OS. No trial was identified evaluating treatments in a population solely comprising patients who were allergic or intolerant to platinum-based chemotherapy. Here, results for patients with platinum-sensitive or platinum-refractory/resistant (PRR) disease are summarised. For trials not limited to either platinum-sensitive or PRR patients (i.e., includes a mix of platinum-free interval [PFI]), results for the full trial population are presented in the main body of the text.

Results for OS for the subgroup of patients with platinum-sensitive (relapse ≥6 months after last platinum-based chemotherapy) ovarian cancer

Ten RCTs evaluating eight different head-to-head comparisons of interventions and comparators of interest were identified.

Trial name	Intervention	Comparator	HR (95%CI)
CALYPSO (Pujade-*Lauraine et al*.[55])	PLDH (30 mg/m^2) plus carboplatin every 21 days	Paclitaxel (175 mg/m^2) plus carboplatin every 21 days	0.99[a] (0.85 to 1.16)
Bafaloukos *et al*.[29]	PLDH (45 mg/m^2) plus carboplatin every 28 days	Paclitaxel (175 mg/m^2) plus carboplatin every 21 days	1.15 (0.78 to 1.66)
ICON4/AGO-OVAR 2.2 (Parmar *et al*.[60])	Paclitaxel plus platinum	Conventional platinum treatment	0.82 (0.69 to 0.97)
Gonzalez Martin *et al*.[47]	Paclitaxel (175 mg/m^2) plus carboplatin every 21 days	Carboplatin alone every 21 days	0.31 (0.14 to 0.68)
ten Bokkel Huinink *et al*. (2004)[51]	Topotecan (1.5 mg/m^2) for 5 days every 21 days	Paclitaxel (175 mg/m^2) every 21 days	1.010 (0.663 to 1.541)
Trial 30-57 (Taken from TA91)	PLDH (50 mg/m^2) every 28 days	Paclitaxel (175 mg/m^2) every 21 days	1.051 (0.663 to 1.667)
Gordon *et al*. (2001)[53]	PLDH (50 mg/m^2) every 28 days	Topotecan (1.5 mg/m^2) for 5 days every 21 days	1.432 (1.066 to 1.923)
Alberts *et al*.[54]	PLDH (30 mg/m^2) plus carboplatin every 4 weeks	Carboplatin alone every 4 weeks	0.70 (0.40 to 1.21)
OVA-301 (Monk *et al*. [2010][30])	Trabectedin (1.1 mg/m^2) plus PLDH (30 mg/m^2) every 3 weeks	PLDH (50 mg/m^2) every 4 weeks	0.83 (0.67 to 1.04)
Pfisterer *et al*.[49]	Gemcitabine (1,000 mg/m^2) plus carboplatin every 21 days	Carboplatin alone every 21 days	0.96 (0.75 to 1.23)

[a] HR as reported is for paclitaxel plus carboplatin versus PLDH plus carboplatin. That is, HR <1 favours paclitaxel plus carboplatin.
[b] HR >1 favours PLDH.
Abbreviations used in table: CI, confidence interval; HR, hazard ratio; PLDH, pegylated liposomal doxorubicin hydrochloride.

To inform the decision problem, a network-meta-analysis (NMA) was carried out. Based on trials identified, it was not possible to construct a complete network. Two discrete networks were generated, one evaluating platinum-based therapies and the second comparing non-platinum-based regimens. It should be stressed that results from the two discrete networks are not directly comparable.

In the network evaluating platinum-based chemotherapies, PLDH plus carboplatin and paclitaxel plus carboplatin were found to significantly improve OS compared with platinum monotherapy. However, no statistically significant differences in OS were identified between the remaining treatments considered in the network.

Comparator	Paclitaxel plus carboplatin	Gemcitabine plus carboplatin	PLDH plus carboplatin	Platinum monotherapy
Paclitaxel plus carboplatin	–	1.247 (0.921 to 1.652)	1.023 (0.889 to1.172)	1.290 (1.096 to1.509)
Gemcitabine plus carboplatin	–	–	0.839 (0.602 to1.135)	1.051 (0.815 to1.335)
PLDH plus carboplatin	–	–	–	1.267 (1.030 to 1.545)
Platinum monotherapy	–	–	–	–

Comparator is listed in the left-hand side column. Results presented are HR and accompanying CrI. HR <1 favours the intervention (listed in the top table row) and HR >1 favours the comparator.
Abbreviations used in table: CrI, credible interval; HR, hazard ratio.

Analysis of non-platinum-based regimens indicates that that PLDH monotherapy and trabectedin plus PLDH are both significantly more effective at prolonging OS than topotecan monotherapy. No other significant OS differences were identified.

Comparator	PLDH monotherapy	Trabectedin plus PLDH	Paclitaxel monotherapy	Topotecan monotherapy
PLDH monotherapy	–	0.835 (0.667 to 1.032)	1.219 (0.850 to 1.690)	1.367 (1.035 to 1.770)
Trabectedin plus PLDH	–	–	1.479 (0.962 to 2.176)	1.658 (1.157 to 2.307)
Paclitaxel monotherapy	–	–	–	1.145 (0.808 to 1.576)
Topotecan monotherapy	–		–	–

Comparator is listed in the left-hand side column. Results presented are HR and accompanying CrI. HR <1 favours the intervention (listed in the top table row) and HR >1 favours the comparator.
Abbreviations used in table: CrI, credible interval; HR, hazard ratio; PLDH, pegylated liposomal doxorubicin hydrochloride.

PFI is a prognostic factor for response. To investigate any potential differences in clinical efficacy between treatments with PFI, where data were available, OS was analysed for the subgroups of patients with full platinum-sensitivity (FPS; relapse >12 months after last platinum-based treatment) and partial platinum-sensitivity (PPS; relapse ≥6–≤12 months after last platinum-based treatment). Few trials involving platinum-sensitive patients evaluated treatment effect in these two subgroups: four trials afforded data on FPS and four trials on PPS. Two trials evaluated platinum-based regimens and two trials non-platinum-based regimens.

Results in patients with FPS

Three of the four trials reported an HR as a measure of treatment effect.[19;53;55] The difference between treatment groups was not statistically significant in any trial. The fourth trial did not report an HR, but the proportion of people having an event was similar in each treatment group.[60]

Trial	Intervention	Comparator	HR (95%CI)
CALYPSO[55]	PLDH (30 mg/m^2) plus carboplatin every 21 days	Paclitaxel (175 mg/m^2) plus carboplatin every 3 weeks	0.99 (0.81 to 1.21)
ICON4/AGO-OVAR 2.2[60]	Paclitaxel plus platinum	Conventional platinum treatment	NR
Gordon *et al*. (2001)[53]	PLDH (50 mg/m^2) every 28 days	Topotecan (1.5 mg/m^2) daily for 5 days every 21 days	1.15[a] (0.714 to 1.852)
OVA-301[30;63]	Trabectedin (1.1 mg/m^2) plus PLDH (30 mg/m^2) every 21 days	PLDH (50 mg/m^2) every 4 weeks	0.89[b] (0.58 to 1.35)

[a] HR >1 favours PLDH.
[b] HR taken from TA222.[19]
Abbreviations used in table: CI, confidence interval; HR, hazard ratio; PLDH, pegylated liposomal doxorubicin hydrochloride.

HR for OS was not available from ICON4/AGO-OVAR 2.2[60] and so it was not possible to carry out an NMA.

Results in patients with PPS

In patients with PPS ovarian cancer, PLDH monotherapy has been found to significantly prolong OS compared with topotecan. Furthermore, trabectedin plus PLDH has been found to be significantly more effective than PLDH alone at increasing OS. The trial comparing platinum-based regimens did not report an HR for OS in this subgroup of patients. However, a similar proportion of patients in each group had had an event at the time of analysis.

Trial	Intervention	Comparator	HR (95%CI)
CALYPSO[55]	PLDH (30 mg/m^2) plus carboplatin every 21 days	Paclitaxel (175 mg/m^2) plus carboplatin every 3 weeks	1.01 (0.80 to 1.28)
ICON4/AGO-OVAR 2.2[60]	Paclitaxel plus platinum	Conventional platinum treatment	NR
OVA-301[30;63]	Trabectedin (1.1 mg/m^2) plus PLDH (30 mg/m^2) every 21 days	PLDH (50 mg/m^2) every 4 weeks	0.64 (0.47 to 0.86)
Gordon *et al*. (2001)[53]	PLDH (50 mg/m^2) every 28 days	Topotecan (1.5 mg/m^2) daily for 5 days every 21 days	1.58[a] (1.071 to 2.335)

[a] HR >1 favours PLDH.
Abbreviations used in table: CI, confidence interval; HR, hazard ratio; PLDH, pegylated liposomal doxorubicin hydrochloride.

The results of the NMA are in agreement with the results of the individual trials. Trabectedin plus PLDH was found to be significantly more effective at increasing OS than PLDH monotherapy and topotecan monotherapy. The difference between PLDH monotherapy and topotecan monotherapy remained significant and favoured PLDH monotherapy.

Comparator	PLDH monotherapy	Trabectedin plus PLDH	Topotecan monotherapy
PLDH monotherapy	–	0.621 (0.493 to 0.771)	1.610 (1.072 to 2.334)
Trabectedin plus PLDH	–	–	2.628 (1.636 to 4.011)
Topotecan monotherapy	–	–	–

Comparator is listed in the left-hand side column. Results presented are HR and accompanying CrI. HR <1 favours the intervention (listed in the top table row) and HR >1 favours the comparator.
Abbreviations used in table: CrI, credible interval; HR, hazard ratio; PLDH, pegylated liposomal doxorubicin hydrochloride.

Results in OS for the subgroup of patients with platinum-resistant/refractory ovarian cancer

Platinum resistant disease has been defined as disease that initially responds followed by relapse <6 months after last platinum-based chemotherapy. Platinum-refractory indicates disease does not respond to or progresses during first-line platinum-based chemotherapy.

Five RCTs reporting results for five different head-to-head comparisons involving PRR patients were identified. Two RCTs enrolled only patients with PRR, with the remaining three RCTs reporting results from a subgroup of patients within the trial. None of the trials identified a significant difference in OS between the two treatment groups evaluated.

Trial name	Intervention	Comparator	HR (95%CI)
ten Bokkel Huinink *et al*. (2004)[51]	Topotecan (1.5 mg/m^2) for 5 days every 21 days	Paclitaxel (175 mg/m^2) every 21 days	0.738 (0.498 to 1.093)
Trial 30-57 (Taken from TA91)	PLDH (50 mg/m^2) every 28 days	Paclitaxel (175 mg/m^2) every 21 days	0.865 (0.61 to 1.24)
Gordon *et al*. (2001)[53]	PLDH (50 mg/m^2) every 28 days	Topotecan (1.5 mg/m^2) for 5 days every 21 days	1.069[a] (0.823 to 1.387)
Sehouli *et al*.[23]	Topotecan (4.0 mg/m^2) (weekly; days 1, 8, and 15) every 28 days	Topotecan (1.25 mg/m^2) for 5 consecutive days every 21 days	1.04 (0.74 to 1.44)
Lortholary *et al*.[61]	Weekly paclitaxel (80 mg/m^2) plus carboplatin	Weekly paclitaxel (80 mg/m^2) on 4 week cycle	1.074 (0.859 to 1.341)

[a] HR >1 favours PLDH.
Abbreviations used in table: CI, confidence interval; HR, hazard ratio; PLDH, pegylated liposomal doxorubicin hydrochloride.

Four of the five identified trials were included in the network; the treatment regimens evaluated in the trial reported by Lortholary *et al*.[61] did not inform the network. Trabectedin plus PLDH is outside of the scope for this review for the population of PRR patients; data have been included within the network to capture all the available evidence but are not included in the economic analysis. The results of the NMA are in alignment with the results of the individual trials, with no statistically significant differences in OS among the treatments evaluated

Comparator	PLDH monotherapy	Trabectedin plus PLDH	Paclitaxel monotherapy	Topotecan monotherapy	Topotecan monotherapy (weekly)
PLDH monotherapy	–	0.928 (0.699 to 1.208)	1.053 (0.783 to 1.382)	0.973 (0.764 to 1.221)	1.026 (0.669 to 1.505)
Trabectedin plus PLDH	–	–	1.155 (0.763 to 1.681)	1.069 (0.734 to 1.508)	1.127 (0.666 to 1.775)
Paclitaxel monotherapy	–	–	–	0.939 (0.694 to 1.244)	0.989 (0.619 to 1.499)
Topotecan monotherapy	–	–	–	–	1.054 (0.744 to 1.447)

Comparator is listed in the left-hand side column. Results presented are HR and accompanying CrI. HR <1 favours the intervention (listed in the top table row) and HR >1 favours the comparator.
Abbreviations used in table: CrI, credible interval; HR, hazard ratio; PLDH, pegylated liposomal doxorubicin hydrochloride; topotecan monotherapy (weekly), topotecan (4.0 mg/m^2) (weekly; days 1, 8, and 15) every 28 days.

Platinum sensitive

Pegylated liposomal doxorubicin hydrochloride plus carboplatin versus paclitaxel plus carboplatin

In the trial carried out by Bafaloukos *et al*.[29], OS was calculated from the initiation of treatment until the date of last follow-up or the patient's death. Analysis of OS was carried out on the ITT population when 122 patients were known to have died. It is important to note that the study was not powered to detect differences in OS. Median OS was 24.7 months in the PLDH plus carboplatin group and 29.4 months in the paclitaxel plus carboplatin group, with no statistically significant difference between the groups (HR 1.15, 95% CI: 0.78 to 1.66; p = 0.455; Table 25). The proportion of patients receiving

post-progression therapy was similar between the groups (61/93 [65.6%] patients in the PLDH plus carboplatin group vs 61/96 [63.5%] patients in the paclitaxel plus carboplatin group).

The authors carried out a univariate and multivariate analysis based on the Cox proportional hazards model to evaluate the influence of prespecified prognostic factors on survival. Results indicated that performance status score of zero and longer PFI (>12 months) were important independent prognostic factors for survival (Table 21).

Table 21. Results from analysis of influence of proposed prognostic factors on overall survival by baseline characteristics[29]

Variable	Univariate			Multivariate		
	HR	95% CI for HR	p value	HR	95% CI for HR	p value
Age (years)						
≤65 years	1	–		–	–	–
>65 years	0.83	0.57 to 1.21	0.329	–	–	–
Performance status						
0	1	–		1		
1–2	1.96	1.32 to 2.90	0.001	1.89	1.25 to 2.88	0.003
Previous exposure to taxanes						
No	1	–		–	–	–
Yes	1.18	0.62 to 2.27	0.610	–	–	–
Disease status						
Non-measurable	1	–		–	–	–
Measurable	1.49	0.88 to 2.55	0.141	–	–	–
Platinum-free interval						
6–12 months	1	–		1	–	
12.1–24 months	0.58	0.37 to 0.89	0.013	0.54	0.34 to 0.86	0.009
>24 months	0.37	0.22 to 0.61	<0.001	0.36	0.21 to 0.61	<0.001
Abbreviations used in table: CI, confidence interval; HR, hazard ratio.						

Wagner *et al.*[55] report mature OS data from CALYPSO (Pujade-Lauraine *et al.*[31]). Based on a median follow-up of 49 months (range 0–68 months) and a total of 663 deaths, median OS was 30.7 months in the PLDH plus carboplatin group and 33.0 months in the paclitaxel plus carboplatin group. The accompanying HR of 0.99 (95% CI: 0.85 to 1.16; p = 0.94; Table 25) indicates that there was no statistically significant difference between treatments in OS; HR reported is for paclitaxel plus carboplatin versus PLDH plus carboplatin. It should be noted that OS was not defined. Analysis of cross-over treatment identified an imbalance between treatment groups, with a significantly larger proportion of patients randomised to paclitaxel plus carboplatin receiving PLDH (68%) compared with the alternative scenario of patients randomised to paclitaxel plus carboplatin receiving subsequent paclitaxel (43%; p <0.001).

In a multivariate analysis, TFI ≥12 months, ECOG performance status 0, CA125 <100 U/ml, non-measurable disease and one involved disease site were identified as factors significantly correlated with OS (Table 22).

Table 22. Results from univariate and multivariate analysis of influence of overall survival by baseline characteristics[55]

Variable	Univariate			Multivariate		
	HR	95% CI for HR	p value	HR	95% CI for HR	p value
Age (years)						
<70 years	0.98	0.83 to 1.16	0.80	–	–	–
≥70 years	1.10	0.76 to 1.58	0.62	–	–	–
BMI (kg/m^2)						
<30	1.00	0.85 to 1.19	0.98	1		
≥30	0.95	0.67 to 1.35	0.76	1.89	1.25 to 2.88	0.003
TFI (months)						
6–12	1.01	0.80 to 1.28	0.92	–	–	–
≥12	0.99	0.81 to 1.21	0.90	0.50	0.43 to 0.59	<0.001
Measurable disease/longest lesion (mm)						
No	0.88	0.65 to 1.21	0.56	–	–	–
Yes	1.07	0.90 to 1.27	0.47	–	–	–
≤50	–	–	–	1.28	1.04 to 1.57	0.02
>50	–	–	–	1.78	1.40 to 2.26	<0.001
CA125 (U/ml)						
<100	–	–	–	–	–	–
≥100	–	–	–	1.78	1.49 to 2.14	<0.001
Number of prior lines of chemotherapy						
1	0.99	0.84 to 1.17	0.92	1	–	
≥2	0.97	0.65 to 1.46	0.74	0.54	0.34 to 0.86	0.009
ECOG performance status						
0	0.99	0.81 to 1.20	0.92	–	–	–
≥1	0.99	0.78 to 1.27	0.95	1.37	1.17 to 1.60	<0.001
Involved disease sites						
1	–	–	–	–	–	–
>1	–	–	–	1.26	1.05 to 1.52	0.014

Abbreviations used in table: BMI, body mass index; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; TFI, treatment-free interval.

Pegylated liposomal doxorubicin hydrochloride plus carboplatin versus carboplatin alone

Data from Alberts *et al*.[28] were immature in terms of OS (based on data for 32 patients who had died). Longer-term data (evaluating 50 patients who had died) reported by Markman *et al*.[54] found a median OS of 31 months in the PLDH plus carboplatin group and 18 months in the carboplatin alone group, giving a median OS gain of 8 months with PLDH plus carboplatin (p = 0.20). Markman *et al*.[54] did not report the HR for the comparison between groups. Using the methods presented by

Tierney *et al*.[76], the TAG calculated an HR of 0.70 (95% CI 0.40 to 1.21; Table 25), where HR <1 favours PLDH plus carboplatin.

Trabectedin plus PLDH versus PLDH alone

At the time of first publication of analysis of PFS from OVA-301 (Monk *et al*. [2010][30]), OS data were immature. Final OS analysis was reported in a follow-up study,[63] in which OS analysis was based on 522 events (analysis planned once 520 deaths had occurred). Various subgroup analyses of OS are reported, including platinum-sensitive versus platinum-resistant.

In the subgroup of patients with platinum-sensitive disease (relapse >6 months after last platinum-based treatment), of 430 patients randomised, 316 had died (156 in the trabectedin plus PLDH group vs 160 in the PLDH alone group). Median OS in the trabectedin plus PLDH group was 27.0 months compared with 24.1 months in the PLDH alone group. The difference between groups did not reach statistical significance (HR 0.83, 95% CI: 0.67 to 1.04; p = 0.106; Table 25).

Observation of an unexpected, and statistically significant, difference in mean baseline PFI that favoured the PLDH group prompted the authors to carry out a *post hoc* analysis based on three categorisations of PFI (6 months vs 6–12 months vs >12 months). The analysis suggested that patients with a longer PFI have longer OS, with median OS in each category of:

- <6 months PFI: 13.6 months (95% CI: 11.7 to 14.8);
- 6–12 months PFI: 20.3 months (95% CI: 17.7 to 21.7);
- >12 months PFI: 32.5 months (95% CI: 28.4 to 38.5).

It should be noted that the analysis carried out (log rank) stratified by dichotomous PFI and could not account for the observed imbalance between treatment groups in baseline PFI.

In the manufacturer's submission PharmaMar present the results of a multivariate analysis Cox regression performed to provide a result for treatment effect adjusting for pre-specified key prognostic factors (including PFI). The HR for OS from this analysis for the platinum-sensitive population was 0.78 (95% CI: 0.62 to 0.98; p = 0.0319; taken from the PharmaMar submission), which suggests a 22% reduction for death in patients randomised to trabectedin plus PLDH. In this analysis, median OS was 28.4 months with trabectedin plus PLDH versus 24.1 months with PLDH monotherapy. As noted earlier, as a result of variation in the reporting of adjusted and unadjusted HRs, the TAG has used unadjusted HRs in the NMA.

Pegylated liposomal doxorubicin hydrochloride versus topotecan

Data for OS for patients with platinum-sensitive disease from Gordon *et al*. (2001)[48] are based on 46% of the full trial population. OS results are based on a modified ITT population and OS was

defined as the time from the start of study drug administration to death. In the longer term follow-up study (Gordon *et al*. [2004][(53)]), for the full population, OS results are also reported based on the ITT population and the more commonly used definition of OS of time from date of randomisation until date of death (presented in Section 4.1.7.1). At the time of analysis, 87% of patients had died and 13% of observations were censored.

In platinum-sensitive patients, Gordon *et al*. (2004)[(53)] found a median OS of 107.9 weeks in the PLDH group compared with 70.1 weeks in the topotecan group, giving a median OS gain of 30.8 weeks with PLDH. The difference between groups was statistically significant and favoured PLDH (HR 1.432, 95% CI: 1.066 to 1.923; p = 0.017; Table 25); in this analysis, HR >1 favours PLDH. The gain in OS corresponded to a 30% reduction in the risk of death for patients treated with PLDH. Survival rates at 1, 2, and 3 years are presented in Table 23. Results for PPS, FPS and platinum-refractory/resistant (PRR) patients are discussed in subsequent sections.

Table 23. Survival rates in platinum-sensitive patients in PLDH and topotecan groups

Treatment	Survival rate		
	1 year	2 years	3 years
PLDH	74.1% (95% CI 65.8% to 82.4%)	51.2% (95% CI 41.6% to 60.7%)	28.4% (95% CI 19.6% to 37.1%)
Topotecan	66.2% (95% CI 57.4% to 75.1%)	31.0% (95% CI 22.2% to 39.7%)	17.5% (95% CI 10.2% to 24.7%)

Pegylated liposomal doxorubicin hydrochloride versus paclitaxel

Trial 30–57 evaluated OS as the primary outcome.[(13)] TA91 presents results for the subgroup of patients with platinum-sensitive disease (44 patients in the PLDH group vs 41 patients in the paclitaxel group). Median OS was 65.4 weeks (range: 3.9–263.7+) with PLDH and 57.0 weeks (range: 14–172.3) with paclitaxel. The corresponding HR of 1.051 (95% CI: 0.663, 1.667; Table 25) indicates that the difference between treatments is not statistically significant; HR >1 favours PLDH.

Topotecan versus paclitaxel

ten Bokkel Huinink *et al*. (1997)[(21)] defined OS as time from initial drug administration to death. Analysis of OS for the subgroup of patients with platinum-sensitive (late relapse) disease is not reported in either publication by ten Bokkel Huinink *et al*. (1997 and 2004)[(21;51)] reporting OS data. TA91 found no statistically significant difference between topotecan and paclitaxel in OS, reporting an unadjusted HR of 1.010 (95% CI: 0.663 to 1.541; Table 25) in platinum-sensitive patients, where HR <1 favours topotecan.[(13)] It should be noted that interpretation of OS results are potentially confounded by the permitted cross-over to the alternative treatment should a patient not respond to their allocated treatment. In the full population, 43.8% (49/112) and 53.5% (61/114) in the topotecan and paclitaxel groups, respectively, crossed-over to the alternative treatment during the trial.

Gemcitabine plus carboplatin versus carboplatin alone

In the trial carried out by Pfisterer *et al*.[49], OS was measured from the date of randomisation to the date of death from any cause. It should be noted that the trial was not powered to detect a difference between treatments in OS. At the time of analysis, 71% of patients had died. The RCT found no statistically significant difference between gemcitabine plus carboplatin and carboplatin alone in median OS (HR 0.96, 95% CI 0.75 to 1.23; p = 0.7349). Median OS was 18.0 months in the gemcitabine plus carboplatin group and 17.3 months in the carboplatin alone group.

Paclitaxel plus carboplatin versus platinum-based therapy alone

ICON4/AGO-OVAR 2.2 defined OS as the time from randomisation to death from any cause.[60] Patients known to be alive at the time of analysis were censored at the time of their last follow-up. At the time of analysis (median follow up of 42 months), 530 patients (66%) had died. Median OS was significantly prolonged in the paclitaxel plus platinum-based chemotherapy compared with platinum-based chemotherapy alone (HR 0.82, 95% CI: 0.69 to 0.97; p = 0.02; Table 25). The difference between groups translates into an absolute difference in 2-year survival of 7% in favour of adding paclitaxel to platinum-based chemotherapy (57% vs 50%). Paclitaxel plus platinum-based chemotherapy was associated with a gain in median OS of 5 months (median OS: 29 months with paclitaxel plus platinum-based chemotherapy vs 24 months with platinum-based therapy alone).

The authors of ICON4/AGO-OVAR 2.2 also carried out an exploratory analysis to investigate the effect of randomisation strata on OS (summarised in Table 24).[60] No statistically significant difference between treatment groups was identified for any of the subgroups analysed but, as the authors noted, many of the subgroups were small and may have lacked the power to detect any real differences between the groups. A non-significant trend was noted within the subgroups of age (<55 vs 55–65 vs >65) and the number of previous lines of chemotherapy (1 vs 2 vs >2).

Table 24. Effect of paclitaxel plus platinum chemotherapy on overall survival in predefined subgroups[60]

Randomisation strata	Number of events per number of patients		p value (interaction or trend)
	Paclitaxel plus platinum	Platinum alone	
Randomisation group			
ICON4 MRC CTU	169/266	176/270	0.84 (interaction)
ICON4 Italy	67/100	80/113	
AGO	19/26	19/27	
Age (years)			
<55	77/127	77/123	0.84 (trend)
55–65	100/151	106/162	
>65	78/114	92/125	

WHO performance			
0	146/246	161/262	0.53 (interaction)
>0	109/146	114/148	
Intended platinum treatment			
Carboplatin	206/332	215/341	0.16 (interaction)
Cisplatin	49/60	60/69	
Previous lines of chemotherapy			
1	227/354	260/380	0.08 (trend)
2	18/22	12/24	
>2	10/15	3/6	
Time since completion of last chemotherapy cycle (months)			
≤12	75/92	88/111	0.21 (interaction)
≥12	180/300	187/299	
Previous exposure to taxane			
No	154/223	176/235	0.49 (interaction)
Yes	101/169	99/175	
Abbreviations used in table: AGO, Arbeitsgemeinschaft Gynaekologische Onkologie; ICON, International Collaborative Ovarian Neoplasm; WHO, World Health Organization.			

The data reported by Gonzalez-Martin *et al*.[47] for OS are immature. At the time of analysis, median OS had not been reached in the paclitaxel plus carboplatin group. Of the 81 patients randomised, 32 patients had died, 23 in the carboplatin alone group and 9 in the paclitaxel plus carboplatin group. Analysis of available OS data found that median OS was prolonged in the paclitaxel plus carboplatin group, being significantly longer than the median OS of 72.7 weeks in the carboplatin alone group (HR 0.31, 95% CI: 0.14 to 0.68; p = 0.0021; Table 25). OS was defined as time from date of randomisation to death. It should be noted that the study was not powered to identify a difference between groups in OS and that the statistical comparative analysis was exploratory.

Table 25. Summary of results for overall survival in the platinum-sensitive recurrent ovarian cancer

Study	Intervention	Comparison	INT	COMP	Hazard ratio	95% CI	P value
			Median overall survival (events/N)				
Alberts *et al*.[54]	PLDH (30 mg/m^2) plus carboplatin (AUC 5) every 4 weeks	Carboplatin (AUC 5) every 4 weeks	31 months (26/31)	18months (24/30)	0.70[a]	0.40 to 1.21	0.20
Bafaloukos *et al*.[29]	PLDH (45 mg/m^2) plus carboplatin (AUC 5) on day 1 every 28 days	Paclitaxel 175 mg/m^2 plus carboplatin AUC 5 on day 1 every 21 days	24.7 months (events NR)	29.4 months (events NR)	1.15	0.78 to 1.66	0.455[c]

Gordon *et al*. (2001)[53]	PLDH (50 mg/m^2) every 28 days	Topotecan 1.5 mg/m^2 per day for 5 days every 21 days	107.9 weeks (N = 109)	70.1 weeks (N = 111)	1.432[b]	1.066 to 1.923	0.017
ICON4/ AGO-OVAR 2.2[60]	Paclitaxel plus platinum	Conventional platinum treatment	29 months	24 months	0.82	0.69 to 0.97	0.02
OVA-301[30;63]	Trabectedin (1.1 mg/m^2) plus PLDH (30 mg/m^2) every 3 weeks	PLDH (50 mg/m^2) every 4 weeks	27.0 months (156/218)	24.1 months (160/211)	0.83	0.67 to 1.04	0.106[c]
CALYPSO[55]	PLDH (30 mg/m^2) plus carboplatin (AUC 5) every 21 days	Paclitaxel (175 mg/m^2) plus carboplatin (AUC 5) every 21 days	33.0 months (346/509)	30.7 months (317/467)	0.99[f]	0.85 to 1.16	0.94[c]
Gonzalez Martin *et al*.[47]	Paclitaxel (175 mg/m^2) plus carboplatin (AUC 5) every 21 days	Carboplatin (AUC 5) alone every 21 days	Not yet reached (9/41)	72.7 weeks (23/40)	0.31	0.14 to 0.68	0.0021[c]
Pfisterer *et al*.[49]	Gemcitabine plus carboplatin every 21 days	Carboplatin alone every 21 days	18.0 months	17.3 months	0.96	0.75 to 1.23	0.7349
ten Bokkel Huinink *et al*. (2004)[51]	Topotecan (1.5 mg/m^2) for 5 days every 21 days	Paclitaxel (175 mg/m^2) every 21 days			1.010[d]	0.663 to 1.541	
Trial 30-57{21736}	PLDH (50 mg/m^2) every 28 days	Paclitaxel (175 mg/m^2) every 21 days	65.4 weeks	57.0 weeks	1.051[e]	0.663 to 1.667	0.833

[a] HR calculated by the Technology Assessment Group using the method provided by Tierney *et al*.[76]

[b] HR >1 favours PLDH.

[c] log-rank.

[d] data not presented in ten Bokkel Huinink *et al*. (2004)[51]. HR taken from TA91; HR <1.0 favours topotecan.

[e] HR >1.0 favours PLDH.

[f] HR in final OS analysis is reported for paclitaxel plus carboplatin versus PLDH plus carboplatin.

Abbreviations used in table: AUC, area under curve; CI, 95% confidence interval; COMP, comparator; INT, intervention; NR, not reported; PLDH, pegylated liposomal doxorubicin hydrochloride.

Network meta-analysis (platinum sensitive)

The RCTs available for inclusion in the NMA evaluating OS in patients with platinum-sensitive recurrent ovarian cancer are summarised in Table 25. Unfortunately, as described earlier, a single network could not be constructed out of the available trials. The two networks constructed for this outcome are depicted in Figure 4.

Network 1 (Figure 4a) consisted of the following comparators:

- paclitaxel plus carboplatin;
- gemcitabine plus carboplatin;
- PLDH plus carboplatin;
- platinum as a monotherapy.

Paclitaxel plus carboplatin was chosen as the baseline treatment as this would best help inform the economic evaluation conducted by the TAG (Section 5.2.7). However, results are reported in Table 26 sequentially covering all possible comparisons. Overall, there was no significant difference (at the 5% level) for any of the doublet chemotherapies assessed compared with paclitaxel plus carboplatin. Platinum monotherapy was associated with a significant reduction in OS compared with all doublet chemotherapies, with the exception of gemcitabine plus carboplatin, where no significant difference was found.

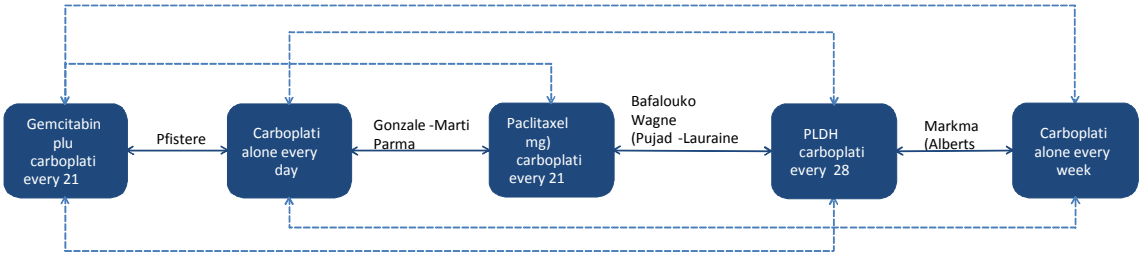
Network 2 (Figure 4b) consisted of the following comparators:

- PLDH monotherapy;
- trabectedin plus PLDH;
- paclitaxel monotherapy;
- topotecan monotherapy.

PLDH monotherapy was chosen as the baseline treatment as this would best help inform the economic evaluation conducted by the TAG (Section 5.2.7). However, results are reported in Table 26 sequentially covering all possible comparisons. Overall, there was no significant difference (at the 5% level) for trabectedin plus PLDH or paclitaxel monotherapy compared with PLDH monotherapy. Topotecan monotherapy was associated with a significant reduction in OS compared with all other chemotherapy regimens assessed, with the exception of paclitaxel monotherapy, where no significant difference was found (albeit with a non-significant trend in favour of paclitaxel monotherapy).

Figure 4. Networks for overall survival for people with platinum-sensitive recurrent ovarian cancer

4a. Network 1



4b. Network 2

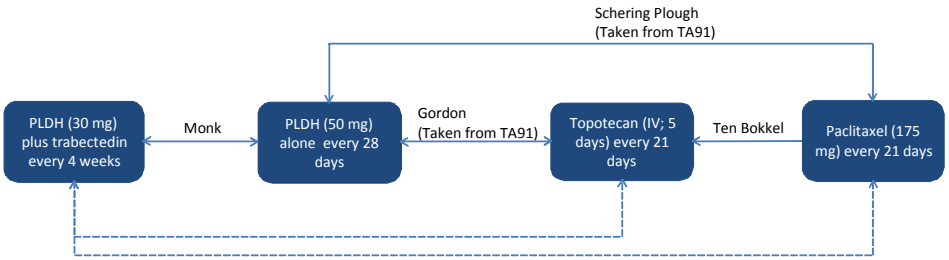


Table 26. Results of the network meta-analysis for overall survival for people with platinum-sensitive recurrent ovarian cancer

Comparison	HR	95% CrI	
		Lower limit	Upper limit
Network 1			
Versus paclitaxel plus carboplatin (HR <1 favours comparator, HR >1 favours paclitaxel plus carboplatin)			
Gemcitabine plus carboplatin	1.247	0.921	1.652
PLDH plus carboplatin	1.023	0.889	1.172
Platinum as a monotherapy	1.290	1.096	1.509
Versus gemcitabine plus carboplatin (HR <1 favours comparator, HR >1 favours gemcitabine plus carboplatin)			
PLDH plus carboplatin	0.839	0.602	1.135
Platinum as a monotherapy	1.051	0.815	1.335
Versus PLDH plus carboplatin (HR <1 favours comparator, HR >1 favours PLDH plus carboplatin)			
Platinum as a monotherapy	1.267	1.030	1.545

Network 2			
Versus PLDH monotherapy ***(HR <1 favours comparator, HR >1 favours PLDH monotherapy)***			
Trabectedin plus PLDH	0.835	0.667	1.032
Paclitaxel monotherapy	1.219	0.850	1.690
Topotecan monotherapy	1.367	1.035	1.770
Versus trabectedin plus PLDH ***(HR <1 favours comparator, HR >1 favours trabectedin plus PLDH)***			
Paclitaxel monotherapy	1.479	0.962	2.176
Topotecan monotherapy	1.658	1.157	2.307
Versus paclitaxel monotherapy ***(HR <1 favours comparator, HR >1 favours paclitaxel monotherapy)***			
Topotecan as a monotherapy	1.145	0.808	1.576
Abbreviations used in table: CrI, Credible Interval; HR, hazard ratio; PLDH, pegylated liposomal doxorubicin hydrochloride.			

Fully platinum sensitive

Pegylated liposomal doxorubicin hydrochloride plus carboplatin versus paclitaxel plus carboplatin

Mature OS data from CALYPSO are reported in a follow-up publication to that of Pujade-Lauraine *et al*.[31;55] A univariate Cox regression analysis was carried out in prespecified patient subgroups, one of which was based on TFI of 6–12 months (PPS) versus ≥12 months (FPS). A total of 631 patients (305 patients in the PLDH plus carboplatin group and 326 patients in the paclitaxel plus carboplatin group) had a TFI of ≥12 months. The univariate analysis identified no statistically significant difference between PLDH plus carboplatin and paclitaxel plus carboplatin in OS in this subgroup of patients (HR 0.99, 95% CI: 0.81 to 1.21; p = 0.90). It should be noted that OS was not defined.

Trabectedin plus PLDH versus PLDH alone

Neither the long-term follow-up study of OVA-301 (Monk *et al*. [2012][63]) nor the accompanying publication presenting results for the subgroup of patients with PPS report data on OS in the FPS subgroup.[64] Although TA222 reports OS data for patients with FPS disease, data are based 81% of the planned 520 deaths for the full trial population and are therefore immature.[19] Data are reported here for completeness but have not been included in the NMA. In TA222, median OS in the FPS subgroup is reported as 31.7 months in the PLDH alone group.[19] Median OS had not been reached in the trabectedin plus PLDH group. Accompanying HR of 0.89 (95% CI: 0.58 to 1.35; p = 0.5746) indicates that there is no statistically significant difference between treatments in OS in this subgroup of patients. In addition to being based immature data, this is a *post hoc analysis*, and as such is exploratory and hypothesis generating.

Pegylated liposomal doxorubicin hydrochloride versus topotecan

In the subgroup of patients with FPS ovarian cancer (PFI of >12 months; 97 patients), Gordon *et al*. (2004)[53] found no statistically significant difference between PLDH and topotecan in OS, with an HR of 1.15 (95% CI: 0.714 to 1.852; p = 0.057; Table 27), where HR >1 favours PLDH. The median OS in each group was not reported. It should be noted that the number of patients with FPS in each treatment group was not reported. Furthermore, although randomisation was stratified by platinum sensitivity (sensitive versus resistant/refractory), patients were not stratified based on PPS versus FPS and these subgroup analyses were not prespecified. As subgroup analyses, the results should be interpreted with caution.

Paclitaxel plus carboplatin versus platinum-based therapy alone

ICON4/AGO-OVAR 2.2 carried out a subgroup analysis to determine the effect of paclitaxel plus platinum chemotherapy on OS in various subgroups, including time since completion of last chemotherapy regimen (≤12 months vs >12 months).[60] Most patients had received only one prior regimen of chemotherapy (92%) and therefore treatment-free interval is akin to PFI. In the subgroup of patients with FPS ovarian cancer (599 patients), a similar proportion of people in each treatment group had died at the time of analysis (180/300 [60.0%] with paclitaxel plus carboplatin vs 187/299 [62.5%] with carboplatin alone). Median OS in each group for this population, or an accompanying HR or p-value for the difference between groups were not reported.

Table 27. Summary of results for overall survival in the fully platinum-sensitive recurrent ovarian cancer

Study	Notes	Intervention	Comparison	INT	COMP	Hazard ratio	95% CI	P value
				Median overall survival (events/N)				
Gordon *et al*. (2001)[53]	Drug-free interval >12 months N = 97	PLDH (50 mg/m^2) every 28 days	Topotecan (1.5 mg/m^2) daily for 5 days every 21 days	NR	NR	1.15[a]	0.714 to 1.852	0.057
CALYPSO[55]	Prespecified subgroup of fully platinum sensitive patients	PLDH (30 mg/m^2) plus carboplatin (AUC 5) every 21 days	Paclitaxel (175 mg/m^2) plus carboplatin (AUC 5) every 3 weeks			0.99	0.81 to 1.21	0.90
ICON4/AGO-OVAR 2.2[60]		Paclitaxel plus platinum	Conventional platinum treatment	180/300	187/299	NR	NR	NR
OVA-301[19;30;63]	Fully platinum sensitive subgroup	Trabectedin (1.1 mg/m^2) plus PLDH (30 mg/m^2) every 21 days	PLDH (50 mg/m^2) every 4 weeks	Not reached	31.7	0.89	0.58 to 1.35[b]	0.5746

[a] HR >1 favours PLDH.

[b] HR taken from TA222.

Abbreviations used in table: AUC, area under curve; CI confidence interval; COMP, comparator; INT, intervention; NR, not reported; PLDH, pegylated liposomal doxorubicin hydrochloride.

Network meta-analysis (fully platinum sensitive)

The trials identified for potential inclusion in the NMA for OS in patients with fully platinum-sensitive recurrent ovarian cancer are detailed in Table 27. Of the three RCTs identified, only two trials reported the required data for analysis[48;55] and as they did not contain a common comparator it was not possible perform an indirect comparison.

Partially platinum sensitive

Pegylated liposomal doxorubicin hydrochloride plus carboplatin versus paclitaxel plus carboplatin

A univariate Cox regression analysis of data from CALYPSO based on TFI of 6–12 months (PPS) included 344 patients (161 patients in the PLDH plus carboplatin group and 183 patients in the paclitaxel plus carboplatin group).[55] The univariate analysis identified no statistically significant difference between PLDH plus carboplatin and paclitaxel plus carboplatin in OS in this subgroup of patients (HR 1.01, 95% CI: 0.80 to 1.28; p = 0.92;Table 28). It should be noted that OS was not defined.

Trabectedin plus PLDH versus PLDH alone

An accompanying publication to OVA-301 (Monk *et al*. [2010][30]) reports results for the subgroup of patients with PPS (relapse within 6–12 months of completion of platinum-based chemotherapy). OS data presented by Poveda *et al*.[64] (419 deaths) are not as mature those in the long-term study reported by Monk *et al*. (2012)[63] (522 deaths) and therefore are not reported here.

In the subgroup of patients with PPS ovarian cancer (relapse 6–12 months after last platinum-based treatment), trabectedin plus PLDH significantly prolonged OS compared with PLDH alone (22.4 months with trabectedin plus PLDH vs 16.4 months with PLDH alone; HR 0.64, 95% CI: 0.47 to 0.86; p = 0.0027; Table 28).[63] The authors highlight that this is a *post hoc analysis*, and as such is exploratory and hypothesis generating.

Pegylated liposomal doxorubicin hydrochloride versus topotecan

In the subgroup of patients with PPS ovarian cancer (PFI of >6–≤12 months; 122 patients), Gordon *et al*. (2004)[53] found that PLDH significantly prolonged OS compared with topotecan (HR 1.58, 95% CI: 1.071 to 2.335; p = 0.021; Table 28), where HR >1 favours PLDH. The median OS in each group was not reported. It should be noted that the number of patients with PPS in each treatment group was not reported. Furthermore, although randomisation was stratified by platinum sensitivity (sensitive versus resistant/refractory), patients were not stratified based on PPS versus FPS and these subgroup analyses were not prespecified.

Paclitaxel plus carboplatin versus platinum-based therapy alone

In ICON4/AGO-OVAR 2.2,[60] to be eligible for randomisation in the MRC CTU and AGO-OVAR protocols, patient had to have been treatment free for more than 6 months. Thus, the subgroup of patients with a treatment-free interval of ≤12 months are, by the definition used in this review, PPS

(213 patients). A similar proportion of people in each treatment group had died at the time of analysis (75/92 [81.5%] with paclitaxel plus carboplatin vs 88/111 [79.3%] with carboplatin alone). Median OS in each group for this population, or an accompanying HR or p-value for the difference between groups were not reported.

Table 28. Summary of results for overall survival for people with partially platinum-sensitive recurrent ovarian cancer

Study	Notes	Intervention	Comparison	INT	COMP	Hazard ratio	95% CI	P value
				Median overall survival (events/N)				
Gordon *et al*. (2001)[53]	Drug free interval 6–≤12 months N=122	PLDH 50 mg/m2 every 28 days	Topotecan 1.5 mg/m^2 per day for 5 days every 21 days	NR	NR	1.58[a]	1.071 to 2.335	0.021
OVA-301[30;63]	Partially platinum sensitive subgroup (6–12 months PFI)	Trabectedin (1.1 mg/m^2) plus PLDH (30 mg/m^2) every 21 days	PLDH (50 mg/m^2) every 4 weeks	22.4 months	16.4 months	0.64	0.47 to 0.86	0.0027*
CALYPSO[55]	Prespecified subgroup of partially sensitive patients (6–12 months)	PLDH (30 mg/m^2) plus carboplatin every 21 days	Paclitaxel (175 mg/m^2) plus carboplatin every 21 days	(N = 161)	(N = 183)	1.01	0.80 to 1.28	0.92
ICON4/AGO-OVAR 2.2[60]		Paclitaxel plus platinum	Conventional platinum treatment	75/92	88/111	NR	NR	

[a] HR >1 favours PLDH.

*log-rank; †data not presented in ten Bokkel Huinink *et al*. (2004)[51]

Abbreviations used in table: AUC, area under curve; CI, confidence interval; COMP, comparator; INT, intervention; NR, not reported; PLDH, pegylated liposomal doxorubicin hydrochloride.

Network meta-analysis (partially platinum sensitive)

The RCTs available for inclusion in the NMA evaluating OS in patients with platinum-sensitive recurrent ovarian cancer are summarised in Table 28. Unfortunately, as described earlier, a single network could not be constructed out of the available trials. The two networks constructed for this outcome are depicted in Figure 5.

Only Wagner *et al.*[55] was able to provide data for Network 1 (Figure 5) and the results are presented in Table 29. The trial demonstrated no significant difference in OS for PLDH plus carboplatin versus paclitaxel plus carboplatin.

Network 2 (Figure 5) consisted of the following comparators:

- PLDH monotherapy;
- trabectedin plus PLDH;
- topotecan monotherapy.

The results of this NMA are presented in Table 29. Trabectedin plus PLDH was associated with significantly greater OS than PLDH monotherapy or topotecan monotherapy. Topotecan monotherapy was associated with a significant reduction in OS compared with all other chemotherapy regimens assessed.

Figure 5. Networks for overall survival for people with partially platinum sensitive recurrent ovarian cancer

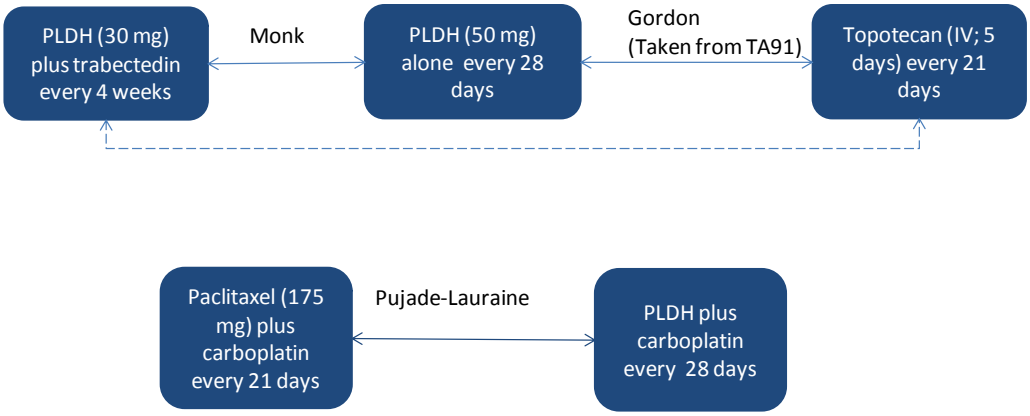


Table 29. Results for network meta-analysis for overall survival for people with partially platinum-sensitive recurrent ovarian cancer

Comparison	HR	95% CrI	
		Lower limit	Upper limit
Versus PLDH monotherapy ***(HR <1 favours comparator, HR >1 favours PLDH monotherapy)***			
Trabectedin plus PLDH	0.621	0.493	0.771
Topotecan monotherapy	1.610	1.072	2.334
Versus trabectedin plus PLDH ***(HR <1 favours comparator, HR >1 favours trabectedin plus PLDH)***			
Topotecan monotherapy	2.628	1.636	4.011
Abbreviations used in table: CrI, Credible Interval; HR, hazard ratio; PLDH, pegylated liposomal doxorubicin hydrochloride.			

Platinum resistant/refractory

Pegylated liposomal doxorubicin hydrochloride versus topotecan

In the subgroup of patients with PRR ovarian cancer (254 patients), Gordon *et al*. (2004)[53] found a median OS of 38.3 weeks in the PLDH group and 42.1 weeks in the topotecan group (median OS taken from TA91[13]). There was no statistically significant difference between the groups in OS (HR 1.069, 95% CI: 0.823 to 1.387; p = 0.618; Table 31); HR >1 favours PLDH. Survival rates at 1, 2, and 3 years are presented in Table 30.

Table 30. Survival rates in platinum-resistant/refractory patients in PLDH and topotecan groups

Treatment	Survival rate		
	1 year	2 years	3 years
PLDH	41.5% (95% CI 32.8% to 50.1%)	21.1% (95% CI 14.1% to 28.2%)	13.8% (95% CI 7.6% to 20.0%)
Topotecan	43.2% (95% CI 34.5% to 51.9%)	17.2% (95% CI 10.5% to 23.8%)	9.5% (95% CI 4.2% to 14.7%)

Pegylated liposomal doxorubicin hydrochloride versus paclitaxel

TA91 presents results for the subgroup of patients with platinum-resistant/refractory disease (64 patients in the PLDH group vs 67 patients in the paclitaxel group).[11] There was no statistically significant difference between PLDH and paclitaxel in this subgroup of patients, with an HR of 0.865 (95% CI: 0.61 to 1.24), where HR >1 favours PLDH. Median OS was 36.7 weeks (range: 2.3–241.1 [upper limit includes a censored observation]) for PLDH and 54.3 weeks (range: 1.7–211.4 [upper limit includes a censored observation]; Table 31) for paclitaxel.

Topotecan versus paclitaxel

Analysis of OS for the subgroup of patients with PRR (refractory, early and interim relapse) disease is not reported in either publication by ten Bokkel Huinink *et al*. (1997 and 2004)[21;51] TA91 found no statistically significant difference between topotecan and paclitaxel in OS, reporting an unadjusted HR of 0.738 (95% CI: 0.498 to 1.093; Table 31) in PRR patients, where HR <1 favours topotecan.[13] It should be noted that interpretation of OS results are potentially confounded by the permitted cross-over to the alternative treatment should a patient not respond to their allocated treatment.

Paclitaxel plus carboplatin versus paclitaxel alone

OS (not defined) was evaluated by Lortholary *et al*.[61] as a secondary outcome and was reported not to differ among treatment groups, with a median OS of 19.9 months, 15.2 months, and 18.6 months for weekly paclitaxel, weekly paclitaxel plus carboplatin, and weekly paclitaxel plus weekly topotecan. The number of events at the time of analysis is unclear. As discussed earlier, results from the weekly paclitaxel plus topotecan group are not of interest to this systematic review. The authors of the study were contacted with a request for the HR for the comparison of weekly paclitaxel versus weekly paclitaxel plus carboplatin. The authors helpfully provided the requested information, which indicates that there is no significant difference between the two treatment groups in median OS (HR 1.074, 95% CI: 0.859 to 1.341; p = 0.53; Table 36).

Topotecan administered on 5 consecutive days (conventional regimen) versus topotecan administered weekly

OS was not defined by Sehouli *et al*.[23] After a median duration of follow-up of 23.4 months, 55 (28.4%) patients remained alive. Median OS in the weekly topotecan group was 9.6 months compared with 9.3 months in the conventional topotecan group. The difference between groups did not reach statistical significance, with an HR of 1.04 (95% CI: 0.74 to 1.44; p = 0.83; Table 31). The authors carried out a multivariate regression analysis that identified the factors listed below as independent predictors of OS:

- duration of chemotherapy (HR 0.99, 95% CI: 0.99 to 1.00; p <0.001);
- baseline ECOG score (HR 1.47, 95% CI: 1.16 to 1.86; p = 0.001)
- administration of follow-up chemotherapy (HR 0.53, 95% CI 0.37 to 0.76; p = 0.001).

Table 31. Summary of results of overall survival for people with platinum-resistant or refractory recurrent ovarian cancer

Study	Notes	Intervention	Comparison	INT	COMP	Hazard ratio	95% CI	P value
				Median overall survival (events/N)				
Gordon *et al*. (2001)[53]	Platinum refractory/resistant	PLDH (50 mg/m^2) every 28 days	Topotecan (1.5 mg/m^2) for 5 days every 21 days	38.3 weeks (N = 130)	42.1 weeks (N = 125)	1.069[a]	0.823 to 1.387	0.618
Sehouli *et al*.[23]	Full population recurrent platinum resistant patients	Topotecan (4.0 mg/m^2) (weekly; days 1, 8, and 15) every 28 days	Topotecan (1.25 mg/m^2) for 5 consecutive days every 21 days	9.6 months (95% CI 6.3 to 14.2)	9.3 months (95% CI 7.5 to 11.4)	1.04	0.74 to 1.44	0.83
ten Bokkel Huinink *et al*.[51]	HR taken from TA91. Data not presented in the published paper	Topotecan 1.5 mg/m^2/day for 5 days	Paclitaxel 175 mg/m^2/day as 3 hour infusion every 21 days.			0.738[b]	0.498 to 1.093	
Trial 30-57[13]	Trial was terminated prematurely	PLDH (50 mg/m^2) every 28 days	Paclitaxel (175 mg/m^2) every 21 days	36.7 weeks (range: 2.3 to 241.1 weeks)	54.3 weeks (range: 1.7 to 211.4 weeks)	0.865	0.61 to 1.24	0.427
Lortholary *et al*.[61]	Full population relapsed within six months	Weekly paclitaxel (80 mg/m^2 on days 1, 8, and 15) plus carboplatin (AUC 5) every 4 weeks	Weekly paclitaxel (80 mg/m^2 on days 1, 8, and 15) every 4 weeks	15.2	19.9	1.074[c]	0.859 to 1.341	0.53

[a] HR >1 favours PLDH. [b] data not presented in ten Bokkel Huinink *et al.* (2004)[51] HR Taken from TA91; HR <1 favours topotecan. [c] Supplied by authors of original paper on request.[61]
Abbreviations used in table: AUC, area under curve; COMP, comparator; INT, intervention; NR, not reported; PLDH, pegylated liposomal doxorubicin hydrochloride.

Network meta-analysis (platinum-resistant or refractory)

The RCTs available for inclusion in the NMA evaluating OS in patients with platinum-resistant or refractory recurrent ovarian cancer are summarised in Table 31. The network of trials constructed for this outcome is depicted in Figure 6 and contains the following comparators:

- PLDH monotherapy;
- trabectedin plus PLDH;
- paclitaxel monotherapy;
- topotecan monotherapy; that is, topotecan 1.25 or 1.5 mg/m^2 daily for 5 days every 21 days;
- topotecan monotherapy (weekly); that is, topotecan 4.0 mg/m^2 (weekly) on days 1, 8, and 15 of a 28-day cycle.

The results from this NMA are presented in Table 32. Overall, there was no significant difference in OS (at the 5% level) for any of the chemotherapies assessed compared with PLDH monotherapy (or with each other).

An RCT that provided results for this population but which did not share a common comparator within the network compared low dose paclitaxel (80 mg/m^2) with low dose paclitaxel (80 mg/m^2) plus carboplatin.[61] However, Lortholary *et al.*[61] identified no significant difference in OS between the two different treatment regimens (Table 31). Trabectedin plus PLDH is outside of the scope for this review for the population of PRR patients; data have been included within the network to capture all the available evidence but are not included in the economic analysis.

Figure 6. Networks for overall survival for people with platinum-resistant or refractory recurrent ovarian cancer

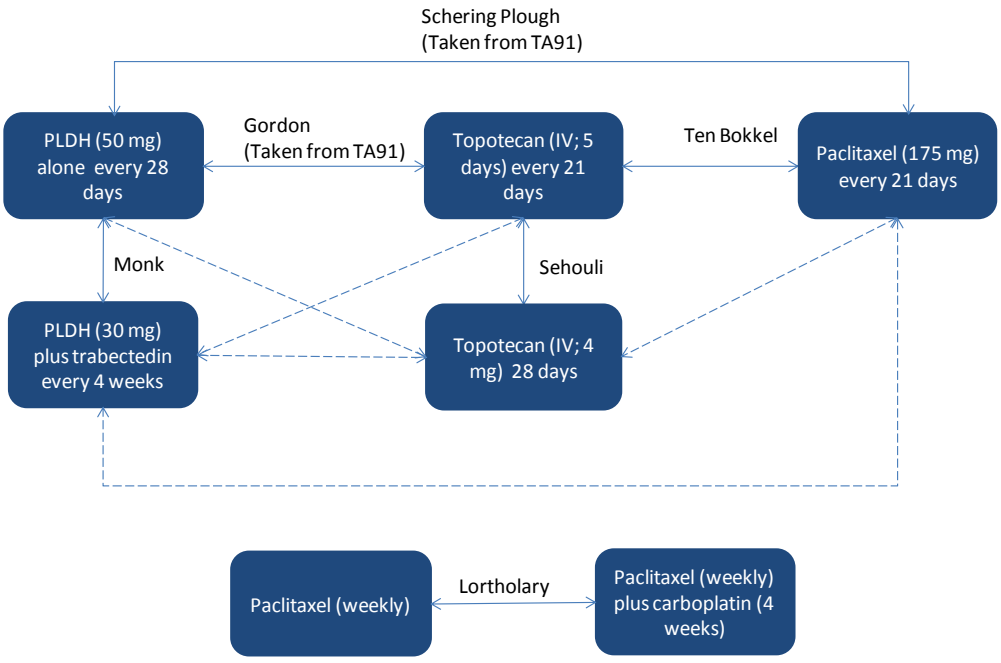


Table 32. Results of network meta-analysis for overall survival for people with platinum-resistant or refractory recurrent ovarian cancer

Comparison	HR	95% CrI	
		Lower limit	Upper limit
Versus PLDH monotherapy ***(HR <1 favours comparator, HR >1 favours PLDH monotherapy)***			
Trabectedin plus PLDH	0.928	0.699	1.208
Paclitaxel monotherapy	1.053	0.783	1.382
Topotecan monotherapy	0.973	0.764	1.221
Topotecan monotherapy (weekly)	1.026	0.669	1.505
Versus trabectedin plus PLDH ***(HR <1 favours comparator, HR >1 favours trabectedin plus PLDH)***			
Paclitaxel monotherapy	1.155	0.763	1.681
Topotecan monotherapy	1.069	0.734	1.508
Topotecan monotherapy (weekly)	1.127	0.666	1.775
Versus paclitaxel monotherapy ***(HR <1 favours comparator, HR >1 favours paclitaxel monotherapy)***			
Topotecan as a monotherapy	0.939	0.694	1.244
Topotecan monotherapy (weekly)	0.989	0.619	1.499
Versus topotecan ***(HR <1 favours comparator, HR >1 favours topotecan)***			
Topotecan monotherapy (weekly)	1.054	0.744	1.447
Abbreviations used in table: CrI, Credible Interval; HR, hazard ratio; PLDH, pegylated liposomal doxorubicin hydrochloride.			

Full population (mixed platinum-free intervals)

Trabectedin plus PLDH versus PLDH alone

Based on 522 deaths (analysis planned at 520 deaths), OVA-301 found no significant difference in OS between the two treatments, with median OS of 22.2 months in the trabectedin plus PLDH group and 18.9 months in the PLDH alone group (HR 0.86, 95% CI: 0.72 to 1.02; p = 0.084; Table 36).[63] Survival rates in the two treatment groups at various time points are presented in Table 33.

Table 33. Survival rates in the full trial population of OVA-301 reported by Monk *et al*. (2012)[63]

Treatment	Survival rate		
	12 months	24 months	30 months
Trabectedin plus PLDH	74% (95% CI 69% to 79%)	45% (95% CI to 40% to 51%)	37% (95% CI 14.9% to 15.5%)
PLDH alone	68% (95% CI 62% to 72%)	41% (95% CI 35% to 46%)	37% (95% CI 31% to 42%)
Abbreviations used in table: CI, confidence interval; PLDH, pegylated liposomal doxorubicin			

Pegylated liposomal doxorubicin hydrochloride versus topotecan

As noted earlier, data for OS from Gordon *et al*. (2001)[48] are based on a modified ITT population and OS was defined as the time from the start of study drug administration to death. In the longer-term study (Gordon *et al*. [2004][53]), additional analyses are presented in which OS results for the full trial population are based on the ITT population and the more commonly used definition of OS of time from date of randomisation until date of death. At the time of analysis, 87% of patients had died and 13% of observations were censored. For completeness, both results are reported here.

Based on the modified ITT population (N = 474) and the original definition of OS, Gordon *et al*. (2004)[53] found that PLDH significantly prolonged median OS compared with topotecan, with a median gain of 3.0 weeks (median OS: 62.7 weeks with PLDH vs 59.7 weeks with topotecan; HR 1.216, 95% CI: 1.00 to 1.478; p = 0.050; Table 36); in this analysis, HR >1 favours PLDH. The gain in OS associated with PLDH corresponded to an 18% reduction in the risk of death. Similar results were observed in the analysis of all patients randomised (N = 481), with a median gain of 6.3 weeks associated with PLDH (median OS: 63.6 weeks with PLDH vs 57.0 weeks with topotecan; HR 1.23, 95% CI: 1.01 to 1.50; p = 0.038; Table 36); in this analysis, HR >1 favours PLDH. Survival rates in the two treatment groups at various time points are presented in Table 34.

Table 34. Survival rates in the full trial population of the trial reported by Gordon *et al*. (2004)[53]

Treatment	Survival rate		
	1 year	2 years	3 years
PLDH	56.3% (95% CI 50.0% to 62.6%)	34.7% (95% CI to 28.6% 40.8%)	20.2% (95% CI 14.9% to 15.5%)
Topotecan	54.0% (95% CI 47.6% to 60.3%)	23.6% (95% CI 18.1% to 29.2%)	13.2% (95% CI 8.8% to 17.7%)
Abbreviations used in table: CI, confidence interval; PLDH, pegylated liposomal doxorubicin			

To investigate the influence of multiple putative prognostic factors on OS, the authors carried out a multivariate Cox regression analysis.[53] Variables evaluated were treatment, platinum sensitivity (sensitive vs resistant/refractory), bulky disease (yes vs no), baseline Karnofsky performance status (<80 vs ≥80). The adjusted HR for OS was similar to that of the primary analysis, which led the authors to conclude that the results were not affected by potential prognostic factors (summarised in Table 35). Results suggest that age <65 years, platinum-sensitive disease and absence of ascites at baseline are associated with improved survival.

Table 35. Overall survival for subgroups according to baseline disease characteristics[53]

Variable	Group	N	HR[a]	95% CI for HR
Age (years)	<65 years	294	1.322	1.022 to 1.710
	≥65 years	180	1.077	0.786 to 1.477
Baseline KPS	<80	76	0.871	0.531 to 1.427
	≥80	394	1.242	0.999 to 1.543
Drug-free interval	≤6 months[b]	211	1.103	0.826 to 1.474
	<12 months	367	1.224	0.983 to 1.523
	>18 months	107	1.088	0.687 to 1.726
Bulky disease	Present	213	1.131	0.849 to 1.506
	Absent	261	1.294	0.991 to 1.691
Platinum sensitivity	Sensitive	219	1.432	1.066 to 1.923
	Refractory	255	1.069	0.823 to 1.387
Baseline ascites	Present	142	0.978	0.689 to 1.389
	Absent	330	1.387	1.088 to 1.768

[a] HR >1 favours pegylated liposomal doxorubicin hydrochloride.

[b] Result taken from TA91.[13]

Abbreviations used in table: CI, confidence interval; HR, hazard ratio; KPS, Karnofsky performance status.

Pegylated liposomal doxorubicin hydrochloride versus paclitaxel

In the full trial population of trial 30–57 (216 patients), there was no statistically significant difference between PLDH and paclitaxel in OS, with an HR of 0.931 (95% CI: 0.702 to 1.234; Table 36);[13] HR >1 favours PLDH. Median OS was 46.6 weeks (range: 2.3–263.7 [includes censored observation]) with PLDH versus 56.3 weeks (range: 1.4–211.4) with paclitaxel.

Topotecan versus paclitaxel

Data reported here are taken from the longer-term follow-up study reported by ten Bokkel Huinink *et al*. (2004)[51] in which data had been collected for more than 4 years. For analysis of OS, 20.5% of patients in the topotecan group and 12.3% of patients in the paclitaxel group were censored. There was no statistically significant difference between topotecan and paclitaxel in median OS (63.0 weeks with topotecan vs 53.0 weeks with paclitaxel; p = 0.44; Table 36).[51] An accompanying HR was not reported in the full publication. However, TA91 reported an HR of 0.914 (95% CI: 0.681 to 1.226) for OS, where HR <1 favours topotecan.[13] The HR had been adjusted for stratification factors. It should be noted that interpretation of OS results are potentially confounded by the permitted cross-over to the alternative treatment should a patient not respond to their allocated treatment.

Paclitaxel versus oxaliplatin

Piccart *et al*.[62] evaluated OS as a secondary outcome measure, with OS defined as the time from day 1 of treatment to death. At the time of analysis, of the 86 patients randomised, 45 had died (52%; 25/41 [61.0%] in the paclitaxel group vs 20/45 [44.4%] in the oxaliplatin group; Table 36). Median

OS was 37 weeks in the paclitaxel group compared with 42 weeks in the oxaliplatin group. Statistical significance was not assessed in the full publication. Neither an accompanying HR nor a p-value for the difference between groups was reported.

Topotecan oral versus topotecan intravenous

In the full trial population, Gore *et al*.[24] found that median OS was significantly prolonged with intravenous topotecan compared with oral topotecan, with a median OS of 51 weeks with oral topotecan compared with 58 weeks with intravenous topotecan (risk ratio of death: 1.361, 95% CI: 1.001 to 1.850; p = 0.033; Table 57). It should be noted that OS was not defined in the full publication.

Paclitaxel high dose (250 mg/m^2) versus paclitaxel standard dose (175 mg/m^2)

Omura *et al*.[66] defined OS as the time from randomisation until the date of death, or last contact if the date of death was unknown. Estimated median OS for the paclitaxel 175 mg/m^2 and the 250 mg/m^2 regimens were 13.1 and 12.3 months, respectively. The accompanying HR of 0.972 (95% CI 0.774 to 1.22; ratio of 250 mg/m^2 versus 175 mg/m^2; Table 36) indicated that OS was not statistically significantly different between the two paclitaxel regimens. The HR was adjusted for initial performance score, cell type, response to prior platinum, cooperative group and measurable disease. An unadjusted HR was not reported.

Paclitaxel weekly versus paclitaxel every 3 weeks

Rosenberg *et al*.[59] defined OS as time from date of randomisation to death or censored observation. In the full trial population, there was no statistically significant difference between treatment regimens in median OS (p = 0.98). Median OS was 13.6 months (95% CI: 10.5 to 18.7) in the group receiving paclitaxel every 7 days compared with 14.7 months (95% CI: 12.3 to 19.1) in the group receiving paclitaxel every 21 days. It is unclear how many events had occurred at the time of analysis.

Table 36. Summary of results of overall survival for a population of mixed platinum-free intervals

Study	Notes	Intervention	Comparison	INT	COMP	Hazard ratio	95% CI	P value
				Median overall survival (events/N)				
Gordon *et al*. (2001)[53]	"Assessable population" – contains mix of platinum sensitive and platinum refractory patients.	PLDH 50 mg/m^2 every 28 days	Topotecan 1.5 mg/m^2 per day for 5 days every 21 days	62.7 weeks	59.7 weeks	1.216[c]	1.00 to 1.478	0.050
				63.6 weeks	57.0 weeks	1.23	1.01 to 1.50	0.038[a]
Piccart *et al*.[62]	Approximately 75% population is platinum refractory, 25% is platinum sensitive	Paclitaxel 175 mg/m^2 over 3 hours every 3 weeks	Oxaliplatin 130 mg/m^2 over 2 hours every 3 weeks	37 weeks (N = 25/41)	42 weeks (N = 20/45)			
OVA-301[63]	Full population contains platinum sensitive and resistant patients	PLDH 30 mg/m^2 IV plus Trabectedin 1.1 mg/m2 every 3 weeks	PLDH 50 mg/m^2 every 4 weeks	22.2 months (95% CI 19.3 to 25) (258/337)	18.9 months (95% CI 17.1 to 21.5) (264/335)	0.86	0.72 to 1.02	0.0835
Gore *et al*.[24]	Full population contains platinum refractory, platinum resistant and platinum sensitive patients.	Oral topotecan 2.3 mg/m^2/day	IV topotecan 1.5 mg/m^2/day for 5 days every 21 days	51 weeks (N = 135)	58 weeks (N = 131)	1.361	1.001 to 1.850	0.033
ten Bokkel Huinink *et al.* (2004)[51]	HR taken from TA91[b]	Topotecan 1.5 mg/m^2/day for 5 days	Paclitaxel 175 mg/m^2/day as 3 hour infusion every 21 days.	63 weeks (range <1 to 238.4+ weeks)	53.0 weeks (range <1 to 226.3+ weeks)	0.914 Adjusted for stratification factors	0.681 to 1.226	0.44
				p = 0.44				
Trial 30-57[13]	Trial was terminated prematurely	PLDH 50 mg/m^2/day every 28 days	Paclitaxel 175 mg/m^2/day every 21 days	46.6 weeks (range: 2.3 to 263.7+ weeks)	56.3 weeks (range 1.4 to 211.4 weeks)	0.931	0.702 to 1.234	0.0618

Rosenberg *et al*.[59]	Mixed population	Paclitaxel weekly	Paclitaxel 3 weekly	13.6 months (10.5 to 18.7) (N = 105)	14.7 months (12.3 to 19.1) (N = 103)			
				p = 0.98				
Omura *et al*.[66]		Paclitaxel 250 mg/m^2 every 21 days	Paclitaxel 175 mg/m^2 every 21 days	12.3		13.1	0.972, 0.774 to 1.22	

[a] Stratified log-rank test.

[b] data not presented in ten Bokkel Huinink *et al*. (2004)[51]

[c] HR >1 favours PLDH.

Abbreviations used in table: AUC, area under curve; CI, confidence interval; COMP, comparator; INT, intervention; NR, not reported; PLDH, pegylated liposomal doxorubicin hydrochloride.

Network meta-analysis (mixed platinum-free intervals)

The RCTs available for inclusion in the NMA evaluating OS in patients with mixed platinum-free intervals in recurrent ovarian cancer are summarised in Table 36. However, based on expert clinical opinion, the TAG decided not to evaluate this mixed patient population as the results would not be considered clinically meaningful.

4.2.2.2 Progression-free survival

In oncology trials, progression of disease is typically assessed according to internationally recognised criteria, such as the RECIST criteria,[67] which are based on clinical signs, ultrasound scans, or X-rays. RECIST criteria encompass measurable and non-measurable disease. Increase in levels of CA125 biomarker is also used to determine disease progression, typically in patients with non-measurable lesions at baseline, according to criteria developed by Rustin *et al*.[77]: increase in CA125 has been shown to predate evidence of disease progression from clinical examinations or radiological scans in 70% of patients with ovarian cancer by a median of 4 months.[73] There are two time to event measures of disease progression (definitions as reported in FDA guidance on conducting oncology trials):[74]

- PFS, which is defined as time from randomisation to disease progression or death (includes all deaths);
- TTP, which is defined as time from randomisation to disease progression (deaths before progression are censored).

The terms PFS and TTP are often used interchangeably. For example, a trial might refer to the outcome of PFS but the definition indicates that all-cause mortality has not been included in the analysis. For the purposes of the review, the TAG has considered PFS and TTP together and has reported the outcome as defined in the individual trials. As for OS, in some cases, PFS and TTP have been measured from the time of treatment initiation rather than randomisation.

Progressive events occur in a shorter timeframe and more frequently than OS events. Therefore, PFS data are available much sooner than OS data, and fewer patients are required for the study to have adequate power. Additionally, there is no confounding from post-progression therapy. However, because PFS is based on assessment of change in tumour size, there is a degree of subjective assessment, with associated potential for measurement errors. Assessment bias is more likely in an open-label trial. Differences in the timing of measurement between the groups may arise if the treatments under evaluation have different cycle lengths, which could lead to a difference in progression date. In clinical trials, it has been reported that an increase in CA125 frequently triggers subsequent post-progression therapy before clinical or radiological confirmation of progression. The practice of using CA125 alone also introduces disparity across trials in terms of the date of disease progression.

The criteria used to determine progression were initially developed for use in clinical trials using response rate as a primary endpoint (e.g., phase II screening trials), with the goal of facilitating evaluation of changes in tumour burden during treatment rather than to associate the changes with a clinical benefit.[75] However, changes in tumour size are recognised as signals of a drug's anti-tumour activity.

Summary of results for PFS/TTP

Results are presented for PFS or TTP, as reported in the trial. PFS and TTP are often used interchangeably and, for the purposes of the results presented here, TTP has been assumed to approximate to PFS. Definitions as reported in the trials are provided in the main text. No trial was identified evaluating treatments in a population solely comprising patients who were allergic or intolerant to platinum-based chemotherapy. Here, results for patients with platinum-sensitive or platinum-refractory/resistant (PRR) disease are summarised. For trials not limited to either platinum-sensitive or PRR patients (i.e., includes a mix of platinum-free interval [PFI]), results for the full trial population are presented in the main text.

Results for PFS/TTP for the subgroup of patients with platinum-sensitive (relapse ≥6 months after last platinum-based chemotherapy) ovarian cancer

Nine RCTs evaluating seven different head-to-head comparisons of interventions and comparators of interest reported on PFS/TTP.

Trial name	Intervention	Comparator	HR (95%CI)
CALYPSO[31]	PLDH (30 mg/m^2) plus carboplatin every 21 days	Paclitaxel (175 mg/m^2) plus carboplatin every 21 days	0.82 (0.72 to 0.94)
Bafaloukos *et al*.[29]	PLDH (45 mg/m^2) plus carboplatin every 28 days	Paclitaxel (175 mg/m^2) plus carboplatin every 21 days	NR
ICON4/AGO-OVAR 2.2[60]	Paclitaxel plus platinum	Conventional platinum treatment	0.76 (0.66 to 0.89)
Gonzalez Martin *et al*.[47]	Paclitaxel (175 mg/m^2) plus carboplatin every 21 days	Carboplatin alone every 21 days	0.54 (0.32 to 0.92)
ten Bokkel Huinink *et al*. (2004)[51]	Topotecan (1.5 mg/m^2) for 5 days every 21 days	Paclitaxel (175 mg/m^2) every 21 days	0.823 (0.538 to 1.261)
Gordon *et al*. (2001)[53]	PLDH (50 mg/m^2) every 28 days	Topotecan (1.5 mg/m^2) for 5 days every 21 days	1.287[a] (0.98 to 1.69)
Alberts *et al*.[54]	PLDH (30 mg/m^2) plus carboplatin every 4 weeks	Carboplatin alone every 4 weeks	0.54 (0.32 to 0.93)
OVA-301[30]	Trabectedin (1.1 mg/m^2) plus PLDH (30 mg/m^2) every 3 weeks	PLDH (50 mg/m^2) every 4 weeks	0.73 (0.56 to 0.95)
Pfisterer *et al*.[49]	Gemcitabine (1,000 mg/m^2) plus carboplatin every 21 days	Carboplatin alone every 21 days	0.72 (0.58 to 0.90)

[a] HR >1 favours PLDH.
Abbreviations used in table: CI, confidence interval; HR, hazard ratio; PLDH, pegylated liposomal doxorubicin hydrochloride.

As for OS, based on trials identified, it was not possible to construct a complete network. Again, two discrete networks were generated, one evaluating platinum-based therapies and the second comparing non-platinum-based regimens. It should be stressed that results from the two discrete

networks are not directly comparable.

In the network evaluating platinum-based chemotherapies, all combination chemotherapy regimens significantly improved PFS compared with platinum monotherapy. In addition, PLDH plus carboplatin was found to be significantly more effective at prolonging PFS than paclitaxel plus carboplatin. No other statistically significant differences were identified between combination regimens.

Comparator	Paclitaxel plus carboplatin	Gemcitabine plus carboplatin	PLDH plus carboplatin	Platinum monotherapy
Paclitaxel plus carboplatin	–	0.985 (0.748 to 1.273)	0.817 (0.717 to 0.927)	1.361 (1.182 to 1.559)
Gemcitabine plus carboplatin	–	–	0.845 (0.624 to 1.116)	1.400 (1.106 to 1.749)
PLDH plus carboplatin	–	–	–	1.672 (1.389 to 1.997)
Platinum monotherapy	–	–	–	–
Comparator is listed in the left-hand side column. Results presented are HR and accompanying CrI. HR <1 favours the intervention (listed in the top table row) and HR >1 favours the comparator. Abbreviations used in table: CrI, credible interval; HR, hazard ratio.				

Analysis of non-platinum-based regimens indicates that trabectedin plus PLDH significantly improves PFS compared with PLDH, paclitaxel and topotecan when given as monotherapy. No statistically significant differences were identified among the monotherapies evaluated (PLDH, topotecan, and paclitaxel).

Comparator	PLDH monotherapy	Trabectedin plus PLDH	Paclitaxel monotherapy	Topotecan monotherapy
PLDH monotherapy	–	0.736 (0.560 to 0.949)	1.615 (0.939 to 2.586)	1.298 (0.979 to 1.688)
Trabectedin plus PLDH	–	–	2.236 (1.209 to 3.795)	1.797 (1.207 to 2.578)
Paclitaxel monotherapy	–	–	–	0.842 (0.539 to 1.262)
Topotecan monotherapy	–	–	–	–
Comparator is listed in the left-hand side column. Results presented are HR and accompanying CrI. HR <1 favours the intervention (listed in the top table row) and HR >1 favours the comparator. Abbreviations used in table: CrI, credible interval; HR, hazard ratio; PLDH, pegylated liposomal doxorubicin hydrochloride.				

Where available, PFS/TTP data were analysed for the subgroups of patients with FPS (relapse >12 months after last platinum-based treatment) and PPS (relapse ≥6–≤12 months after last platinum-based treatment). As for OS, few trials involving platinum-sensitive patients evaluated treatment effect in these two subgroups: three trials afforded data on FPS and four trials on PPS. Two trials evaluated platinum-based regimens and two trials non-platinum-based regimens.

Results in patients with FPS

One of the three trials reported an HR as a measure of treatment effect.[55] The difference between trabectedin plus PLDH and PLDH monotherapy was not statistically significant.[64] The two remaining trials did not report an HR for PFS, but the proportion of people having an event was similar in each treatment group.[49;60] The lack of HRs for two of the trials precluded carrying out an NMA.

Trial	Intervention	Comparator	HR (95%CI)
ICON4/AGO-OVAR 2.2[60]	Paclitaxel plus platinum	Conventional platinum treatment	NR
OVA-301[64]	Trabectedin (1.1 mg/m^2) plus PLDH (30 mg/m^2) every 3 weeks	PLDH (50 mg/m^2) every 4 weeks	0.70 (0.47 to 1.03)
Pfisterer *et al*.[49]	Gemcitabine (1,000 mg/m^2) plus carboplatin every 21 days	Carboplatin alone every 21 days	NR
Abbreviations used in table: CI, confidence interval; HR, hazard ratio; NR, not reported; PLDH, pegylated liposomal doxorubicin hydrochloride.			

Results in patients with PPS

Two of the four trials evaluating treatments in the subgroup of patients with PPS ovarian cancer reported HR as a measure of effect.[55;64] PLDH plus carboplatin was found to significantly prolong PFS compared with paclitaxel plus carboplatin.[55] In addition, trabectedin plus PLDH significantly improved PFS compared with PLDH alone.[64] The two remaining trials did not report HRs. The proportion of patients experiencing an event was similar in the two treatment groups in each trial. The lack of HRs for two of the trials precluded carrying out an NMA.

Trial	Intervention	Comparator	HR (95%CI)
CALYPSO[55]	PLDH (30 mg/m^2) plus carboplatin every 21 days	Paclitaxel (175 mg/m^2) plus carboplatin every 3 weeks	0.73 (0.58 to 0.90)
ICON4/AGO-OVAR 2.2[60]	Paclitaxel plus platinum	Conventional platinum treatment	NR
OVA-301[64]	Trabectedin (1.1 mg/m^2) plus PLDH (30 mg/m^2) every 21 days	PLDH (50 mg/m^2) every 4 weeks	0.65 (0.45 to 0.92)
Pfisterer *et al*.[49]	Gemcitabine (1,000 mg/m^2) plus carboplatin every 21 days	Carboplatin alone every 21 days	NR
Abbreviations used in table: CI, confidence interval; HR, hazard ratio; NR, not reported; PLDH, pegylated liposomal doxorubicin hydrochloride.			

Results in PFS for the subgroup of patients with platinum-resistant/refractory ovarian cancer

Four RCTs reporting results for four different head-to-head comparisons involving PRR patients were identified. Two RCTs enrolled only patients with PRR, with the remaining two RCTs reporting results from a subgroup of patients within the trial. None of the trials identified a significant difference in PFS/TTP between the two treatment groups evaluated.

Trial name	Intervention	Comparator	HR (95%CI)
ten Bokkel Huinink *et al*. (2004)[51]	Topotecan (1.5 mg/m^2) for 5 days every 21 days	Paclitaxel (175 mg/m^2) every 21 days	0.749 (0.501 to 1.121)
Gordon *et al*. (2001)[53]	PLDH (50 mg/m^2) every 28 days	Topotecan (1.5 mg/m^2) for 5 days every 21 days	0.99[a] (0.77 to 1.28)
Sehouli *et al*.[23]	Topotecan (4.0 mg/m^2) (weekly; days 1, 8, and 15) every 28 days	Topotecan (1.25 mg/m^2) for 5 consecutive days every 21 days	1.29 (0.96 to 1.76)
Lortholary *et al*.[61]	Weekly paclitaxel (80 mg/m^2) plus carboplatin	Weekly paclitaxel (80 mg/m^2) on 4 week cycle	0.924 0.763 to 1.119
[a] HR >1 favours PLDH. Abbreviations used in table: CI, confidence interval; HR, hazard ratio; NR, not reported; PLDH, pegylated			

liposomal doxorubicin hydrochloride.

Three of the four identified trials were included in the network; the treatment regimens evaluated in the trial reported by Lortholary *et al*.[61] did not inform the network. Trabectedin plus PLDH is outside of the scope for this review for the population of PRR patients; data have been included within the network to capture all the available evidence but are not included in the economic analysis. The results of the NMA are in alignment with the results of the individual trials, with no statistically significant differences in PFS among PLDH, paclitaxel and topotecan monotherapy.

Comparator	PLDH monotherapy	Trabectedin plus PLDH	Paclitaxel monotherapy	Topotecan monotherapy	Topotecan monotherapy (weekly)
PLDH monotherapy	–	0.961 (0.697 to 1.292)	1.360 (0.817 to 2.123)	0.998 (0.767 to 1.277)	1.302 (0.859 to 1.894)
Trabectedin plus PLDH	–	–	1.450 (0.791 to 2.454)	1.064 (0.698 to 1.555)	1.389 (0.811 to 2.216)
Paclitaxel monotherapy	–		–	0.765 (0.502 to 1.122)	0.999 (0.585 to 1.599)
Topotecan monotherapy	–		–	–	1.305 (0.951 to 1.744)
Topotecan monotherapy (weekly)	–		–	–	–
Comparator is listed in the left-hand side column. Results presented are HR and accompanying CrI. HR <1 favours the intervention (listed in the top table row) and HR >1 favours the comparator. Abbreviations used in table: CrI, credible interval; HR, hazard ratio; PLDH, pegylated liposomal doxorubicin hydrochloride; topotecan monotherapy (weekly), topotecan (4.0 mg/m^2) (weekly; days 1, 8, and 15) every 28 days.					

Platinum sensitive

Pegylated liposomal doxorubicin hydrochloride plus carboplatin versus paclitaxel plus carboplatin

Bafaloukos *et al*.[29] evaluated TTP, which was defined as the time from the initiation of treatment to the first disease progression. Deaths as a result of disease without previous documentation of progression were considered events in TTP. Median TTP was 11.8 months in PLDH plus carboplatin group compared with 10.8 months in the paclitaxel plus carboplatin group (Table 42), with no statistically significant difference between treatments for this outcome (p = 0.904). It is important to note that the study was not powered to detect differences in TTP. An accompanying HR was not reported.

PFS was the primary outcome in the CALYPSO trial (Pujade-Lauraine *et al*.[31]) and primary analysis was based on the ITT population. Although a comprehensive description of criteria for categorisation of disease progression is provided, it is unclear when monitoring for progression began, that is, from randomisation or from first administration of study drug. Tumour assessment was carried out every 3 months while patients were receiving treatment.

After a median follow-up of 22 months, 832 PFS events had occurred. PLDH plus carboplatin significantly prolonged median PFS compared with carboplatin plus paclitaxel, with a median PFS gain of 1.9 months (median PFS: 11.3 months with PLDH plus carboplatin vs with paclitaxel plus carboplatin; HR 0.823, 95% CI: 0.72 to 0.94; p = 0.005). The test for non-inferiority of PLDH plus carboplatin afforded a p value of <0.001. A similar proportion of patients in each group had disease progression based on RECIST criteria (Table 37).

Table 37. Breakdown of patients by measure used to evaluate disease progression

Disease progression measure	PLDH plus carboplatin		Paclitaxel plus carboplatin	
	Number of patients	%	Number of patients	%
RECIST criteria	301	79	363	80
CA125 GCIG criteria	79	21	89	20
Abbreviations used in table: GCIG, Gynecologic Cancer Intergroup; PLDH, pegylated liposomal doxorubicin hydrochloride; RECIST, Response Evaluation Criteria in Solid Tumors.				

Exploratory analysis of the effects of several baseline characteristics on PFS was carried out using Cox proportional hazards regression. Factors evaluated were: age; number of previous lines of chemotherapy; TFI; surgery at relapse; measurability status of tumour; size of tumour (< or >5 cm); number of tumour sites (1 or >1); tumour grade; histologic classification of tumour cells; CA125 level; ECOG performance score; and treatment arm. Limited results are available in the full publication (summarised in Table 38). TFI, measurable disease, CA125 level ≥100 and PLDH plus carboplatin were found to be associated with a significant effect on PFS. It is unclear whether the remainder of the putative prognostic factors had no effect on PFS.

Table 38. Multivariate regression analysis to evaluate the effect of baseline factors on PFS

Baseline factor	No	HR	95% CI	p value
TFI, months				
6–12	342	1.00	0.48 to 0.65	<0.001
>12	617	0.56	–	–
Measurable disease				
No	362	1.00	1.27 to 1.70	<0.001
Yes	597	1.47	–	–
CA125 (U/ml)				
<100	316	1.00	1.52 to 2.07	<0.001
≥100	643	1.77	–	
Treatment group				
Paclitaxel plus carboplatin	499	1.00	0.71 to 0.93	0.003
PLDH plus carboplatin	460	0.80	–	
Abbreviations used in table: CI, confidence interval; HR, hazard ratio; PLDH, pegylated liposomal doxorubicin hydrochloride; TFI, treatment-free interval.				

Pegylated liposomal doxorubicin hydrochloride plus carboplatin versus carboplatin alone

Alberts *et al*.[28] reported that PFS was measured as a secondary outcome, but a definition of PFS was not provided. Based on 55 out of 61 women having progressed or died, Alberts *et al*.[28] found a median PFS (unadjusted) of 12 months in the PLDH plus carboplatin group and 8 months in the carboplatin alone group (HR 0.54, 95% CI: 0.32 to 0.93; p = 0.03; Table 42). Longer-term data (all women had progressed or died) reported by Markman *et al*.[54] found similar results, with median PFS of 12 and 8 months in the PLDH plus carboplatin and carboplatin alone groups, respectively (HR not reported; p = 0.02).

Trabectedin plus PLDH versus PLDH alone

PFS was the primary outcome of the OVA-301 trial, and was defined as time from random assignment to disease progression or death.[30] Three analyses for PFS were performed, based on review by independent radiologists, independent oncologists, and investigator. The primary analysis was based on review by independent radiologists who were masked to treatment allocation, with disease progression determined by radiological evaluation alone according to RECIST criteria. The primary analysis included only those patients who had measurable disease at baseline. A secondary analysis was based on review by independent oncologists who were also masked to treatment and who categorised disease progression based on radiological assessments together with clinical data. The secondary analysis included all randomised patients.

The sample size calculation estimates that 415 progressive events would be needed to test statistical difference as a 2-sided 5% significance level with at least 90% power, based on assumed median PFS of 16 weeks and 22 weeks for PLDH alone and trabectedin plus PLDH, respectively. At the time of analysis of PFS, in the full trial population (includes platinum-resistant patients), 389 events had occurred according to independent radiology review and 432 events based on independent oncologist review. Based on event rate, the primary analysis of PFS could be underpowered. In the FAD for TA222, the Committee concluded that "despite the technical difficulties, the analysis based on the independent radiologists' assessment was the most robust".[70] For this reason, the TAG has used results from the primary analysis of PFS in the NMA.

In the subgroup of patients with platinum-sensitive disease, all three analyses found that median PFS was significantly prolonged with trabectedin plus PLDH compared with PLDH alone (Table 39). Multivariate analysis of potential prognostic factors found that treatment with trabectedin plus PLDH remained significant after adjustment of prognostic factors; the multivariate analysis was based on the full trial population and is presented in the section outlining results in the full trial population.

Table 39. Summary of progression-free survival in platinum-sensitive patients in OVA-301[30]

Review	Median PFS (months)		HR (95% CI)	p value
	Trabectedin plus PLDH	PLDH alone		
Independent radiologist	9.2	7.5	0.73 (0.56 to 0.95)	0.0170
Independent oncologist	9.7	7.2	0.66 (0.52 to 0.85)	0.0010
Investigator	9.4	5.8	0.62 (0.50 to 0.78)	<0.0001

Abbreviations used in table: CI, confidence interval; HR, hazard ratio; PLDH, pegylated liposomal doxorubicin hydrochloride; PFS, progression-free survival.

Pegylated liposomal doxorubicin hydrochloride versus topotecan

In Gordon *et al*. (2001)[48], PFS was defined as the time from the first day of study drug dosing to documented disease progression or death due to any cause while the patient was on the study drug or during the long-term follow-up period. In platinum-sensitive patients, Gordon *et al*. (2001)[48] found that PLDH significantly prolonged PFS compared with topotecan (p = 0.037; HR not reported). Median PFS was reported to be 28.9 weeks and 23.3 weeks in the PLDH and topotecan groups, respectively. However, results presented in TA91, which are based on data provided by the manufacturer as part of the appraisal process, indicate that there is no statistically significant difference between PLDH and topotecan in PFS in platinum-sensitive patients, with a median PFS of 27.3 weeks with PLDH and 22.7 weeks with topotecan treated group (HR 1.287, 95% CI: 0.98 to 1.69; HR >1 favours PLDH). As data reported in TA91 are more mature, the TAG has used the HR reported in TA91 in its NMA.[13]

Topotecan versus paclitaxel

ten Bokkel Huinink *et al*. (1997)[21] evaluated TTP as a secondary outcome, defining TTP as time from first study drug to documented progression or administration of third-line therapy. Analysis of TTP for the subgroup of patients with platinum-sensitive (late relapse) disease is not reported in either publication by ten Bokkel Huinink *et al*. (1997 and 2004)[21;51] TA91 found no statistically significant difference between topotecan and paclitaxel in TTP, reporting an unadjusted HR of 0.823 (95% CI: 0.538 to 1.261; Table 42) in platinum-sensitive patients, where HR <1 favours topotecan. There was no significant difference between topotecan and paclitaxel in TTP (p = 0.08), with a median TTP of 18.9 weeks in the topotecan group compared with 14.7 weeks in the paclitaxel group.

Gemcitabine plus carboplatin versus carboplatin alone

PFS was the primary outcome in the trial reported by Pfisterer *et al*.[49] and was defined as time from the date of randomisation to the date of disease progression or death from any cause. Progressive disease was based on clinical and/or radiological evaluation. CA125 elevation without accompanying

clinical or radiological evidence was not sufficient to determine disease progression. Analysis occurred after observation of 325 events. Gemcitabine plus carboplatin was associated with a gain in median PFS of 3.2 months, with the difference between groups reaching statistical significance (HR 0.72, 95% CI: 0.58 to 0.90; p = 0.0031). Median PFS was 8.6 months (95% CI: 7.9 to 9.7 months) with gemcitabine plus carboplatin compared with 5.8 months (95% CI: 5.2 to 7.1 months) with carboplatin alone.

Univariate analysis to investigate the effect of prespecified prognostic factors on PFS found PFI to be an important prognostic factor (p = 0.0015; Table 40).

Table 40. Results of univariate analysis of prespecified prognostic factors affecting progression-free survival

Covariate	Univariate analysis		
	HR	(95% CI)	Wald's p value
Age (years)			
60	1		0.7528
>60	1.04	0.83 to 1.29	
ECOG performance			
0	1		0.1994
1 or 2	1.16	0.93 to 1.44	
Prior platinum treatment			
Platinum plus non-paclitaxel	1		0.6575
Platinum plus paclitaxel	1.06	0.83 to 1.34	
Disease status			
Assessable	1		0.4143
Bidimensionally measured	0.81	0.48 to 1.36	
Platinum-free interval (months)[a]			
6–12	1		0.0015
>12	0.70	0.56 to 0.87	

[a] Results of multivariate analysis for PFI 6–12 months versus > 12 months gave HR 0.69, 95% CI 0.55 to 0.86 (p = 0.010).
Abbreviations used in table: ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio.

Paclitaxel plus carboplatin versus platinum-based therapy alone

ICON4/AGO-OVAR 2.2 defined PFS as the time from randomisation to first appearance of progressive disease or death from any cause, which is the definition most commonly used across trials.[60] Raised CA125 level without clinical or radiological evidence of progressive disease was not considered to demonstrate disease progression. As for OS, patients known to be alive and without progressive disease at the time of analysis were censored at their last follow-up. At analysis (median follow-up of 42 months), 717 (89%) of patients had developed progressive disease or died. Paclitaxel plus platinum-based chemotherapy was associated with a significantly improved PFS compared with platinum-based therapy alone (HR 0.76, 95% CI 0.66 to 0.89; p = 0.0004). The improvement

translates into an estimated absolute difference in 1-year PFS of 10% (40% vs 50%) and an absolute difference in median PFS of 3 months in favour of combination treatment (median PFS: 12 months with paclitaxel plus platinum-based chemotherapy vs 9 months with platinum-based chemotherapy alone).

The authors carried out an exploratory analysis to investigate the effect of randomisation strata on PFS (summarised in Table 41).[60] Again, as for OS, no statistically significant difference between treatment groups was identified for any of the subgroups analysed. A non-significant trend was observed within the subgroups of age (<55 vs 55–65 vs >65) and the number of previous lines of chemotherapy (1 vs 2 vs >2).

Table 41. Effect of paclitaxel plus platinum chemotherapy on progression-free survival in predefined subgroups[60]

Randomisation strata	Number of events per number of patients		p value (interaction or trend)
	Paclitaxel plus platinum	Platinum alone	
Randomisation group			
ICON4 MRC CTU	243/266	253/270	0.93 (interaction)
ICON4 Italy	80/100	94/113	
AGO	23/26	24/27	
Age (years)			
<55	114/127	111/123	0.08 (trend)
55–65	135/151	146/162	
>65	97/114	114/125	
WHO performance			
0	212/246	232/262	0.53 (interaction)
>0	134/146	139/148	
Intended platinum treatment			
Carboplatin	294/332	303/341	0.66 (interaction)
Cisplatin	52/60	68/69	
Previous lines of chemotherapy			
1	310/354	343/380	0.19 (trend)
2	22/22	22/24	
>2	14/15	6/6	
Time since completion of last chemotherapy cycle (months)			
≤12	90/92	109/111	0.87 (interaction)
≥12	256/300	262/299	
Previous exposure to taxane			
No	195/223	214/235	0.49 (interaction)
Yes	151/169	157/175	

Abbreviations used in table: AGO, Arbeitsgemeinschaft Gynaekologische Onkologie; ICON, International Collaborative Ovarian Neoplasm; WHO, World Health Organization.

Gonzalez-Martin *et al*.[47] reported that paclitaxel plus carboplatin was associated with a significantly prolonged TTP compared with carboplatin alone (median TTP: 33.7 weeks with carboplatin alone vs

49.1 weeks with paclitaxel plus carboplatin; HR 0.54, 95% CI: 0.32 to 0.92; p = 0.021). TTP was defined as the time from date of randomisation to date of documentation of tumour progression. It should be noted that the study was not powered to identify a difference between groups in TTP and that the statistical comparative analysis was exploratory.

Table 42. Summary of results for progression-free survival for people with platinum-sensitive recurrent ovarian cancer

Study	Population notes	Intervention	Comparison	Median PFS, (events, n/N)		Hazard ratio	95% CI	P Value
				INT	COMP			
Gonzalez Martin *et al*.[47] TIME TO PROGRESSION	Platinum sensitive	Paclitaxel (175 mg/m^2) plus carboplatin (AUC 5) every 21 days	Carboplatin (AUC 5) every 21 days	49.1 weeks (95% CI 36.9 to 61.3)	33.7 weeks (95% CI 25.8 to 41.5)	0.54	0.32 to 0.92	0.021[b]
Gordon *et al*. (2001)[48]	Platinum sensitive subgroup ***HR from TA91 (not reported in Gordon 2001)***	PLDH (50 mg/m^2) every 28 days	Topotecan (1.5 mg/m^2) for 5 days every 21 days	27.3 weeks (N = 109)	22.7 weeks (N = 111)	1.287[a]	0.98 to 1.69	
ICON4/AGO-OVAR 2.2[60]		Paclitaxel plus platinum	Conventional platinum treatment	12 months	9 months	0.76	0.66 to 0.89	0.0004
CALYPSO[31]	Platinum-sensitive patients (overall population)	PLDH (30 mg/m^2) plus carboplatin every 21 days	Paclitaxel (175 mg/m^2) plus carboplatin every 21 days	11.3 months (N = 467)	9.4 months (N = 507) N=363 had disease progression according to RECIST; N=89 had progression according to CA-125 GCIG criteria.	0.82	0.72 to 0.94	0.005[b]

OVA-301[30]	Platinum-sensitive subgroup	Trabectedin (1.1 mg/m^2) plus PLDH (30 mg/m^2) every 3 weeks	PLDH (50 mg/m^2) every 4 weeks	9.2 months (115/218)	7.5 months (111/213)	0.73	0.56 to 0.95	0.017
Alberts *et al.*[54]	Platinum-free interval of 6–24 months	PLDH (30 mg/m^2) plus carboplatin (AUC 5) every 4 weeks	Carboplatin (AUC 5) every 4 weeks	12 months (26/30)	8 months (29/30)	0.54	0.32 to 0.93	0.02
Bafaloukos *et al.*[29] TIME TO PROGRESSION		PLDH (45 mg/m^2) plus carboplatin (AUC 5) every 28 days	Paclitaxel (175 mg/m^2; 3 hr infusion) plus carboplatin (AUC 5) every 21 days	11.8 months	10.8 months			
				p = 0.904				
Pfisterer *et al*.[49]	Platinum-sensitive	Gemcitabine (1,000 mg/m^2) plus carboplatin every 21 days	Carboplatin alone every 21 days	8.6 months (95% CI 7.9 to 9.7 months) (N = 178)	5.8 months (95% CI 5.2 to 7.1 months) (N = 178)	0.72	0.58 to 0.90	0.0031[b]
ten Bokkel Huinink *et al*. (2004)[51] TIME TO PROGRESSION	HR taken from TA91. Data are not presented in the published paper.	Topotecan (1.5 mg/m^2) for 5 days every 21 days	Paclitaxel (175 mg/m^2) every 21 days			0.823	0.538 to 1.261	

[a] HR >1 favours PLDH.

[b] log-rank.

Abbreviations used in table: AUC, area under curve; COMP, comparator; INT, intervention; NR, not reported; PLDH, pegylated liposomal doxorubicin hydrochloride.

Network meta-analysis (platinum sensitive)

The RCTs available for inclusion in the NMA evaluating PFS in patients with platinum-sensitive recurrent ovarian cancer are summarised in Table 42. Unfortunately, as described earlier, a single network could not be constructed out of the available trials. The two networks constructed for this outcome are depicted in Figure 7.

Network 1 (Figure 7a) consisted of the following comparators:

- paclitaxel plus carboplatin;
- gemcitabine plus carboplatin;
- PLDH plus carboplatin;
- platinum as a monotherapy.

Paclitaxel plus carboplatin was chosen as the baseline treatment as this would best help to inform the economic evaluation conducted by the TAG (Section 5.2.7). However, results are reported in Table 43 sequentially covering all possible comparisons. Overall, only PLDH plus carboplatin had a significantly improved PFS (at the 5% level) compared with paclitaxel plus carboplatin. Platinum monotherapy was associated with a significant reduction in PFS compared to all doublet chemotherapies assessed.

Network 2 (Figure 7b) consisted of the following comparators:

- PLDH monotherapy;
- trabectedin plus PLDH;
- paclitaxel monotherapy;
- topotecan monotherapy.

PLDH monotherapy was chosen as the baseline treatment as this would best help to inform the economic evaluation conducted by the TAG (Section 5.2.7). However, results are reported in Table 43 sequentially covering all possible comparisons. Overall, only trabectedin plus PLDH demonstrated a significant difference increase in PFS (at the 5% level) compared with PLDH monotherapy. Trabectedin plus PLDH would also be considered to have a statistically significant prolonged PFS when compared directly with paclitaxel monotherapy or topotecan monotherapy. None of the other comparisons of chemotherapies would be considered significantly different from one another.

Figure 7. Networks for progression-free survival for people with platinum-sensitive recurrent ovarian cancer

Figure 7a. Network 1

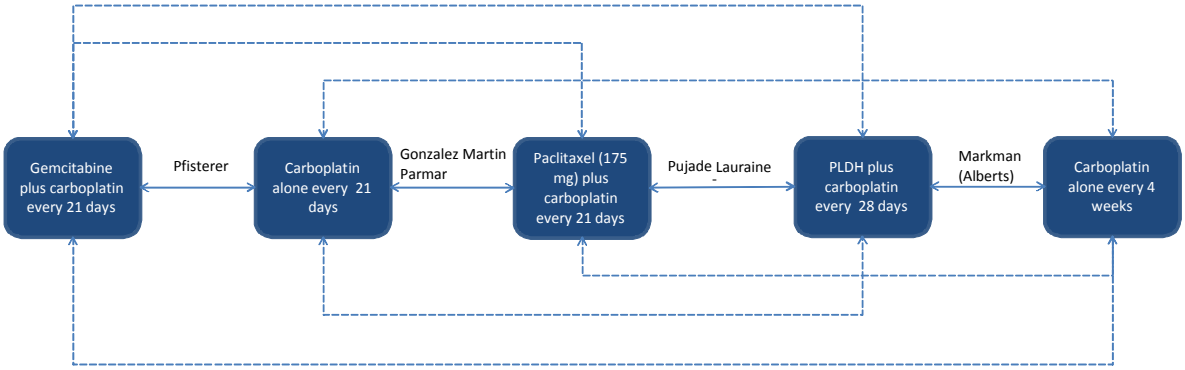


Figure 7b. Network 2

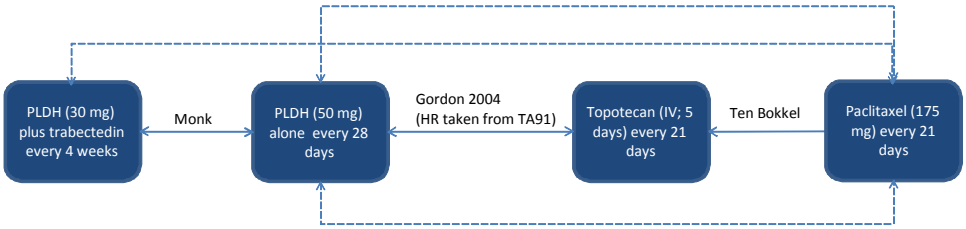


Table 43. Results of the network meta-analysis for progression-free survival for people with platinum-sensitive recurrent ovarian cancer

Comparison	HR	95% CrI	
		Lower limit	Upper limit
Network 1			
Versus paclitaxel plus carboplatin (HR <1 favours comparator, HR >1 favours paclitaxel plus carboplatin)			
Gemcitabine plus carboplatin	0.985	0.748	1.273
PLDH plus carboplatin	0.817	0.717	0.927
Platinum as a monotherapy	1.361	1.182	1.559
Versus gemcitabine plus carboplatin (HR <1 favours comparator, HR >1 favours gemcitabine plus carboplatin)			
PLDH plus carboplatin	0.845	0.624	1.116
Platinum as a monotherapy	1.400	1.106	1.749
Versus PLDH plus carboplatin (HR <1 favours comparator, HR >1 favours PLDH plus carboplatin)			
Platinum as a monotherapy	1.672	1.389	1.997

Network 2			
Versus PLDH monotherapy ***(HR <1 favours comparator, HR >1 favours PLDH monotherapy)***			
Trabectedin plus PLDH	0.736	0.560	0.949
Paclitaxel monotherapy	1.615	0.939	2.586
Topotecan monotherapy	1.298	0.979	1.688
Versus trabectedin plus PLDH ***(HR <1 favours comparator, HR >1 favours trabectedin plus PLDH)***			
Paclitaxel monotherapy	2.236	1.209	3.795
Topotecan monotherapy	1.797	1.207	2.578
Versus paclitaxel monotherapy ***(HR <1 favours comparator, HR >1 favours paclitaxel monotherapy)***			
Topotecan as a monotherapy	0.842	0.539	1.262
Abbreviations used in table: CrI, Credible Interval; HR, hazard ratio; PLDH, pegylated liposomal doxorubicin hydrochloride.			

Fully platinum sensitive

Trabectedin plus PLDH versus PLDH alone

In the subgroup of patients with FPS disease, in the primary analysis of PFS (independent radiologist), OVA-301 found no statistically significant difference between treatment groups in median PFS, with median PFS of 11.1 months in the trabectedin plus PLDH group compared with 8.9 months in the PLDH alone group (HR 0.70, 95% CI: 0.47 to 1.03; Table 44).[64] Secondary analysis based on independent review by oncologists found the difference in PFS to be statistically significant and favouring trabectedin plus PLDH (median PFS: 11.1 months with trabectedin plus PLDH vs 9.0 months with PLDH alone; HR 0.66, 95% CI: 0.46 to 0.97; p = 0.0311 [log-rank]). The FAD of the STA of trabectedin plus PLDH (TA222) states that the primary analysis was thought to be the most robust analysis.

It is important to reiterate that, in the full trial population, fewer events had occurred than the planned event rate required to generate 90% power and, as a consequence, the analysis might have been underpowered. In a subgroup analysis, the power to detect a statistically significant difference is further reduced. In addition, analysis of results for FPS patients was not preplanned and is therefore hypothesis generating.

Gemcitabine plus carboplatin versus carboplatin alone

In the trial reported by Pfisterer *et al*.[49], in the subgroup of patients with FPS, at the time of analysis, a similar proportion in each treatment group had progressed or died (93/106 [87.7%] with gemcitabine plus carboplatin vs 97/107 [90.7%] with carboplatin alone). Median PFS in each treatment group for this population was not reported. An accompanying HR or p-value for the difference between treatment groups was not available in the full publication.

Paclitaxel plus carboplatin versus platinum-based therapy alone

As for OS, ICON4/AGO-OVAR 2.2 carried out a subgroup analysis to determine the effect of paclitaxel plus platinum chemotherapy on PFS in various subgroups, including time since completion of last chemotherapy regimen (≤12 months vs >12 months).[60] In the subgroup of patients with FPS ovarian cancer (599 patients), a similar proportion of people in each treatment group had progressed or died at the time of analysis (256/300 [85.3%] with paclitaxel plus carboplatin vs 262/299 [87.3%] with carboplatin alone). Median PFS in each treatment group for this population was not reported. An accompanying HR or p-value for the difference between treatment groups was not available in the full publication.

Table 44. Summary of results for progression-free survival in people with fully platinum-sensitive recurrent ovarian cancer

Study	Intervention	Comparison	Median PFS, (events, n/N)		Hazard ratio	95% CI	P Value
			INT	COMP			
OVA-301[64]	Trabectedin (1.1 mg/m^2) plus PLDH (30 mg/m^2) every 3 weeks	PLDH (50 mg/m^2) every 4 weeks	11.1 months (N = 94)	9.0 months (N = 122)	0.70	0.47 to 1.03	0.0152
Pfisterer *et al*.[49]	Gemcitabine (1,000 mg/m^2) plus carboplatin every 21 days	Carboplatin alone every 21 days	93/106	97/107			
ICON4/AGO-OVAR 2.2[60]	Paclitaxel plus platinum	Conventional platinum treatment	256/300	262/299			

*log-rank

Abbreviations used in table: AUC, area under curve; COMP, comparator; INT, intervention; NR, not reported; PLDH, pegylated liposomal doxorubicin hydrochloride.

Network meta-analysis (fully platinum sensitive)

The trials identified for potential inclusion in the NMA for PFS in patients with fully platinum-sensitive recurrent ovarian cancer are detailed in Table 44. Of the three RCTs identified, only one trial reported the required data for analysis[30] and so it was not possible perform an indirect comparison.

Partially platinum sensitive

Pegylated liposomal doxorubicin hydrochloride plus carboplatin versus paclitaxel plus carboplatin

A separate publication of CALYPSO (Pujade-Lauraine *et al*.[31]) reported an analysis of PFS in the subgroup of patients with PPS.[56] The PPS subgroup comprised 161 patients in the PLDH plus carboplatin group and 183 patients in the paclitaxel plus carboplatin group. Baseline characteristics were comparable in the two treatment groups. Median follow-up was 23 months and 326 patients experienced an event (progression or death).

PLDH plus carboplatin significantly prolonged median PFS compared with paclitaxel plus carboplatin in this subgroup of patients, with a gain of 0.6 months in PFS (median PFS: 9.4 months with PLDH plus carboplatin vs 8.8 months with paclitaxel plus carboplatin; HR 0.73, 95% CI 0.58 to 0.90; p = 0.004 for superiority; Table 45).

Trabectedin plus PLDH versus PLDH alone

In the subgroup of patients with PPS, in the primary analysis of PFS (independent radiologist), OVA-301 found that trabectedin plus PLDH significantly prolonged median PFS compared with PLDH alone (HR 0.65, 95% CI: 0.45 to 0.92; Table 45).[63] Median PFS was 7.4 months in the trabectedin plus PLDH group compared with 5.5 months in the PLDH alone group. Results based on review by independent oncologist align with those of the primary analysis (HR 0.54, 95% CI 0.39 to 0.76). As noted above, analysis of results for PPS patients is potentially underpowered and was not preplanned.

Gemcitabine plus carboplatin versus carboplatin alone

At the time of analysis of PFS in Pfisterer *et al*.[49], most patients categorised as having PPS ovarian cancer had progressed or died (69/71 [97.2%] with gemcitabine plus carboplatin vs 65/71 [91.5%] with carboplatin alone). Median PFS in each treatment group for this population was not reported. An accompanying HR or p-value for the difference between treatment groups was not available in the full publication.

Paclitaxel plus carboplatin versus platinum-based therapy alone

In the subgroup of patients with PPS disease in ICON4/AGO-OVAR 2.2, almost all patients in each treatment group had progressed or died at the time of analysis (90/92 [97.8%] with paclitaxel plus carboplatin vs 109/111 [98.2%] with carboplatin alone). Median PFS in each treatment group for this population was not reported. An accompanying HR or p-value for the difference between treatment groups was not available in the full publication.

Table 45. Summary of results for progression-free survival in people with partially platinum-sensitive recurrent ovarian cancer

Study	Population notes	Intervention	Comparison	Median PFS, (events, n/N)		Hazard ratio	95% CI	P Value
				INT	COMP			
OVA-301[64]	Platinum-free interval 6-12 months	Trabectedin (1.1 mg/m^2) plus PLDH (30 mg/m^2) every 21 days	PLDH (50 mg/m^2) every 4 weeks	7.4 months (N = 123) Independent radiologist: (69/122) Independent oncologist: (68/91)	5.5 months (N = 91) Independent radiologist: (55/86) Independent radiologist: (73/123)	0.65	0.45 to 0.92	0.0152
CALYPSO[56]	Prespecified subgroup of ***partially sensitive patients***	PLDH (30 mg/m^2) plus carboplatin every 21 days	Paclitaxel (175 mg/m^2) plus carboplatin every 3 weeks	9.4 months (N = 161)	8.8 months (N = 183)	0.73	0.58 to 0.90	0.004
ICON4/AGO-OVAR 2.2[60]		Paclitaxel plus platinum	Conventional platinum treatment	90/92	109/111			
Pfisterer *et al*.[49]	Platinum-sensitive	Gemcitabine plus carboplatin every 21 days	Carboplatin alone every 21 days	69/71	65/71			

*log-rank

Abbreviations used in table: AUC, area under curve; COMP, comparator; INT, intervention; NR, not reported; PLDH, pegylated liposomal doxorubicin hydrochloride.

Network meta-analysis (partially platinum sensitive)

The trials identified for potential inclusion in the NMA for PFS in patients with partially platinum-sensitive recurrent ovarian cancer are detailed in Table 45. Of the four RCTs identified, only two trials reported the required data for analysis[30;31] and as they did not contain a common comparator it was not possible perform an indirect comparison.

Platinum resistant/refractory

Pegylated liposomal doxorubicin hydrochloride versus topotecan

In the subgroup of patients with PRR, Gordon *et al*. (2001)[48] found no statistically significant difference in PFS between PLDH and topotecan (p = 0.733; HR not reported). Median PFS with PLDH was 9.1 weeks compared with 13.6 weeks with topotecan. Results presented in TA91 for this subgroup of patients are analogous to those reported in Gordon *et al*. (2001)[48] with an HR reported of 0.99 (95% CI: 0.77 to 1.28).[13]

Topotecan versus paclitaxel

Analysis of TTP for the subgroup of patients with PRR (refractory, early and interim relapse) disease is not reported in either publication by ten Bokkel Huinink *et al*. (1997 and 2004).[21;51] TA91 found no statistically significant difference between topotecan and paclitaxel in TTP, reporting an unadjusted HR of 0.749 (95% CI: 0.501 to 1.121; Table 46) in PRR patients, where HR <1 favours topotecan.[13] There was no significant difference between topotecan and paclitaxel in TTP (p = 0.08), with a median TTP of 18.9 weeks in the topotecan group compared with 14.7 weeks in the paclitaxel group.

Paclitaxel plus carboplatin versus paclitaxel alone

PFS was the primary outcome of the trial carried out by Lortholary *et al*.[61] and was determined according to criteria set out by GCIG. Median PFS is based on 162 events occurring in a median follow-up of 15 months. No statistically significant differences in PFS were identified among the treatment arms, with a median PFS of 3.7, 4.8, and 5.4 months for weekly paclitaxel, weekly paclitaxel plus carboplatin, and weekly paclitaxel plus weekly topotecan, respectively. As discussed earlier, results from the weekly paclitaxel plus topotecan group are not of interest to this systematic review. The authors of the study were contacted with a request for the HR for the comparison of weekly paclitaxel versus weekly paclitaxel plus carboplatin. The authors helpfully provided the requested information, which indicates that there is no significant difference between the two treatment groups in median PFS (HR 0.924, 95% CI: 0.763 to 1.119; p = 0.42; Table 46).

In addition, an exploratory analysis of PFS was carried out using a Cox model that adjusted for: age; number of metastatic sites; number of prior lines of chemotherapy (1 vs ≥2); PFI (progression ≤1 month vs >1 month from last platinum dose); ECOG performance status (0 vs 1 or 2); and tumour size

(<5 cm or ≥5 cm). The analysis found that (monotherapy vs combination therapy) was not predictive of PFS. However, PFI and ECOG PS were identified as independent predictors of PFS, with p values of 0.03 and 0.01, respectively.

not to differ among treatment groups, with a median OS of 19.9 months, 15.2 months, and 18.6 months for weekly paclitaxel, weekly paclitaxel plus carboplatin, and weekly paclitaxel plus weekly topotecan. The number of events at the time of this analysis is unclear. As discussed earlier, results from the weekly paclitaxel plus carboplatin group are not of interest to this systematic review. As part of the process, the authors of the study were contacted with a request for the HR for the comparison of weekly paclitaxel versus weekly paclitaxel plus carboplatin. The authors helpfully provided the requested information, which indicates that there is no significant difference between the two treatment groups in median OS (HR 1.074, 95% CI: 0.859 to 1.341; p = 0.53; Table 46).

Topotecan administered on 5 consecutive days (conventional regimen) versus topotecan administered weekly

PFS was evaluated as a secondary outcome by Sehouli *et al*.[23] A definition for PFS was not provided in the full publication. There was no statistically significant difference between treatments in PFS (HR 1.29, 95% CI: 0.96 to 1.76; p = 0.088). Median PFS was 3.0 months with conventional topotecan compared with 4.4 months with weekly topotecan.

Table 46. Summary of results for progression-free survival in people with platinum-resistant or refractory recurrent ovarian cancer

Study	Population notes	Intervention	Comparison	Median PFS, (events, n/N)		Hazard ratio	95% CI	P Value
				INT	COMP			
Gordon *et al*. (2001)[48]	Platinum resistant patients (refractory term used in methods, resistant used in results) ***HR from TA91 (not calculated in Gordon 2001)***	PLDH (50 mg/m^2) every 28 days	Topotecan (1.5 mg/m^2) for 5 days every 21 days	9.1 weeks (N = 130)	13.6 weeks (N=124)	0.99	0.77 to 1.28	0.733
ten Bokkel Huinink *et al*. (2004)[51]	HR taken from TA91. Data are not presented in the published paper.	Topotecan (1.5 mg/m^2) for 5 days every 21 days	Paclitaxel (175 mg/m^2) every 21 days			0.749	0.501 to 1.121	
Lortholary 2012[61]	Full population relapsed within six months	Weekly paclitaxel (80 mg/m^2) plus carboplatin	Weekly paclitaxel (80 mg/m^2) on 4 week cycle	4.8 (95% CI 3.3 to 6.3) (N = 51)	3.7 (95% CI 3.1 to 4.3) (N=57)	0.924	0.763 to 1.119	0.42
Sehouli 2010[23]	Full population recurrent platinum resistant patients	Topotecan (4.0 mg/m^2) (weekly; days 1, 8, and 15) every 28 days	Topotecan (1.25 mg/m^2) for 5 consecutive days every 21 days	4.4 months	3.0 months	1.29	0.96 to 1.76	0.088

*log-rank

Abbreviations used in table: AUC, area under curve; COMP, comparator; INT, intervention; NR, not reported; PLDH, pegylated liposomal doxorubicin hydrochloride.

Network meta-analysis (platinum-resistant or refractory)

The RCTs available for inclusion in the NMA evaluating PFS in patients with platinum-resistant or refractory recurrent ovarian cancer are summarised in Table 46. The network of trials constructed for this outcome is depicted in Figure 8 and contains the following comparators:

- PLDH monotherapy;
- trabectedin plus PLDH;
- paclitaxel monotherapy;
- topotecan monotherapy; that is, topotecan 1.25 or 1.5 mg/m^2 daily for 5 days every 21 days;
- topotecan monotherapy (weekly); that is, topotecan 4.0 mg/m^2 (weekly) on days 1, 8, and 15 of a 28-day cycle.

The results from this NMA are presented in Table 47. Overall, there was no significant difference in PFS (at the 5% level) for any of the chemotherapies assessed compared with PLDH monotherapy (or with each other).

An RCT that provided results for this population but which did not share a common comparator within the network compared low dose paclitaxel (80 mg/m^2) with low dose paclitaxel (80 mg/m^2) plus carboplatin.[61] However, Lortholary *et al.*[61] identified no significant difference in PFS between the two different treatment regimens (Table 47). Trabectedin plus PLDH is outside of the scope for this review for the population of PRR patients; data have been included within the network to capture all the available evidence but are not included in the economic analysis.

Figure 8. Networks for progression-free survival for people with platinum-resistant or refractory recurrent ovarian cancer

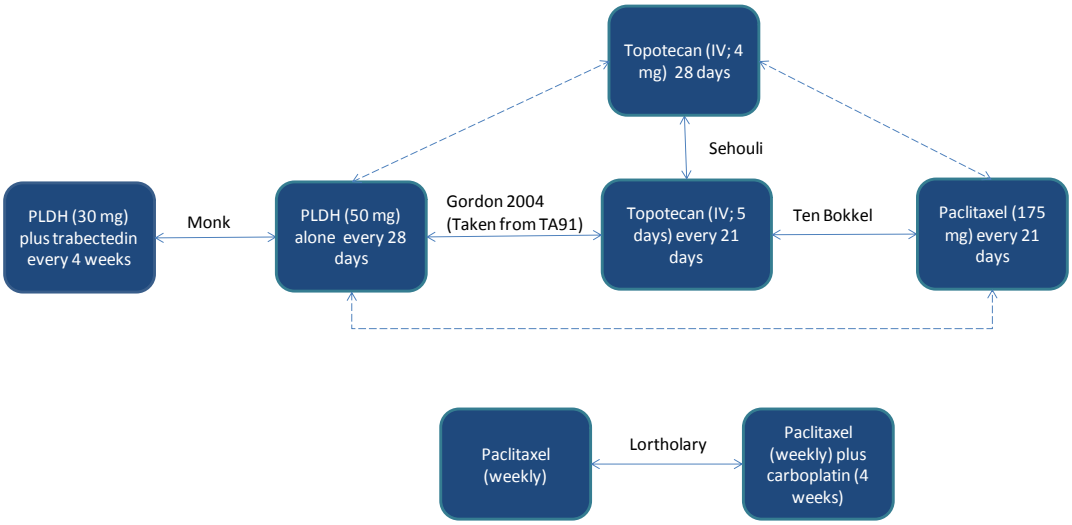


Table 47. Results of the network meta-analysis for progression-free survival for people with platinum-resistant or refractory recurrent ovarian cancer

Comparison	HR	95% CrI	
		Lower limit	Upper limit
Versus PLDH monotherapy (HR <1 favours comparator, HR >1 favours PLDH monotherapy)			
Trabectedin plus PLDH	0.961	0.697	1.292
Paclitaxel monotherapy	1.360	0.817	2.123
Topotecan monotherapy	0.998	0.767	1.277
Topotecan monotherapy (weekly)	1.302	0.859	1.894
Versus trabectedin plus PLDH (HR <1 favours comparator, HR >1 favours trabectedin plus PLDH)			
Paclitaxel monotherapy	1.450	0.791	2.454
Topotecan monotherapy	1.064	0.698	1.555
Topotecan monotherapy (weekly)	1.389	0.811	2.216
Versus paclitaxel monotherapy (HR <1 favours comparator, HR >1 favours paclitaxel monotherapy)			
Topotecan monotherapy	0.765	0.502	1.118
Topotecan monotherapy (weekly)	0.999	0.585	1.599
Versus topotecan monotherapy (HR <1 favours comparator, HR >1 favours topotecan monotherapy)			
Topotecan monotherapy (weekly)	1.305	0.951	1.744
Abbreviations used in table: CrI, Credible Interval; HR, hazard ratio; PLDH, pegylated liposomal doxorubicin hydrochloride.			

Full population (mixed platinum-free intervals)

Trabectedin plus PLDH versus PLDH alone

In OVA-301 (all patients), after 389 events based on independent radiological review, trabectedin plus PLDH was found to significantly prolong PFS by 1.5 months compared with PLDH alone (median PFS: 7.3 months with trabectedin plus PLDH vs 5.8 months with PLDH alone; HR 0.79, 95% CI: 0.65 to 0.96; p = 0.0190; Table 49).[30]

Multivariate analysis of baseline characteristics that are potential prognostic factors affecting PFS (based on independent radiology review) identified treatment with trabectedin plus PLDH and PFI (analysed as a continuum) as factors having a statistically significant effect on PFS (Table 48).[30]

Table 48. Multivariate analysis for prognostic factors potentially affecting progression-free survival in OVA-301[30]

Prognostic Factor	PFS		p value
	HR	95% CI	
Treatment arm (trabectedin/PLDH vs PLDH alone)	0.784	0.64 to 0.96	0.0195
Platinum-free interval, continuous	0.97	0.96 to 0.98	<0.0001
ECOG performance status (1–2 vs 0)	1.226	0.99 to 1.52	0.0591
Race (non-white vs white)	1.229	0.97 to 1.56	0.0890
Baseline CA125 (≥2× ULN vs <2× ULN)	1.175	0.91 to 1.53	0.2245
Age, continuous	1.001	0.99 to 1.01	0.8542
Baseline liver/lungs involvement (yes vs no)	1.207	0.98 to 1.49	0.0760
Prior taxane (yes vs no)	0.999	0.77 to 1.29	0.9957
Abbreviations used in table: ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; PFS, progression-free survival; PLDH, pegylated liposomal doxorubicin hydrochloride; ULN, upper limit of normal.			

Pegylated liposomal doxorubicin hydrochloride versus topotecan

For the full trial population, Gordon *et al*. (2001)[48] observed a median PFS of 16.1 weeks with PLDH and of 17.0 weeks with topotecan, with no statistically significant difference between groups (HR 1.118, 95% CI: 0.93 to 1.35; p = 0.095; Table 49). The HR was not reported in the full publication and is as reported in TA91.[13]

Topotecan versus paclitaxel

Data reported here are taken from the longer-term follow-up study reported by ten Bokkel Huinink *et al*. (2004)[51] in which data had been collected for more than 4 years. For analysis of TTP, 25% of patients in the topotecan group and 12.3% of patients in the paclitaxel group were censored. There was no statistically significant difference between topotecan and paclitaxel in TTP (p = 0.08), with a median TTP of 18.9 weeks in the topotecan group compared with 14.7 weeks in the paclitaxel group (Table 49).[51] An accompanying HR was not reported in the full publication.[51] However, TA91 reported an HR of 0.811 (95% CI: 0.603 to 1.092) for TTP, where HR <1 favours topotecan.[13] The HR was adjusted for stratification factors.

Paclitaxel versus oxaliplatin

The methods section of Piccart *et al*.[62] indicates that TTP was a secondary outcome measure, with TTP defined as the time from day 1 of treatment to first observation of disease progression as per WHO criteria. However, results are presented for both TTP and PFS. At the time of analysis, of the 86 patients randomised, 69 had progressed (80.2%). Of the remaining 17 patients who had not progressed, 9 were in the paclitaxel group and 8 were in the oxaliplatin group.

Median TTP (the number of patients reported includes only those who have progressed) and PFS were the same and were reported as 14 weeks in the paclitaxel group compared with 12 weeks in the oxaliplatin group. Statistical significance was not assessed in the full publication.

Topotecan oral versus topotecan intravenous

Gore *et al*.[24] evaluated TTP; TTP was not defined in the full publication. In the full trial population, median TTP was 13 weeks with oral topotecan compared with 17 weeks with intravenous topotecan (difference reported to be non-significant; p value not reported; Table 49).[24]

Paclitaxel high dose (250 mg/m^2) versus paclitaxel standard dose (175 mg/m^2)

In the trial carried out by Omura *et al*.[66] PFS did not differ appreciably between treatment regimens. Patients assigned to paclitaxel 175 mg/m^2 had an estimated median PFS of 4.8 months compared 5.5 months for patients receiving paclitaxel 250 mg/m^2 (Table 49). The statistical significance between the groups was not assessed.

Paclitaxel weekly versus paclitaxel every 3 weeks

Rosenberg *et al*.[59] evaluated TTP as a secondary outcome, and defined TTP as time from first day of study treatment to the date of documented tumour progression (as per WHO criteria) or censored observation. In the full trial population, median TTP was 6.1 months (95% CI: 5.0 to 8.0 months) in the group receiving paclitaxel every 7 days compared with 8.1 months (95% CI: 6.4 to 9.7 months) in the paclitaxel every 21 days group. The difference between groups in TTP did not reach statistical significance (p = 0.85). It is unclear how many events had occurred at the time of analysis.

Table 49. Summary of results for progression-free survival in a population of mixed platinum-free interval

Study	Population notes	Intervention	Comparison	Median PFS, (events, n/N)		Hazard ratio	95% CI	P Value
				INT	COMP			
Piccart 2000[62]	Approximately 75% population is platinum refractory, 25% is platinum sensitive	Paclitaxel 175 mg/m^2 over 3 hours every 3 weeks	Oxaliplatin 130 mg/m^2 over 2 hours every 3 weeks	14 weeks (N = 41)	12 weeks (N = 45)			
OVA-301[30]	Full population contains platinum sensitive and resistant patients	PLDH 30 mg/m^2 IV plus trabectedin 1.1 mg/m^2 every 3 weeks	PLDH 50 mg/m^2 every 4 weeks	7.3 months (N = 337)	5.8 months (N = 335)	0.79	0.65 to 0.96	0.0190
Gordon *et al*. (2001)[48]	Combination of platinum sensitive and platinum refractory patients ***HR from TA91 (not calculated in Gordon 2001)***	PLDH 50 mg/m^2 every 28 days	Topotecan 1.5 mg/m^2 per day for 5 days every 21 days	16.1 weeks (N = 239)	17.0 weeks (N = 235)	1.118	0.93 to 1.35	0.095
Gore *et al*.[24] TIME TO PROGRESSION	Approximately 30% refractory; 27.5% resistant; 43% sensitive	Oral topotecan 2.3 mg/m^2/day	IV topotecan 1.5 mg/m^2/day for 5 days every 21 days	13 weeks (range: 1.6 to 76.6) (N = 135)	17 weeks (range: 0.1 to 91.6) (N = 135)			
Rosenberg *et al*.[59] TIME TO PROGRESSION	Platinum resistant: relapse ≤6 months and >6 months after primary platinum-based therapy	Paclitaxel weekly	Paclitaxel 3 weekly	6.1 months (95% CI 5.0 to 8.0) (N = 105)	8.1 months (95% CI 6.4 to 9.7) (N = 103)			
				p = 0.85				

ten Bokkel Huinink *et al*. (2004)[51] TIME TO PROGRESSION	HR taken from TA91. Data are not presented in the published paper.	Topotecan 1.5 mg/m^2/day for 5 days	Paclitaxel 175 mg/m^2/day as 3 hour infusion every 21 days.	18.9 weeks (range <1 to 92.6+ weeks)	14.7 weeks (range: <1 to 137.3+)	0.811 (adjusted for stratification factors)	0.603 to 1.092	0.08
Omura *et al*.[66]		Paclitaxel 250 mg/m^2 every 21 days	Paclitaxel 175 mg/m^2 every 21 days	5.5	4.8	NR		
*log-rank Abbreviations used in table: AUC, area under curve; COMP, comparator; INT, intervention; NR, not reported; PLDH, pegylated liposomal doxorubicin hydrochloride.								

Network meta-analysis (mixed platinum-free intervals)

The RCTs available for inclusion in the NMA evaluating PFS in patients with mixed platinum-free intervals in recurrent ovarian cancer are summarised in Table 49. However, based on expert clinical opinion, the TAG decided not to evaluate this mixed patient population as the results would not be considered clinically meaningful.

4.2.2.3 Tumour response

Like PFS and TTP, for patients with measurable disease, assessment of tumour response is based standard criteria, such as RECIST criteria. In patients without measurable disease, changes in CA125 are used to evaluate tumour response as per the algorithm outlined by Rustin *et al*.[73] There is some controversy over the use of CA125 alone as an indicator for disease progression, and for tumour response. However, an alternative opinion is that it is difficult to radiologically follow changes in measurable disease from baseline. Overall response rate (ORR) is typically reported as the combination of patients with a complete response (CR) or those with a partial response (PR), as defined by the criteria implemented in the trial. ORR is considered to be a direct measure of the antitumor activity of a drug but not a direct measure of clinical benefit.[74] As for PFS and TTP, evaluation of CR and PR is open to assessment bias, particularly in an open-label trial. Where CR and PR have been reported separately, for the purposes of the NMA, the TAG has combined CR and PR results. Results for stable disease and progressive disease are also reported for completeness.

Summary of results for tumour response

Results are presented for ORR, which has been defined as the number of patients achieving CR or PR as their best response. Definitions of CR and PR as reported in the trials are provided in the main text. No trial was identified evaluating treatments in a population solely comprising patients who were allergic or intolerant to platinum-based chemotherapy. Here, results for patients with platinum-sensitive or platinum-refractory/resistant (PRR) disease are summarised. For trials not limited to either platinum-sensitive or PRR patients (i.e., includes a mix of platinum-free interval [PFI]), results for the full trial population are presented in the main text.

Results for ORR for the subgroup of patients with platinum sensitive (relapse ≥6 months after last platinum-based chemotherapy) ovarian cancer

Twelve RCTs evaluating 11 different head-to-head comparisons of interventions and comparators of interest reported on ORR. Of the 11 comparisons identified, only two trials reported a statistical significance in ORR. A larger proportion of patients treated with gemcitabine plus carboplatin achieved CR or PR than with those treated with carboplatin alone. Trabectedin plus PLDH was also found to significantly improve rate of CR or PR achieved compared with PLDH (50 mg/m^2) alone.

Trial name	Intervention	Comparator	OR (95%CI)
Bafaloukos *et al*.[29]	PLDH (45 mg/m^2) plus carboplatin every 28 days	Paclitaxel (175 mg/m^2) plus carboplatin every 21 days	0.866 (0.535 to 1.402)
OVA-301[30]	Trabectedin (1.1 mg/m^2) plus PLDH (30 mg/m^2) every 3 weeks	PLDH (50 mg/m^2) every 4 weeks	1.567 (1.043 to 2.354)
Gordon *et al*. (2001)[53]	PLDH (50 mg/m^2) every 28 days	Topotecan (1.5 mg/m^2) for 5 days every 21 days	0.987 (0.563 to 1.727)
ten Bokkel Huinink *et al*. (2004)[51]	Topotecan (1.5 mg/m^2) for 5 days every 21 days	Paclitaxel (175 mg/m^2) every 21 days	1.442 (0.607 to 3.427)
Alberts *et al*.[54]	PLDH (30 mg/m^2) plus carboplatin every 4 weeks	Carboplatin alone every 4 weeks	2.148 (0.792 to 5.825)
ICON4/AGO-OVAR 2.2[60]	Paclitaxel plus platinum	Conventional platinum treatment	1.182 (0.831 to 1.682)
Gonzalez Martin *et al*.[47]	Paclitaxel (175 mg/m^2) plus carboplatin every 21 days	Carboplatin alone every 21 days	0.661 (0.325 to 1.347)
Pfisterer *et al*.[49]	Gemcitabine (1,000 mg/m^2) plus carboplatin every 21 days	Carboplatin alone every 21 days	1.527 (1.025 to 2.275)
Rosenberg *et al*.[59]	Paclitaxel (67 mg/m^2) weekly (1 course = 3 weeks)	Paclitaxel (200 mg/m^2) every 3 weeks	1.127 (0.574 to 2.212)
Gore *et al*.[24]	Oral topotecan (2.3 mg/m^2) daily	Intravenous topotecan (1.5 mg/m^2) for 5 days every 21 days	0.531 (0.233 to 1.208)
Piccart *et al*.[62]	Paclitaxel (175 mg/m^2) every 3 weeks	Oxaliplatin (130 mg/m^2) every 3 weeks	0.520 (0.083 to 3.259)
Omura *et al*.[66]	Paclitaxel 250 mg/m^2 every 21 days	Paclitaxel 175 mg/m^2 every 21 days	0.748 (0.273 to 2.051)
Abbreviations used in table: CI, confidence interval; OR, odds ratio; PLDH, pegylated liposomal doxorubicin hydrochloride.			

Based on the trials identified, it was not possible to construct a complete network. Again, two discrete networks were generated, one evaluating platinum-based therapies and the second comparing non-platinum-based regimens. It should be stressed that results from the two discrete networks are not directly comparable.

In the network evaluating platinum-based chemotherapies, paclitaxel plus carboplatin and gemcitabine plus carboplatin were found to have a significantly higher ORR than platinum monotherapy. There was no significant difference between PLDH plus carboplatin and any of the chemotherapeutic treatments with which it was assessed.

Comparator	Paclitaxel plus carboplatin	PLDH plus carboplatin	Platinum monotherapy	Gemcitabine plus carboplatin
Paclitaxel plus carboplatin	–	0.994 (0.574 to 1.609)	0.666 (0.474 to 0.908)	1.370 (0.765 to 2.261)
PLDH plus carboplatin	–	–	0.713 (0.386 to 1.208)	1.467 (0.672 to 2.793)
Platinum monotherapy			–	2.058 (1.305 to 3.108)
Gemcitabine plus carboplatin	–	–	–	–
Comparator is listed in the left-hand side column. Results presented are OR and accompanying CrI. OR >1 favours the intervention (listed in the top table row) and OR <1 favours the comparator. Abbreviations used in table: CrI, credible interval; OR, odds ratio; PLDH, pegylated liposomal doxorubicin hydrochloride.				

Analysis of non-platinum-based regimens indicates that trabectedin plus PLDH significantly improves ORR compared with PLDH, and oral topotecan. Compared with oral topotecan, intravenous topotecan was found to be associated with a significant increase in the proportion of patients achieving CR or PR. No other statistically significant differences were identified.

Comparator	PLDH monotherapy	Trabectedin plus PLDH	Topotecan monotherapy (intravenous)	Paclitaxel monotherapy (every 3 weeks)	Topotecan monotherapy (oral)	Paclitaxel monotherapy (weekly)
PLDH monotherapy	–	1.932 (1.231 to 2.905)	1.072 (0.565 to 1.858)	0.734 (0.207 to 1.871)	0.483 (0.145 to 1.169)	1.024 (0.204 to 3.097)
Trabectedin plus PLDH	–	–	0.582 (0.260 to 1.122)	0.399 (0.102 to 1.077)	0.262 (0.071 to 0.674)	0.556 (0.102 to 1.773)
Topotecan monotherapy (intravenous)	–	–	–	0.683 (0.243 to 1.514)	0.451 (0.170 to 0.951)	0.953 (0.230 to 2.642)
Paclitaxel monotherapy (every 3 weeks)	–	–	–	–	0.822 (0.191 to 2.337)	1.393 (0.578 to 2.852)
Topotecan monotherapy (oral)	–	–	–	–	–	2.554 (0.431 to 8.493)
Paclitaxel monotherapy (weekly)	–	–	–	–	–	–

Comparator is listed in the left-hand side column. Results presented are OR and accompanying CrI. OR >1 favours the intervention (listed in the top table row) and OR <1 favours the comparator.
Abbreviations used in table: CrI, credible interval; OR, odds ratio; PLDH, pegylated liposomal doxorubicin hydrochloride.

Most identified trials involving platinum-sensitive patients did not present data on tumour response separately for the subgroup of patients with FPS (relapse >12 months after last platinum-based treatment) and PPS (relapse ≥6–≤12 months after last platinum-based treatment. No data were available for the subgroup of patients with FPS ovarian cancer.

Results in patients with PPS

Only the CALYPSO trial presented results (in an accompanying publication) for tumour response in patients with PPS.[56] There was no significant difference between PLDH plus carboplatin and paclitaxel plus carboplatin in the proportion of patients achieving CR or PR as their best response (OR 0.863, 95% CI: 0.584 to 1.274).

Results in tumour response for the subgroup of patients with platinum-resistant/refractory ovarian cancer

Eight RCTs reporting results for eight different head-to-head comparisons involving PRR patients were identified. Two RCTs enrolled only patients with PRR, with the remaining six RCTs reporting results from a subgroup of patients within the trial. None of the trials identified a significant difference

in ORR between the two treatment groups evaluated.

Trial name	Intervention	Comparator	OR (95%CI)
ten Bokkel Huinink *et al*. (2004)[51]	Topotecan (1.5 mg/m^2) for 5 days every 21 days	Paclitaxel (175 mg/m^2) every 21 days	1.967 (0.562 to 6.884)
Gordon *et al*. (2001)[48]	PLDH (50 mg/m^2) every 28 days	Topotecan (1.5 mg/m^2) for 5 days every 21 days	1.908 (0.788 to 4.616)
Sehouli *et al*.[23]	Topotecan (4.0 mg/m^2) (weekly; days 1, 8, and 15) every 28 days	Topotecan (1.25 mg/m^2) for 5 consecutive days every 21 days	0.491 (0.190 to 1.271)
Lortholary *et al*.[61]	Weekly paclitaxel (80 mg/m^2) plus carboplatin	Weekly paclitaxel (80 mg/m^2) on 4 week cycle	1.06 (0.510 to 2.209)
Gore *et al*.[24]	Oral topotecan (2.3 mg/m^2) daily	Intravenous topotecan (1.5 mg/m^2) for 5 days every 21 days	0.974 (0.301 to 3.155)
Rosenberg *et al*.[59]	Paclitaxel (67 mg/m^2) weekly (1 course = 3 weeks)	Paclitaxel (200 mg/m^2) every 3 weeks	0.757 (0.312 to 1.839)
Piccart *et al*.[62]	Paclitaxel (175 mg/m^2) every 3 weeks	Oxaliplatin (130 mg/m^2) every 3 weeks	2.581 (0.466 to 14.306)
Omura *et al*.[66]	Paclitaxel 250 mg/m^2 every 21 days	Paclitaxel 175 mg/m^2 every 21 days	1.659 (0.930 to 2.961)
Abbreviations used in table: CI, confidence interval; OR, odds ratio; PLDH, pegylated liposomal doxorubicin hydrochloride.			

An NMA was carried out using five of the identified RCTs. Based on clinical expert advice, the decision was taken not to include the trial by Piccart *et al*.[62] comparing paclitaxel versus oxaliplatin as oxaliplatin is not licensed for the treatment of ovarian cancer and is rarely used in UK clinical practice. In addition, the treatment regimens evaluated in the trial reported by Lortholary *et al*.[61] did not inform the network. In the NMA, PLDH was found to significantly increase ORR compared with paclitaxel (175 mg/m^2) every 21 days and with an alternative regimen in which paclitaxel was given weekly at a dose of 67 mg/m^2. PLDH monotherapy was also significantly more effective than an unconventional regimen of topotecan in which topotecan was administered weekly at a dose of 4 mg/m^2.

No chemotherapeutic regimen was found to have a significantly higher ORR than PLDH monotherapy. However, paclitaxel monotherapy, paclitaxel monotherapy (weekly), and topotecan monotherapy (IV, weekly) were found to have significantly lower ORR compared to PLDH monotherapy. No other comparison of chemotherapies was found to have a statistically significant difference.

Comparator	PLDH monotherapy	Topotecan monotherapy intravenous (conventional)	Paclitaxel monotherapy (every 3 weeks)	Topotecan monotherapy (oral)	Paclitaxel monotherapy (weekly)	Topotecan monotherapy (unconventional intravenous regimen)
PLDH monotherapy	–	0.529 (0.184 to 1.166)	0.290 (0.040 to 0.982)	0.622 (0.098 to 2.116)	0.224 (0.022 to 0.884)	0.253 (0.051 to 0.761)
Topotecan monotherapy intravenous (conventional)	–	–	0.548 (0.111 to 1.553)	1.176 (0.283 to 3.283)	0.423 (0.059 to 1.470)	0.478 (0.154 to 1.086)
Paclitaxel monotherapy (every 3 weeks)	–	–	–	3.387 (0.379 to 13.810)	0.771 (0.271 to 1.736)	1.383 (0.191 to 5.216)
Topotecan monotherapy (oral)	–	–	–	–	0.530 (0.041 to 2.321)	0.601 (0.090 to 2.090)
Paclitaxel monotherapy (weekly)	–	–	–	–	–	2.251 (0.215 to 9.439)
Topotecan monotherapy (unconventional intravenous regimen)	–	–	–	–	–	–

Comparator is listed in the left-hand side column. Results presented are OR and accompanying CrI. OR >1 favours the intervention (listed in the top table row) and OR <1 favours the comparator.
Abbreviations used in table: CrI, credible interval; OR, odds ratio; PLDH, pegylated liposomal doxorubicin hydrochloride.

Platinum sensitive

Pegylated liposomal doxorubicin hydrochloride plus carboplatin versus paclitaxel plus carboplatin

In Bafaloukos *et al*.[29], tumour response was evaluated using either WHO criteria for patients with measurable disease at baseline or repetitive CA125 measurements using the algorithm proposed by Rustin *et al*.[77] and based on CA125 Rustin's criteria for patients without measurable disease at baseline. Bafaloukos *et al*.[29] included a small proportion of women with only CA125 elevation at baseline as a marker of presence of disease (16/186 [8.6%]) for whom results were analysed both as part of the full trial population and as a subgroup. Tumour assessments for response were carried out every 2 cycles. A similar proportion of women achieved overall response (CR or PR) in the two treatment groups (47/93 [50.5%] with PLDH plus carboplatin vs 56/96 [58.3%] with paclitaxel plus carboplatin; OR 0.886, 95% CI 0.535 to 1.402; Table 50). Bafaloukos *et al*.[29] found no statistically significant difference between PLDH plus carboplatin and paclitaxel plus carboplatin for overall response in any of the populations assessed: the full trial population (p = 0.309); patients with measurable disease at baseline (p = 0.427); and patients with evaluable disease (elevated CA125

and/or effusions) (p = 0.713). It is unclear whether the clinicians evaluating response had been masked to treatment, or whether tumour response was evaluated by a central review panel.

Pegylated liposomal doxorubicin hydrochloride plus carboplatin versus carboplatin alone

Alberts *et al*.[28] based the primary analysis of response rate on confirmed response rates for CR or PR, with CR and PR assigned according to RECIST criteria. Women with only CA125 elevation at baseline as a marker of disease at study entry (6 women) were excluded from the analysis of objective response. It is unclear whether the clinicians evaluating response had been masked to treatment, or whether tumour response was evaluated by a central review panel. Alberts *et al*.[28] found no statistically significant difference between PLDH plus carboplatin and carboplatin alone in confirmed response rate (14/27 [52%] with PLDH plus carboplatin vs 8/28 [29%] with carboplatin alone; p = 0.10). However, a follow-up publication by Markman *et al*.[54] reporting more mature data found the difference between groups to be statistically significant favouring PLDH plus carboplatin (16/27 [59%] with PLDH plus carboplatin vs 8/29 [28%] with carboplatin alone; p = 0.10; OR 2.148, 95% CI 0.792 to 5.825; Table 50). As noted earlier, the duration of follow-up in the longer-term study is unclear. In addition, the follow-up publication does not discuss the inclusion of one additional patient in the analysis of the carboplatin group.

Trabectedin plus PLDH versus PLDH alone

OVA-301 (Monk *et al*. [2010][30]) evaluated tumour response as the overall response rate (CR or PR) with response maintained ≥4 weeks based on RECIST criteria. The schedule for tumour assessment is unclear. The primary analysis was based on assessments by independent radiology review. In the subgroup of patients with platinum-sensitive ovarian cancer (218 patients in the trabectedin plus PLDH group vs 213 patients in the PLDH alone group), trabectedin plus PLDH significantly improved ORR compared with PLDH alone (77/218 [35.3%] with trabectedin plus PLDH vs 48/213 [22.5%] with PLDH alone; p = 0.042; OR 1.567, 95% CI: 1.043 to 2.354;Table 50). It should be noted that most patients achieved PR. In the full trial population, only 6 patients achieved a CR, 2 in the trabectedin plus PLDH group and 4 in the PLDH alone group.

Pegylated liposomal doxorubicin hydrochloride versus topotecan

In Gordon *et al*. (2001)[48], tumour response was determined by overall response rate, which comprised CR and PR. Patients achieving either a CR or PR underwent repeat radiologic assessment at least 4 weeks later to confirm the response. CR was defined as complete disappearance of all measurable and assessable disease, no new lesions and no disease-related symptoms. PR was defined as ≥50% reduction in the sum of products of the perpendicular diameters of all measurable lesions for at least 4 weeks. Although open-label in design, scans for assessment of disease response and progression underwent independent radiological review.

In the subgroup of patients with platinum-sensitive disease, a similar proportion in the PLDH and topotecan groups achieved either CR or PR as their best response (31/109 [28.4%] with PLDH vs 32/111 [28.8%] with topotecan; p = 0.964; OR 0.987, 95% CI: 0.563 to 1.727; Table 50). The difference between groups did not reach statistical significance. In addition, a similar proportion of patients in each group achieved stable disease as their best response (41/109 [37.6%] with PLDH vs 42/111 [37.8%] with topotecan; Table 50).

Topotecan versus paclitaxel

Response rate was a primary outcome evaluated by ten Bokkel Huinink *et al*. (1997)[21] Response included patients achieving either CR or PR as their best response, with CR or PR assigned as per WHO criteria. All claimed responses were independently reviewed and scans confirmed by a radiologist masked to treatment allocation. The timing of tumour assessment is unclear. Patients who were not fully assessed for efficacy or who were not evaluated for response were considered to be non-responders. Data for the subgroup of patients with platinum-sensitive disease (late relapse; relapse >6 months after cessation of chemotherapy) were reported separately. In this subgroup of patients, a larger proportion of patients in the topotecan group achieved either CR or PR compared with paclitaxel (15/52 [28.8%] with topotecan vs 11/55 [20.0%] with paclitaxel; Table 50), but the statistical significance of this result was not evaluated in the full publication.[21] The OR calculated by the TAG indicates the difference to be non-significant (OR 1.442, 95% CI: 0.607 to 3.427; Table 50).

Gemcitabine plus carboplatin versus carboplatin alone

Pfisterer *et al*.[49] implemented SWOG criteria to determine degree of tumour response. The outcome evaluated was overall response, which included patients achieving a CR or PR as their best response. SWOG defines a CR as complete disappearance of all measurable and evaluable disease and no evidence of non-evaluable disease and PR as sum of products of all lesions decreased by >50% for at least 3–6 weeks, with no new lesions and no progression of evaluable lesions. Patients were assessed before random assignment, before every cycle during treatment, and every 2 to 3 months after treatment for at least 2 years. It is unclear from the full publication whether there was an independent review of claimed CR or PR.

Gemcitabine plus carboplatin significantly improved overall response rate compared with carboplatin alone, with 47.2% (84/178) of patients treated with gemcitabine plus carboplatin achieving CR or PR compared with 30.9% (55/178) of patients treated with carboplatin (p = 0.0016; OR 1.527, 95% CI: 1.025 to 2.275; Table 50).[49]

Paclitaxel plus carboplatin versus platinum-based therapy alone

The ICON4/AGO-OVAR2.2 investigators defined response rate as patients achieving CR or PR.[60] It is unclear from the full publication which criteria (e.g., WHO, SWOG, or RECIST) were used to

assign CR or PR. Timing of response assessment varied with protocol, with those in the AGO protocol assessed after the second and fourth cycles of treatment and those in the Italian ICON4 protocol assessed after three cycles. No further details are reported.

The authors reported that there was no statistically significant difference between treatment regimens in response rate, with 66% (78/119) patients in the paclitaxel plus platinum-based treatment achieving CR or PR compared with 54% (69/128) patients in the platinum chemotherapy alone group, which translates to a difference of 12% (95% CI –0.1% to 24%; p = 0.06). Although the methods state that all efficacy analyses are based on the ITT principle, it should be noted that the number of patients included in the analysis of response is not equal to the number of patients randomised to each group. One potential explanation of this potential discrepancy could be that the patients included in the analysis were those with measurable disease at baseline; number of patients with measurable disease was not reported in the table of baseline characteristics presented in the full publication.

Gonzalez-Martin *et al*.[47] used the WHO criteria to evaluate response in those with measurable disease at baseline, with tumour response assessed every 3 cycles. For patients without measurable disease at baseline, response was determined according to Rustin's criteria. The RCT found that paclitaxel plus carboplatin significantly improved overall response rate (CR plus PR) compared with carboplatin alone (75.6% with paclitaxel plus carboplatin vs 50.0% with carboplatin alone (p = 0.017; Table 50). The authors commented that based on study design, paclitaxel plus carboplatin was the "winner". Although analysis was based on the ITT population, it should be noted that the comparative statistical analysis was carried out as an exploratory exercise and the reported p value should be interpreted with caution. In addition, overall response combines data for women with and without measurable disease at baseline.

Paclitaxel versus oxaliplatin

Objective confirmed response rate was the primary efficacy endpoint in the trial carried out by Piccart *et al*.[62] Confirmed response was defined as CR or PR as per WHO criteria and that was observed on at least two consecutive evaluations at least 4 weeks apart. Confirmed response was verified by two independent radiologists. Overall response rate was defined by the total number of patients in each treatment group. Only patients receiving at least two treatment cycles were considered assessable for response. Of the 86 patients randomised, only 5 were not assessable, 2 in the paclitaxel group and 3 in the oxaliplatin group; four patients were deemed ineligible and one patient died 6 days after the first dose of oxaliplatin due to causes unrelated to treatment.

In the subgroup of patients with platinum-sensitive disease (23 patients), 20% (2/10) of patients in the paclitaxel group achieved PR compared with 38% (5/13) of patients in the oxaliplatin group. The statistical significance of the difference was not assessed in the full publication. The TAG calculated

the OR to be 0.520 (paclitaxel vs oxaliplatin), with a 95% CI of 0.083 to 3.259 (non-significant difference). No patient achieved a CR. The authors caution that, because of the low number of patients in the analysis, conclusions cannot be drawn on the comparative effectiveness of treatments in this subgroup.

Topotecan oral versus topotecan intravenous

In Gore *et al*.[24], tumour response was assessed based on WHO criteria such that a CR was the complete disappearance of all known measurable and evaluable disease determined by two measurements not less than 4 weeks apart. A PR was defined as a greater than 50% decrease in measurable lesion size for at least 4 weeks, with no simultaneous increase in a known lesion or appearance of new lesions or increase in evaluable disease. Timing of assessment was determined by radiological method used to measure disease at baseline. Patients evaluated by CT or MRI at baseline were assessed for response at the end of alternate cycles, whereas those evaluated by chest X-ray or photography were assessed at the end of every cycle.

In the platinum-sensitive subgroup (relapse at >6 months after initial response), although a larger proportion of patients in the intravenous topotecan group achieved a CR or PR as their best response, the difference between treatment groups did not reach statistical significance (11/58 [19%] with oral topotecan vs 20/56 [36%] with intravenous topotecan; reported as not significant; p value not reported; Table 50).

Paclitaxel high dose (250 mg/m^2) versus paclitaxel standard dose (175 mg/m^2)

Omura *et al*.[66] analysed ORR based on platinum sensitivity. A statistically significant treatment–sub-group interaction was identified (p = 0.041). In the subgroup of patients with platinum-sensitive disease, there was no statistically significant difference between paclitaxel 250 mg/m^2 and paclitaxel 175 mg/m^2 in the proportion of patients achieving a CR or PR compared with (OR 0.63; 95% CI 0.191 to 2.07; Table 50). The OR was adjusted for histologic cell type (papillary serous versus clear-cell or mucinous vs other cell types), co-operative group, performance status, and prior platinum sensitivity. The proportion of patients achieving either CR or PR in each group was 36.0 % (9/25) and 48.1% (13/27) in the 250 mg/m^2 and 175 mg/m^2 groups, respectively. Unadjusted OR as calculated by the TAG was 0.748 (95% CI: 0.273 to 2.051). For the purposes of the NMA, based on clinical expert advice, it has been assumed that doses of paclitaxel of 175 mg/m^2 up to 250 mg/m^2 are of equivalent clinical effectiveness and thus this trial has not been included in the NMA.

Paclitaxel weekly versus paclitaxel every 3 weeks

In the trial carried out by Rosenberg *et al*.[59], patients were stratified at randomisation based on platinum resistance (relapse ≤6 months vs >6 months after primary platinum-based treatment). Results for the primary outcome of tumour response were reported separately for the subgroups categorised

by platinum resistance. Evaluations of tumour size were carried out at baseline and subsequently every 6 weeks using the same imaging technique for all assessments. Tumour response was categorised as per WHO criteria, with overall response including CR or PR as a best response.

In the subgroup of patients with platinum-sensitive disease, a similar proportion of patients achieved either CR or PR in each treatment group (26/48 [54.2%] with paclitaxel every 7 days vs 25/52 [48.1%] with paclitaxel every 21 days; Table 50). The statistical significance of the result in this subgroup of patients was not reported in the full publication. The OR calculated by the TAG indicates that the difference between groups did not reach statistical significance (OR 1.127, 95% CI: 0.574 to 2.212; Table 50). It should be noted that the results include patients with unconfirmed CR and PR. In the full trial population, 3 patients in each group had unconfirmed CR, and 7 and 6 patients in the paclitaxel every 7 days and paclitaxel every 21 days, respectively, had unconfirmed PR. The corresponding number of patients in the platinum-sensitive subgroup is not reported.

Table 50. Summary of results for response rate in people with platinum-sensitive recurrent ovarian cancer

Study	Intervention	Comparison	Overall response (OR, 95% CI)[b]		Complete response		Partial response		Stable disease		Progressive disease	
			INT	COMP	INT	COMP	INT	COMP	INT	COMP	INT	COMP
Gordon *et al*. (2001)[53]	PLDH (50 mg/m^2) every 28 days	Topotecan (1.5 mg/m^2) for 5 days every 21 days	31/109	32/111	8/109	10/111	23/109	22/111	41/109	42/111		
			OR 0.987 (0.563 to 1.727)									
ICON4/AGO-OVAR 2.2[60]	Paclitaxel plus platinum every 21 days	Conventional platinum-based treatment every 21 days	78/392	69/410								
			OR 1.182 (0.831 to 1.682)									
Gonzalez Martin *et al*.[47]	Carboplatin alone (AUC 5) every 21 days	Paclitaxel (175 mg/m^2) plus carboplatin (AUC 5) every 21 days	20/40 (50.0 %)	31/41 (75.6 %)	8/40 (20.0%)	11/41 (26.8%)	12/40 (30.0%)	20/41 (48.8%)	5/40 (12.5%)	2/41 (4.9%)	13/40 (32.5%)	2/41 (4.9%)
			OR 0.661 (0.325 to 1.347)									

Bafaloukos *et al*.[29]	PLDH (45 mg/m^2) plus carboplatin (AUC 5) every 28 days	Paclitaxel (175 mg/m^2) plus carboplatin (AUC 5) on every 21 days	47/93 (50.5 %)	56/96 (58.3 %)	21/93 (22.6%)	33/96 (34.3%)	26/93 (28.0%)	23/96 (24.0%)				
			OR 0.886 (0.535 to 1.402)									
Alberts *et al*.[54]	PLDH (30 mg/m^2) plus carboplatin (AUC 5) every 4 weeks	Carboplatin alone (AUC 5) every 4 weeks	16/27	8/29								
			OR 2.148 (0.792 to 5.825)									
Rosenberg *et al*.[59]	Paclitaxel 67 mg/m^2 weekly	Paclitaxel 200 mg/m^2 every 3 weeks	26/48	25/52								
			OR 1.127 (0.574 to 2.212)									
Gore *et al*.[24]	Oral topotecan 2.3 mg/m^2/day	IV topotecan 1.5 mg/m^2/day for 5 days every 21 days	11/58	20/56								
			OR 0.531 (0.233 to 1.208)									

ten Bokkel Huinink *et al*. (1997)[21]	Topotecan 1.5 IV mg/m^2/day for 5 days	Paclitaxel 175 mg/m^2/day every 21 days	15/52	11/55	4/52	3/55	11/52	8/55				
			OR 1.442 (0.607 to 3.427)									
Piccart *et al*.[62]	Paclitaxel (175 mg/m^2) every 3 weeks	Oxaliplatin (130 mg/m^2) every 3 weeks	2/10	5/13	0/10	0/13	2/10	5/13				
			OR 0.520 (0.083 to 3.259)									
Pfisterer *et al*.[49]	Gemcitabine (1,000 mg/m^2) plus carboplatin every 21 days	Carboplatin alone every 21 days	84/178	55/178	26/178	11/178	58/178	44/178	68/178	69/178	14/178	29/178
			OR 1.527 (1.025 to 2.275)									
OVA-301[30]	PLDH 30 mg/m^2 plus trabectedin 1.1 mg/m^2 every 3 weeks	PLDH 50 mg/m^2 every 4 weeks	77/218	48/213								
			OR 1.567 (1.043 to 2.354)									
Omura *et al*.[66]	Paclitaxel 250 mg/m^2 every 21 days	Paclitaxel 175 mg/m^2 every 21 days	9/25	13/27	4/25	4/27	5/25	9/27				
			OR 0.748 (0.273 to 2.051)									

[a] Numerator calculated from percentage provided in full publication.

[b] OR and 95% CI calculated by TAG.

Abbreviations used in table: AUC, area under curve; COMP, comparator; INT, intervention; PLDH, pegylated liposomal doxorubicin hydrochloride.

Network meta-analysis (platinum sensitive)

The RCTs available for inclusion in the NMA evaluating ORR in patients with platinum-sensitive recurrent ovarian cancer are summarised in Table 50. Unfortunately, as described earlier, a single network could not be constructed out of the available trials. The two networks constructed for this outcome are depicted in Figure 9.

Network 1 (Figure 9a) consisted of the following comparators:

- paclitaxel plus carboplatin;
- PLDH plus carboplatin;
- platinum as a monotherapy;
- gemcitabine plus carboplatin.

While ORR does not inform the economic evaluation conducted by the TAG (Section 5.2), for consistency with OS and PFS, paclitaxel plus carboplatin was chosen as the baseline treatment. However, results are reported in Table 51 sequentially covering all possible comparisons. Overall, there was no significant difference (at the 5% level) for any of the doublet chemotherapies assessed compared with paclitaxel plus carboplatin (or with each other). Platinum monotherapy was associated with a significant reduction in ORR compared with all doublet chemotherapies, with the exception of PLDH plus carboplatin, where no significant difference was found.

Network 2 (Figure 9b) consisted of the following comparators:

- PLDH monotherapy;
- trabectedin plus PLDH;
- topotecan monotherapy (IV);
- paclitaxel monotherapy; that is, 175mg/m2 or 200 mg/m2 every 21 days;
- topotecan (oral);
- paclitaxel monotherapy (weekly); that is, paclitaxel 67 mg/m2 every week for 21 days.

PLDH monotherapy was chosen as the baseline treatment in order to maintain consistency with the results reported for the NMAs for OS and PFS. However, results are reported in Table 51 sequentially covering all possible comparisons. Overall, only trabectedin plus PLDH demonstrated a significant difference increase in ORR (at the 5% level) compared with PLDH monotherapy. Trabectedin plus PLDH would also be considered to have a statistically significant increased ORR when compared directly with topotecan monotherapy (oral) but to have no significant difference from any other treatment assessed. None of the other comparisons of chemotherapies would be considered

significantly different from one another, with the exception of topotecan monotherapy (oral) which was found to have a significantly lower ORR than topotecan monotherapy (IV).

Figure 9. Networks for overall response rate for people with platinum-sensitive recurrent ovarian cancer

Figure 9a. Network 1

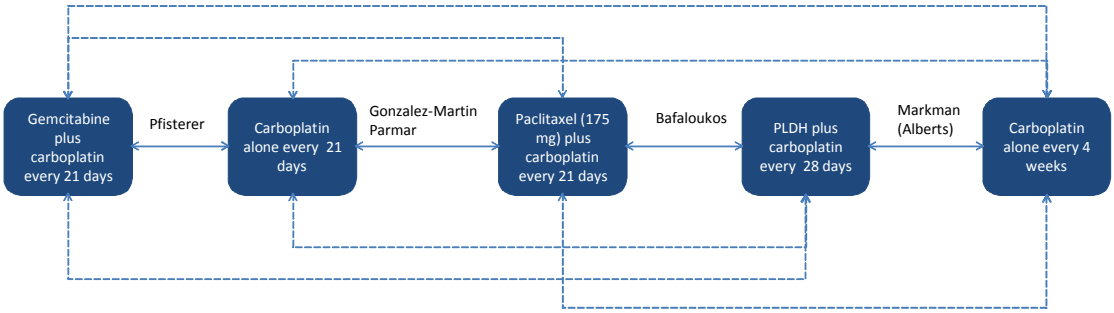


Figure 9b. Network 2

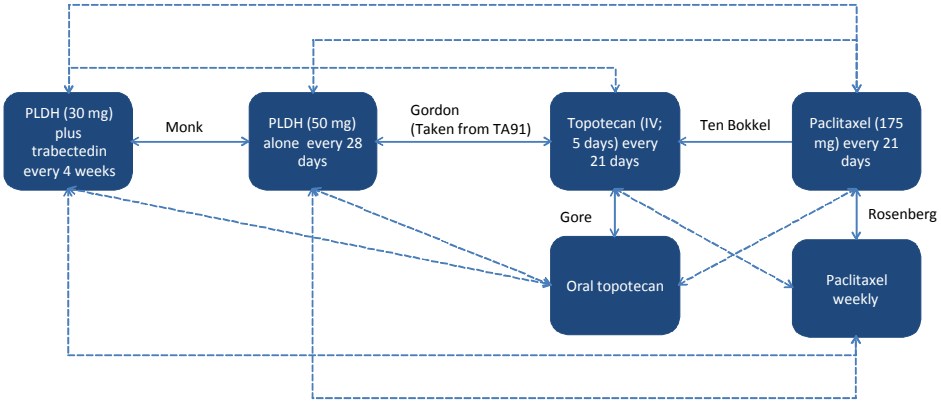


Table 51. Results of the network meta-analysis for overall response rate for people with platinum-sensitive recurrent ovarian cancer

Comparison	OR	95% CrI	
		Lower limit	Upper limit
Network 1			
Versus paclitaxel plus carboplatin ***(OR >1 favours comparator, OR <1 favours paclitaxel plus carboplatin)***			
PLDH plus carboplatin	0.994	0.574	1.609
Platinum as a monotherapy	0.666	0.474	0.908
Gemcitabine plus carboplatin	1.370	0.765	2.261
Versus PLDH plus carboplatin ***(OR >1 favours comparator, OR <1 favours PLDH plus carboplatin)***			
Platinum as a monotherapy	0.713	0.386	1.208
Gemcitabine plus carboplatin	1.467	0.672	2.793
Versus platinum monotherapy ***(OR >1 favours comparator, OR <1 favours platinum monotherapy)***			
Gemcitabine plus carboplatin	2.058	1.305	3.108

Network 2			
Versus PLDH monotherapy (OR >1 favours comparator, OR <1 favours PLDH monotherapy)			
Trabectedin plus PLDH	1.932	1.231	2.905
Topotecan monotherapy (IV)	1.072	0.565	1.858
Paclitaxel monotherapy	0.734	0.207	1.871
Topotecan monotherapy (oral)	0.483	0.145	1.169
Paclitaxel monotherapy (weekly)	1.024	0.204	3.097
Versus trabectedin plus PLDH (OR >1 favours comparator, OR <1 favours trabectedin plus PLDH)			
Topotecan monotherapy (IV)	0.582	0.260	1.122
Paclitaxel monotherapy	0.399	0.102	1.077
Topotecan monotherapy (oral)	0.262	0.071	0.674
Paclitaxel monotherapy (weekly)	0.556	0.102	1.773
Versus topotecan monotherapy (IV) (OR >1 favours comparator, OR <1 favours topotecan monotherapy (IV))			
Paclitaxel monotherapy	0.683	0.243	1.514
Topotecan monotherapy (oral)	0.451	0.170	0.951
Paclitaxel monotherapy (weekly)	0.953	0.230	2.642
Versus paclitaxel monotherapy (OR >1 favours comparator, OR <1 favours paclitaxel monotherapy)			
Topotecan monotherapy (oral)	0.822	0.191	2.337
Paclitaxel monotherapy (weekly)	1.393	0.578	2.852
Versus topotecan oral monotherapy (OR >1 favours comparator, OR <1 favours topotecan monotherapy (oral))			
Paclitaxel monotherapy (weekly)	2.554	0.431	8.493
Abbreviations used in table: CrI, Credible Interval; OR, odds ratio; PLDH, pegylated liposomal doxorubicin hydrochloride.			

Partially platinum sensitive

Pegylated liposomal doxorubicin hydrochloride plus carboplatin versus paclitaxel plus carboplatin

An accompanying publication to CALYPSO (Pujade-Lauraine *et al*.[31]) presents results for PFS and response rate (secondary outcome) for a subgroup of patients with PPS (TFI 6–12 months).[56] The principal publication provided a comprehensive description of the criteria for progression and indicated that tumour assessments occurred every 3 months and states that ORR was "response maintained ≥4 weeks by RECIST".[31] Table 2 in the accompanying publication indicates that confirmed best responses are based on RECIST criteria, and overall response rate is the total of confirmed CR and PR.[56]

There was no statistically significant difference between PLDH plus carboplatin and paclitaxel plus carboplatin in overall response rate (63/161 [39%] with PLDH plus carboplatin vs 83/183 [45%] with paclitaxel plus carboplatin; p = 0.691). The proportion of patients achieving CR, PR, and SD, together with PD, are presented in Table 52.

Table 52. Summary of results for response rate in people with partially platinum-sensitive recurrent ovarian cancer

Study	Intervention	Comparison	Overall response (OR, 95% CI)		Complete response (95% CI)		Partial response (95% CI)		Stable disease (95% CI)		Progressive disease (95% CI)	
			INT	COMP	INT	COMP	INT	COMP	INT	COMP	INT	COMP
CALYPSO[56] Prespecified subgroup of partially sensitive patients	PLDH (30 mg/m^2) plus carboplatin every 21 days	Paclitaxel (175 mg/m^2) plus carboplatin every 3 weeks	63/161	83/183	19/161	14/183	44/161	69/183	64/161	61/183	17/161	19/183
			OR 0.863 (0.584 to 1.274)									
Abbreviations used in table: AUC, area under curve; COMP, comparator; INT, intervention; PLDH, pegylated liposomal doxorubicin hydrochloride.												

Network meta-analysis (partially platinum sensitive)

As only a single trial was identified with data to inform ORR in patients with partially platinum-sensitive recurrent ovarian cancer Table 52, no NMA was possible for this subgroup.

Platinum resistant/refractory

Pegylated liposomal doxorubicin hydrochloride versus topotecan

Gordon *et al*. (2001)[48] found no statistically significant difference between PLDH and topotecan in the proportion of patients with PRR ovarian cancer achieving either CR or PR as their best response (16/130 [12.3%] with PLDH vs 8/124 [6.5%] with topotecan; p = 0.118; Table 54). However, a larger proportion of patients in the topotecan group achieved stable disease as their best response (36/130 [27.7%] with PLDH vs 53/124 [42.7%] with topotecan; significance not assessed; Table 54).

Topotecan versus paclitaxel

In the subgroup of patients with PRR disease (resistant, early relapse and interim relapse; 119 patients), ten Bokkel Huinink *et al*. (1997)[21] that 13.3% (8/60) of patients treated with topotecan and 6.8% (4/59) of patients treated with paclitaxel achieved either CR or PR as their best response (significance not assessed; Table 54). Results for the individual categories that make up PRR are presented in Table 53.

Table 53. Response rate for resistant, early relapse and interim relapse

Platinum sensitivity	Resistant		Early relapse		Interim relapse		Total	
	Number	%	Number	%	Number	%	Number	%
Topotecan	N = 34		N = 6		N = 20		N = 60	
CR	0	0.0	0	0.0	1	5.0	1	1.67
PR	3	8.8	1	16.7	3	15.0	7	11.67
Total (CR + PR)	3	8.8	1	16.7	4	20.0	8	13.3
Paclitaxel	N = 33		N = 10		N = 16		N = 59	
CR	0	0.0	0	0.0	0	0.0	0	0
PR	1	3.0	1	10.0	2	12.5	4	6.8
Total (CR + PR)	1	3.0	1	10.0	2	12.5	4	6.8
Abbreviations used in table: CR, complete response; PR. partial response.								

Paclitaxel plus carboplatin versus paclitaxel alone

Lortholary *et al*.[61] based response rate on the proportion of patients who achieved either a CR or PR as their best response. Patient response was determined according to RECIST criteria for patients with measurable disease and Rustin's criteria for CA125 levels for patients with non-measurable disease. Chest CT and abdominopelvic or MRI were obtained every 2 cycles or as needed for assessment of duration of response. Objective response was to be confirmed radiologically at least 4 weeks after initial response. Lortholary *et al*.[61] found that a similar response rate was achieved in the weekly paclitaxel and weekly paclitaxel plus carboplatin groups (20/57 [35.1%] with weekly paclitaxel vs 19/51 [37.3%] with weekly paclitaxel plus carboplatin; Table 54). The statistical significance of the difference between groups was not assessed by Lortholary *et al*.[61] The TAG calculated an OR of 1.06 (95% CI 0.510 to 2.209), which indicates that the difference between groups is not statistically significant.

Paclitaxel versus oxaliplatin

In the subgroup of patients with PRR ovarian cancer (63 patients), Piccart *et al*.[62] found that 16% (5/31) of patients in the paclitaxel group achieved PR compared with 6% (2/32) of patients in the oxaliplatin group (Table 54). No patient achieved a CR. The statistical significance of the difference was not assessed in the full publication.[62] The authors caution that, because of the low number of patients in the analysis, conclusions cannot be drawn on the comparative effectiveness of treatments in this subgroup.

Topotecan oral versus topotecan intravenous

In the subgroup of patients with PRR (progression or stable disease during treatment or relapse at <6 months after initial response), Gore *et al*.[24] found that a small proportion of patients in each group achieved a CR or PR as their best response, with no statistically significant difference between groups

(6/77 [7.8%] with oral topotecan vs 6/75 [8.0%] with intravenous topotecan; reported as not significant; p value not reported; Table 54).

Topotecan administered on 5 consecutive days (conventional regimen) versus topotecan administered weekly

Clinical benefit rate was the primary outcome in the trial carried out by Sehouli *et al*.[23] Clinical benefit rate comprised CR, PR and SD as best response. By contrast, most trials identified have evaluated overall response rate of CR or PR. In the trial, tumour response could be determined radiologically and categorised as per RECIST criteria or by change in CA125 level as per GCIG criteria, with choice of method of assessment at the discretion of the investigator. Schedule of assessment of response was not reported. It should be noted that, despite most patients having measurable disease at baseline, only a small proportion of women were evaluated radiologically for response (19.8%).

For the primary outcome of clinical benefit, 58% (46/80) of patients treated with the conventional dose of topotecan achieved CR, PR or SD compared with 47% (36/76) of patients receiving topotecan weekly. The statistical significance of the difference between groups was not reported. Considering overall response rate (CR or PR), the proportion of patients achieving CR or PR as best response was 18.8% (15/80) and 9.2% (7/76) in the conventional topotecan versus weekly topotecan groups, respectively.

Of the 80 patients in the conventional topotecan group, response was evaluated by CA125 alone in 62 patients (CR or PR = 13 patients). By comparison, 63 out of 76 patients were evaluated by CA125 alone (CR or PR = 5 patients).

Paclitaxel high dose (250 mg/m^2) versus paclitaxel standard dose (175 mg/m^2)

In the subgroup of patients with PRR disease, Omura *et al*.[66] found that paclitaxel 250 mg/m^2 significantly increased the proportion of patients achieving a CR or PR compared with paclitaxel 175 mg/m^2 (OR 2.59, 95% CI: 1.36 to 4.95; Table 54). The OR was adjusted for histologic cell type (papillary serous versus clear-cell or mucinous vs other cell types), co-operative group, performance status, and prior platinum sensitivity. The proportion of patients achieving either CR or PR in each group was 36.7 % (40/109) and 22.1% (23/104) in the 250 mg/m^2 and 175 mg/m^2 groups, respectively. Unadjusted OR as calculated by the TAG was 1.659 (95% CI: 0.930 to 2.961), which is a non-statistically significant difference.

Paclitaxel weekly versus paclitaxel every 3 weeks

In the subgroup of patients with PRR, Rosenberg *et al*.[59] found that a similar proportion of patients achieved either CR or PR in each treatment group (11/57 [19.3%] with paclitaxel every 7 days vs 13/51 [25.5%] with paclitaxel every 21 days; Table 54). The statistical significance of the result in this subgroup of patients was not reported in the full publication. As noted earlier, unconfirmed CR and PR is not broken down by subgroup and it is unclear how many patients in the PRR analysis had unconfirmed CR or PR.

Table 54. Summary of results for response rate in population with platinum-resistant or refractory recurrent ovarian cancer

Study	Intervention	Comparison	Overall response (OR, 95% CI)[c]		Complete response (95% CI)		Partial response (95% CI)		Stable disease (95% CI)		Progressive disease (95% CI)	
			INT (95% CI)	COMP (95% CI)	INT (95% CI)	COMP (95% CI)	INT (95% CI)	COMP (95% CI)	INT (95% CI)	COMP (95% CI)	INT (95% CI)	COMP (95% CI)
Gordon *et al*. (2001)[48]	PLDH (50 mg/m^2) every 28 days	Topotecan (1.5 mg/m^2) for 5 days every 21 days	16/130	8/124	1/130	1/124	15/130	7/124	36/130	53/124		
			1.908 (0.788 to 4.616)									
Gore *et al*.[24]	Oral topotecan (2.3 mg/m^2) daily	Intravenous topotecan (1.5 mg/m^2) for 5 days every 21 days	6/77	6/75								
			0.974 (0.301 to 3.155)									
Sehouli *et al*.[23]	Topotecan (4.0 mg/m^2) (weekly; days 1, 8, and 15) every 28 days	Topotecan (1.25 mg/m^2) for 5 consecutive days every 21 days	7/76	15/80	4/76	3/80	3/76	12/80	29/76	31/80	40/76	34/80
			0.491 (0.190 to 1.271)									
Rosenberg *et al*.[59]	Paclitaxel (67 mg/m^2) weekly (1 course = 3 weeks)	Paclitaxel (200 mg/m^2) every 3 weeks	11/57[a]	13/51[a]								
			0.757 (0.312 to 1.839)									

Lortholary *et al*.[61]	Weekly paclitaxel (80 mg/m^2) plus carboplatin	Weekly paclitaxel (80 mg/m^2) on 4 week cycle	19/51	20/57	7/51	3/57	12/51	17/57	29/51	23/57	26/51	26/57
			1.06 (0.510 to 2.209)									
Piccart *et al*.[62]	Paclitaxel 175 mg/m^2 over 3 hours every 3 weeks	Oxaliplatin 130 mg/m^2 over 2 hours every 3 weeks	5/31	2/32	0/31	0/32	5/31	2/32				
			2.581 (0.466 to 14.306)									
ten Bokkel Huinink *et al*. (1997)[21]b	Topotecan (1.5 mg/m^2) for 5 days every 21 days	Paclitaxel (175 mg/m^2) every 21 days	8/60	4/59	1/60	0/59	7/60	4/59				
			1.967 (0.562 to 6.884)									
Omura *et al*.[66]	Paclitaxel 250 mg/m^2 every 21 days	Paclitaxel 175 mg/m^2 every 21 days	40/109	23/104	13/109	5/104	27/109	18/104				
			1.659 (0.930 to 2.961)									

[a] Numerator calculated from percentage provided in full publication.

[b] Based on definitions in full publication, the subgroups of “resistant, early and interim” relapse as reported in the full publication have been combined to fulfil the definition of relapsed or refractory as relapse within 6 months of last platinum-based treatment or progression during treatment used in this TAG report.

[c] OR calculated by TAG.

Abbreviations used in table: AUC, area under curve; COMP, comparator; INT, intervention; PLDH, pegylated liposomal doxorubicin hydrochloride; TAG, Technology Assessment Group.

Network meta-analysis (platinum-resistant or refractory)

The RCTs available for inclusion in the NMA evaluating ORR in patients with platinum-resistant or refractory recurrent ovarian cancer are summarised in Table 54. The network of trials constructed for this outcome is depicted in Figure 10 and contains the following comparators:

- PLDH monotherapy;
- topotecan monotherapy (IV); that is, topotecan 1.25 or 1.5 mg/m2 daily for 5 days every 21 days;
- paclitaxel monotherapy; that is, 175mg/m2 or 200 mg/m2 every 21 days;
- topotecan monotherapy (oral);
- paclitaxel monotherapy (weekly); that is, paclitaxel 67 mg/m2 every week for 21 days.
- topotecan monotherapy (IV, weekly); that is, topotecan 4.0 mg/m2 (weekly) on days 1, 8, and 15 of a 28-day cycle.

The results from this NMA are presented in Table 55. Overall, no chemotherapy was found to have a significantly higher ORR (at the 5% level) than PLDH monotherapy. However, paclitaxel monotherapy, paclitaxel monotherapy (weekly), and topotecan monotherapy (IV, weekly) were found to have significantly lower ORR compared to PLDH monotherapy. No other comparison of chemotherapies was found to have a statistically significant difference.

An RCT that provided results for this population but which did not share a common comparator within the network compared low dose paclitaxel (80 mg/m^2) with low dose paclitaxel (80 mg/m^2) plus carboplatin.[61] However, Lortholary *et al.*[61] identified no significant difference in OS between the two different treatment regimen (OR 1.062, 95% CI: 0.510 to 2.209).

Figure 10. Networks for overall response rate in people with platinum-resistant or refractory recurrent ovarian cancer

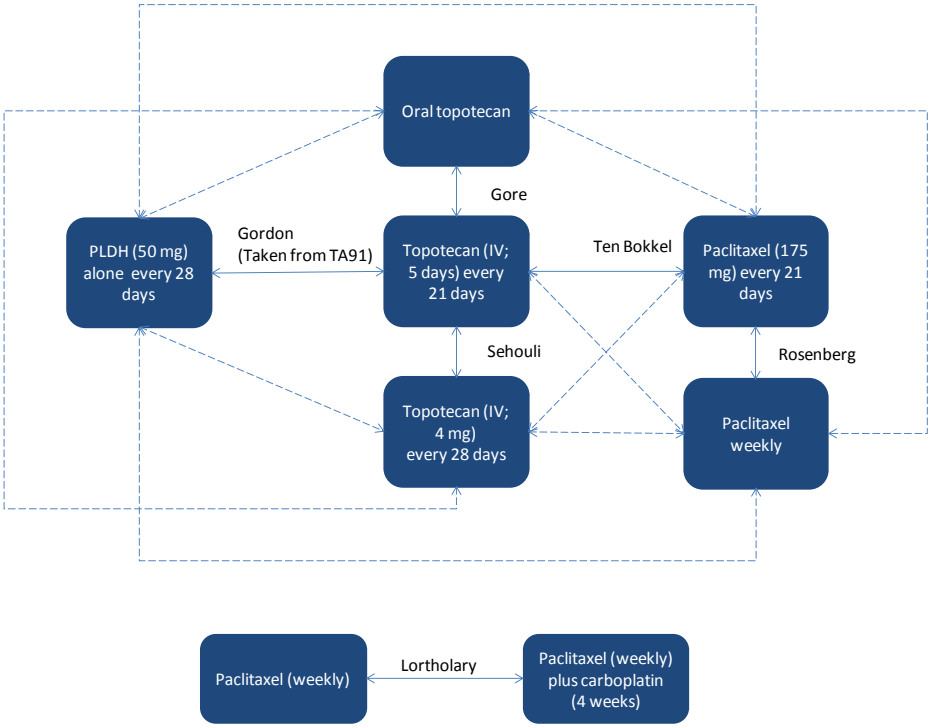


Table 55. Results from network meta-analysis for overall response rate in people with platinum-resistant or refractory recurrent ovarian cancer

Comparison	OR	95% CrI	
		Lower limit	Upper limit
Versus PLDH monotherapy (OR >1 favours comparator, OR <1 favours PLDH monotherapy)			
Topotecan monotherapy (IV)	0.529	0.184	1.166
Paclitaxel monotherapy	0.290	0.040	0.982
Topotecan monotherapy (oral)	0.622	0.098	2.116
Paclitaxel monotherapy (weekly)	0.224	0.022	0.884
Topotecan monotherapy (IV, weekly)	0.253	0.051	0.761
Versus topotecan monotherapy (IV) (OR >1 favours comparator, OR <1 favours topotecan monotherapy (IV))			
Paclitaxel monotherapy	0.548	0.111	1.553
Topotecan monotherapy (oral)	1.176	0.283	3.283
Paclitaxel monotherapy (weekly)	0.423	0.059	1.470
Topotecan monotherapy (IV, weekly)	0.478	0.154	1.086
Versus paclitaxel monotherapy (oral) (OR >1 favours comparator, OR <1 favours paclitaxel monotherapy (oral))			
Topotecan monotherapy (oral)	3.387	0.379	13.810
Paclitaxel monotherapy (weekly)	0.771	0.271	1.736

Topotecan monotherapy (IV, weekly)	1.383	0.191	5.216
Versus topotecan monotherapy (oral) ***(OR >1 favours comparator, OR <1 favours topotecan monotherapy (oral))***			
Paclitaxel monotherapy (weekly)	0.530	0.041	2.321
Topotecan monotherapy (IV, weekly)	0.601	0.090	2.090
Versus paclitaxel monotherapy (weekly) ***(OR >1 favours comparator, OR <1 favours paclitaxel monotherapy (weekly))***			
Topotecan monotherapy (IV, weekly)	2.251	0.215	9.439
Abbreviations used in table: CrI, Credible Interval; OR, odds ratio; PLDH, pegylated liposomal doxorubicin hydrochloride.			

Full population (mixed platinum-free intervals)

Trabectedin plus PLDH versus PLDH alone

OVA-301 (Monk *et al*. [2010][30]) evaluated tumour response as the overall response rate (CR or PR) with response maintained ≥4 weeks based on RECIST criteria. In the full trial population, trabectedin plus PLDH significantly improved ORR compared with PLDH alone (93/337 [27.6%] with trabectedin plus PLDH vs 63/335 [18.8%] with PLDH alone; p = 0.080; Table 57). It should be noted that most patients achieved PR, with only 6 patients being assessed as CR, 2 in the trabectedin plus PLDH group and 4 in the PLDH alone group.

Pegylated liposomal doxorubicin hydrochloride versus topotecan

In the full trial population, Gordon *et al*. (2001)[48] found no statistically significant difference between PLDH and topotecan in the proportion of patients achieving either CR or PR as their best response (47/239 [19.7%] with PLDH vs 40/235 [17.0%] with topotecan; p = 0.390; Table 57). In addition, a similar proportion of patients in each group achieved stable disease as their best response (77/239 [32.2%] with PLDH vs 95/235 [40.4%] with topotecan; Table 57).

Topotecan versus paclitaxel

In patients who received at least one dose of study drug (226 patients), ten Bokkel Huinink *et al*. (1997)[21] found no statistically significant difference between topotecan and paclitaxel in ORR (CR or PR; 23/112 [20.5%] with topotecan vs 15/114 [13.2%] with paclitaxel; p = 0.138; Table 57). It should be noted that, of the 226 patients included in the analysis, only 202 were evaluated for response, with the remaining 24 patients considered to be non-responders.

The authors carried out an analysis of response rate relative to baseline disease characteristics. Higher response rates in both groups were observed in patients without ascites at baseline, with better performance status scores (lower score is better), with smaller tumour burden (<5 cm), and those who responded to first-line chemotherapy (summarised in Table 56).

Table 56. Response rate relative to baseline characteristics for topotecan relative to paclitaxel

Baseline status	Topotecan response (%)	Paclitaxel response (%)
Age, years		
≤40	0	0
41–64	19.7	12.0
≥65	23.7	16.7
Ascites		
Present	18.9	7.5
Absent	21.3	16.2
Performance status		
0	22.0	14.3
1	25.5	13.2
2	5.0	11.8
Tumour burden (cm)		
<5 cm	33.3	18.0
5≤10cm	10.9	12.5
First-line response		
Responders	15.2	10.5
Non-responders	5.4	2.6

Paclitaxel versus oxaliplatin

Piccart *et al*.[62] found that a similar proportion of patients achieved PR in the paclitaxel and oxaliplatin groups (7/41 [17.1%] with paclitaxel vs 7/45 [15.6% with oxaliplatin). No patient achieved a CR. The statistical significance of the difference was not assessed in the full publication.

Topotecan oral versus topotecan intravenous

In the full trial population, Gore *et al*.[24] found no statistically significant difference between oral and intravenous topotecan in the proportion of patients achieving a CR or PR as their best response (17/135 [13%] with oral topotecan vs 26/131 [20%] with intravenous topotecan; reported as not significant; p value not reported; Table 57).

Paclitaxel high dose (250 mg/m^2) versus paclitaxel standard dose (175 mg/m^2)

Omura *et al*.[66] evaluated only patients with measurable disease for tumour response (131 patients treated with paclitaxel 175 mg/m^2 vs 134 patients treated with paclitaxel 250 mg/m^2). Overall response rate comprised patients with CR (disappearance of all gross evidence of disease for at least 4 weeks) or PR (50% or greater reduction in the product of perpendicular measurements of each lesion for at least 4 weeks). Response was assessed before every other cycle of therapy. It is unclear from the methods whether the assessor was masked to treatment allocation.

In the full trial population, a significantly larger proportion of patients in the paclitaxel 250 mg/m^2 group than in the 175 mg/m^2 group achieved either CR or PR as their best response (49/134 [36%] with paclitaxel 250 mg/m^2 vs 36/131 [27%] with paclitaxel 175 mg/m^2; Table 57). The accompanying OR was 1.89 (95% CI 1.07 to 3.31; p = 0.027). The OR had been adjusted for histologic cell type (papillary serous versus clear-cell or mucinous vs other cell types), co-operative group, performance status, and prior platinum sensitivity.

In patients randomised to paclitaxel 250 mg/m^2 and who were subsequently randomised to filgrastim 5 μg/kg or 10 μg/kg, there was no statistically significant difference among the filgrastim groups in the proportion of patients achieving CR or PR (24/68 [35%] with 5 μg/kg filgrastim vs 25/66 [37.9%] with 10 μg/kg filgrastim).

Paclitaxel weekly versus paclitaxel every 3 weeks

Rosenberg *et al*.[59] found no statistically significant difference between paclitaxel every 7 days and paclitaxel every 21 days in the proportion of patients achieving either CR or PR (37/105 [35.2%] with paclitaxel every 7 days vs 38/103 [36.9%] with paclitaxel every 21 days; reported as not significant; p value not reported). As noted, patients with unconfirmed CR (6 patients) and PR (13 patients) are included in this analysis and this should be borne in mind when interpreting the results.

Table 57. Summary of results for response rate in population with mixed platinum-free intervals

Study	Intervention	Comparison	Overall response (95% CI)		Complete response (95% CI)		Partial response (95% CI)		Stable disease (95% CI)		Progressive disease (95% CI)	
			INT	COMP	INT	COMP	INT	COMP	INT	COMP	INT	COMP
Gordon *et al*. (2001)[53]	PLDH 50 mg/m^2 every 28 days	Topotecan 1.5 mg/m^2/day for 5 days every 21 days	47/239	40/235	9/239	11/235	38/239	29/235	77/239	95/235		
			1.155 (0.730 to 1.827)									
Gore *et al*.[24]	Oral topotecan 2.3 mg/m^2/day	IV topotecan 1.5 mg/m^2/day for 5 days every 21 days	17/135	26/131	2/135	4/131	15/135	22/131	39/135	35/131	65/135	59/131
			0.634 (0.329 to 1.224)									
ten Bokkel Huinink *et al*. (1997)[21]	Topotecan 1.5 mg/m^2/day for 5 days	Paclitaxel 175 mg/m^2/day as 3 hour infusion every 21 days.	23/112	15/114	5/112	3/114	18/112	12/114				
			1.561 (0.774 to 3.145) p = 0.138									
Rosenberg *et al*.[59]a	Paclitaxel 67 mg/m^2 every 7 days	Paclitaxel 200 mg/m^2 every 21 days	37/105	38/103	13/105	17/103	24/105	21/103	43/105	33/103	15/105	19/103
			0.955 (0.563 to 1.620)									
Piccart *et al*.[44]	Paclitaxel 175 mg/m^2 over 3 hours every 3 weeks	Oxaliplatin 130 mg/m^2 over 2 hours every 3 weeks	7/41	7/45	0/41	0/45	7/41	7/45	14/41	15/45	18/41	20/45
			1.098 (0.355 to 3.397)									

OVA-301[30]	PLDH 30 mg/m^2 plus trabectedin 1.1 mg/m^2 every 3 weeks	PLDH 50 mg/m^2 every 4 weeks	93/337	63/335	91/337	59/335	2/337	4/335				
			1.467 (1.030 to 2.090)									
Omura *et al*.[66]	Paclitaxel 250 mg/m^2 every 21 days	Paclitaxel 175 mg/m^2 every 21 days	49/134	36/131	17/134	9/131	32/134	27/131				
			1.331 (0.813 to 2.179)									

[a] Numerator calculated from percentage provided in full publication.
Abbreviations used in table: COMP, comparator; INT, intervention; PLDH, pegylated liposomal doxorubicin; TAG, Technology Assessment Group.

Network meta-analysis (mixed platinum-free intervals)

The RCTs available for inclusion in the NMA evaluating ORR in patients with mixed platinum-free intervals in recurrent ovarian cancer are summarised in Table 57. However, based on expert clinical opinion, the TAG decided not to evaluate this mixed patient population as the results would not be considered clinically meaningful.

4.2.2.4 Quality of life

Of the 16 RCTs identified, 10 reported some level of data on QoL.[21;23;30;31;47-49;60-62] A systematic review of health-related QOL reporting in ovarian cancer trials identified considerable disparity in the level of reporting of QoL results, the questionnaires used to evaluate QoL, and the time points for evaluation.[8] Given the often palliative nature of second and subsequent line chemotherapeutic treatments for ovarian cancer, there has been a move to place greater emphasis on assessment of QoL in this condition.

The most commonly used scale in the identified trials is the EORTC QLQ-C30 questionnaire, which was developed to assess the QoL of cancer patients and can be supplemented with disease-specific modules for individual cancers, including ovarian cancer.[78] The QLQ-C30 questionnaire comprises six questions on that address dyspnoea, sleep disturbance, appetite loss, constipation, diarrhoea and financial impact, in addition to one global QoL scale, 5 functional scales (physical, role, emotional, cognitive, and social) and 3 symptom scales (fatigue, pain, and nausea/vomiting).

Here, a narrative description of QoL is presented for those trials providing data on this outcome.

Summary of results for QoL

Due to a paucity of data, results for individual trials assessing QoL are summarised here. It should be noted that, generally, reporting of results was limited, with few trials reporting scores generated from responses to the questionnaires.

Pegylated liposomal doxorubicin hydrochloride (PLDH) plus carboplatin versus paclitaxel plus carboplatin

Baseline QoL scores showed impaired global health scores and considerable symptom burden. At 3 months, PLDH plus carboplatin was associated with a significant improvement in global health compared with paclitaxel plus carboplatin. However, this benefit was not maintained at 6 months.

The QLQ-OV28 questionnaire indicated that paclitaxel plus carboplatin was associated with significantly worse peripheral neuropathy and other chemotherapy side effects at 3 months and 6 months compared with PLDH plus carboplatin.

Trabectedin plus PLDH versus PLDH alone

Mean change in scores from baseline to end of treatment were similar between trabectedin plus PLDH and PLDH monotherapy, with no differences reaching statistical significance on any

questionnaire. The difference between groups in mean scores for the QLQ-C30 global health status scale did not reach 5 or more at any time point, which indicated non-significance. Additional information on QoL in the subgroup of patients with PPS provided in the manufacturer's submission indicates a difference in global health status score among responding patients beyond cycle 5, with patients in the trabectedin plus PLDH group having a higher score than those receiving PLDH monotherapy (higher score is favourable).

Topotecan versus paclitaxel

EORTC QOL-C30 scores were similar between the groups and neither paclitaxel nor topotecan was associated with any compromise of QoL.

Paclitaxel plus carboplatin versus platinum-based monotherapy

The ICON4/AGO-OVAR2.2 investigators evaluated QoL using the EORTC QLQ-C30 questionnaire. It was reported that, in the first 6 months after randomisation, patients receiving platinum monotherapy scored significantly worse on the nausea and vomiting symptom scale than did the paclitaxel plus platinum-based chemotherapy group. However, this difference seemed to be transient and was observed for only the first 15 weeks after randomisation. All other worst scores or AUCs were reported to be similar between treatment groups for the remaining eight symptom scales, the five functional scales, and global health status of the QLQ-C30.

Gonzalez-Martin *et al*.[47] also evaluated QoL using the QLQ-C30 questionnaire. No differences between treatments in the five functional components of the QLQ-C30 were reported.

PLDH versus topotecan

QoL was assessed using the EORTC QLQ-C30 questionnaire. At week 12, no significant differences between the groups in any of the measured scores were noted. The proportion of patients who had a worsened global QoL score was also reported to be similar in the two treatment groups. Topotecan was associated with a significantly more favourable rating on the pain sub-scale of the EORTC QLQ-C30.

Gemcitabine plus carboplatin versus carboplatin alone

Based on responses to the EORTC QLQ-C30 and QLQ-C28, no statistically significant differences between treatment groups for all scales/items at baseline or in changes in score from baseline to treatment discontinuation were noted.

Paclitaxel plus carboplatin versus paclitaxel alone

Response to EORTC QLQ-C30 indicated that global health scores were stable over time and similar across treatment arms. Among symptom and functional scales, patients receiving weekly paclitaxel plus carboplatin experienced improvements in constipation, abdominal/gastrointestinal symptoms, appetite loss, pain, and emotional functioning. Patients treated with weekly paclitaxel alone experienced improvements in attitude to disease and insomnia, but worsening of dyspnoea and peripheral neuropathy.

Paclitaxel versus oxaliplatin

Mean QoL score on the EORTC QLQ-C30 increased by more than 10 points between baseline and cycle 4 for patients in the paclitaxel group, irrespective of study withdrawal. By contrast, in the oxaliplatin group, the mean QoL score decreased through cycle 2, but by less than 10 points, after

which most patients' mean scores returned to baseline levels.

Topotecan administered on 5 consecutive days (conventional regimen) versus topotecan administered weekly

It was reported that there were no differences between treatment groups in EORTC QLQ-OV28 scores.

Pegylated liposomal doxorubicin hydrochloride plus carboplatin versus paclitaxel plus carboplatin

QoL data were collected during CALYPSO (Pujade-Lauraine *et al.*[31]) using the EORTC QLQ-C30 questionnaire and supplemented by the ovarian cancer-specific OV28 module. QoL was assessed at baseline and subsequently at the 3, 6, 9, and 12 month assessments. QoL was not assessed after progression of disease. Results for QoL are presented in full in an accompanying publication.[58]

Analyses of QoL were restricted to those patients with both a completed baseline questionnaire and at least one QoL form completed during follow-up. At baseline, 90% of patients completed the questionnaires (421/467 [90.1%] with PLDH plus carboplatin vs 458/509 [90.0%] in the paclitaxel plus carboplatin group). Compliance remained high at 3 months' follow-up (79.3% with PLDH plus carboplatin vs 73.5% with paclitaxel plus carboplatin), but steadily declined over the remaining 9 months (completed questionnaires: 6 months: 68.3% with PLDH plus carboplatin vs 60.3% with paclitaxel plus carboplatin; 12 months: 50.6% with PLDH plus carboplatin vs 49.7% with paclitaxel plus carboplatin). Given that only 50% of patients were compliant at 12 months, the authors restricted reporting of results to data collected up to 9 months' follow-up.

Baseline QoL scores showed impaired global health scores and considerable symptom burden (Table 58).

At 3 months, PLDH plus carboplatin was associated with a significant improvement in global health compared with paclitaxel plus carboplatin (mean score at 3 months [standard deviation; SD: –2.2 [22.7] with paclitaxel plus carboplatin vs 2.6 [26.0] with PLDH plus carboplatin; $p = 0.01$). However, this benefit was not maintained at 6 months, at which time the difference between groups for this measure was not statistically significant (4.8 [24.4] with paclitaxel plus carboplatin vs 2.4 [26.4] with PLDH plus carboplatin; $p = 0.31$). It should be noted that the difference between groups is modest. Results from QoL analyses are presented in Table 58.

Other symptom scores for which there was a significant difference at 3 months that was not maintained at 6 months are: physical functioning; nausea and vomiting; pain; dyspnoea; and sexual functioning.

Assessment of QLQ-OV28 indicated that paclitaxel plus carboplatin was associated with significantly worse peripheral neuropathy and other chemotherapy side effects at 3 months and 6 months compared with PLDH plus carboplatin.

Table 58. QLQ-C30 and QLQ-OV28 scores at baseline and at 3 and 6 months' follow-up

Item/domain	Baseline scores				3-month change[a]					6-month change[a]				
	CP		CD		CP		CD		*P* value	CP		CD		*P* value
	N	Mean (SD)	*N*	Mean (SD)	*N*	Mean (SD)	*N*	Mean (SD)		*N*	Mean (SD)	*N*	Mean (SD)	
Functional scales scores														
Physical functioning	452	79.5 (20.7)	414	79.8 (20.1)	313	−7.4 (18.1)	309	−3.7 (18.8)	**0.01**	228	−1.1 (20.6)	242	−2.8 (19.1)	0.36
Role functioning	447	72.6 (30.4)	413	72.3 (31.9)	310	−9.2 (31.2)	305	−4.5 (33.8)	0.07	225	2.4 (34.7)	241	−1.7 (31.5)	0.18
Emotional functioning	447	63.4 (25.6)	410	64.4 (25.2)	308	6.5 (21.8)	303	8.3 (22.6)	0.31	225	6.8 (25.3)	239	5.1 (23.7)	0.46
Cognitive functioning	448	83.9 (20.2)	412	83.8 (20.2)	309	−6.4 (20.3)	305	−3.6 (19.1)	0.08	226	−3.1 (21.3)	242	−5.2 (22.6)	0.31
Social functioning	445	74.2 (28.2)	411	78.4 (27.2)	303	−5.2 (28.3)	304	−5.1 (28.5)	0.95	224	0.1 (31.2)	242	−4.3 (23.8)	0.09
Global health status score														
Global health Status/QoL	447	62.2 (23.0)	408	61.4 (24.2)	307	−2.2 (22.7)	301	2.6 (26.0)	**0.01**	227	4.8 (24.4)	238	2.4 (26.4)	0.31
Symptoms scales scores														
Fatigue	450	34.7 (25.7)	413	34.4 (27.5)	310	−9.4 (25.3)	306	−6.3 (27.0)	0.13	225	1.2 (25.9)	243	−4.6 (27.6)	**0.02**
Nausea and vomiting	449	8.0 (17.3)	413	10.9 (20.7)	309	−3.5 (22.9)	308	−8.4 (26.1)	**0.01**	225	3.2 (21.9)	244	−0.3 (24.9)	0.11
Pain	450	27.1 (28.4)	414	25.9 (28.2)	310	1.3 (31.2)	306	6.2 (28.7)	**0.04**	227	6.4 (31.3)	243	6.0 (29.3)	0.86
Dyspnea	444	17.9 (25.3)	409	19.4 (27.8)	307	−11.8 (29.6)	305	−3.2 (30.0)	**<0.001**	224	−4.5 (30.1)	244	−5.7 (29.4)	0.64
Insomnia	447	36.8 (32.9)	413	36.6 (32.8)	306	2.2 (31.7)	304	5.7 (31.4)	0.16	223	3.6 (30.2)	242	4.6 (32.6)	0.73
Appetite loss	445	18.7 (29.2)	413	21.5	305	−2.3	306	0.6 (30.1)	0.24	225	7.3 (27.9)	242	5.3 (31.3)	0.47

				(30.8)		(31.5)								
Constipation	449	22.6 (31.1)	409	23.6 (31.7)	309	−4.5 (33.2)	301	−5.5 (34.9)	0.74	227	3.6 (34.2)	239	−2.7 (34.3)	**0.05**
Diarrhoea	447	10.3 (21.1)	409	13.5 (24.8)	307	0.5 (24.0)	300	3.4 (25.2)	0.15	227	−1.0 (24.5)	238	3.8 (22.5)	**0.03**
Financial difficulties	441	14.7 (27.3)	405	12.4 (24.8)	303	−4.6 (26.8)	297	−2.4 (22.6)	0.28	221	−2.6 (30.5)	239	−2.0 (22.9)	0.81
QLQ–OV28														
Abdominal/gastrointestinal symptoms	442	29.1 (22.6)	411	30.3 (24.0)	306	5.0 (22.0)	305	4.7 (21.7)	0.83	223	6.8 (23.1)	238	5.1 (23.9)	0.43
Peripheral neuropathy	434	17.7 (22.0)	402	15.3 (20.6)	300	−27.4 (26.8)	297	−6.1 (18.9)	**<0.001**	218	−24.2 (30.5)	233	−9.8 (20.1)	**<0.001**
Other chemotherapy side-effect	435	15.0 (14.9)	405	14.2 (15.1)	301	−24.7 (18.4)	301	−7.6 (16.8)	**<0.001**	219	−16.2 (19.9)	236	−9.5 (15.9)	**<0.001**
Hormonal/menopausal symptoms	435	26.4 (28.0)	405	24.2 (28.6)	300	−1.6 (24.2)	301	−0.6 (28.3)	0.62	219	−2.4 (28.4)	235	−2.9 (28.4)	0.84
Body image	431	23.9 (27.6)	401	24.3 (28.0)	297	−12.2 (29.3)	292	−1.2 (28.2)	**<0.001**	212	−10.4 (31.4)	234	−3.8 (27.0)	**0.02**
Attitude to disease and treatment	432	57.2 (28.2)	397	56.3 (28.5)	295	−0.4 (25.4)	290	1.7 (25.8)	0.32	216	0.0 (28.0)	228	1.8 (24.3)	0.48
Sexual functioning	385	20.4 (23.5)	358	16.3 (21.7)	241	4.5 (17.8)	232	0.4 (18.5)	**0.02**	173	0.8 (19.7)	187	0.2 (18.5)	0.78
[a] Positive values indicate an increase in improvement, whereas negative values indicate deterioration.														

Trabectedin plus PLDH versus PLDH alone

OVA-301 (Monk *et al*. [2010][30]) evaluated patient reported outcomes as an exploratory endpoint using the cancer-specific EORTC QLQ-C30 and QLQ-OV28 questionnaires, together with the generic EQ-5D questionnaire, which is the utility measure preferred by NICE. Results from the analyses were reported in a follow-up publication by Krasner *et al*.[52]

Patients completed questionnaires at baseline, on day 1 of each treatment cycle before administration of the allocated treatment, and at the end of treatment. Statistical analyses of QoL were based on all randomised patients. Non-random withdrawal from treatment across groups, most frequently as a result of disease progression or poor tolerability, is well-recognised in trials evaluating treatments in cancer. To account for the potential imbalance in patients lost to follow-up between the groups, the authors implemented a pattern mixture model.

Compliance was high, with an overall rate of missing questionnaires of 15%, which was balanced across the groups (14.4% with trabectedin plus PLDH vs 15.2% with PLDH alone). At most time points, the rate of missing questionnaires was <10, but, at the end of treatment, the rate rose to 34%.

Mean change in scores from baseline to end of treatment were similar between trabectedin plus PLDH and PLDH alone, with no differences reaching statistical significance on any questionnaire. The authors report that the difference between groups in mean scores for the QLQ-C30 global health status scale did not reach 5 or more at any time point, which indicated non-significance. Mean change in QLQ-C30 global health status scale over time is presented in Figure 11. Minor, sporadic differences in the fatigue symptom scale were observed in cycles 3 and 9, with some worsening of fatigue for subjects with trabectedin plus PLDH.

In the submission received from PharmaMar, additional information on QoL in the subgroup of patients with PPS is provided. The manufacturer notes that a difference in global health status score was observed among responding patients beyond Cycle 5 in the PPS subgroup, with patients in the trabectedin plus PLDH group having a higher score than those receiving PLDH alone (higher score is favourable) (Figure 12). The manufacturer comments that the benefit associated with trabectedin plus PLDH is clinically meaningful. It should be noted that the analysis seems to be based on patients with PPS who responded to treatment (N is reported to be 51) rather than the full PPS subgroup. In addition, all QoL analyses are exploratory.

Figure 11. Mean QLQ-C30 global health status score over time (reproduced with permission from PharaMar's submission)

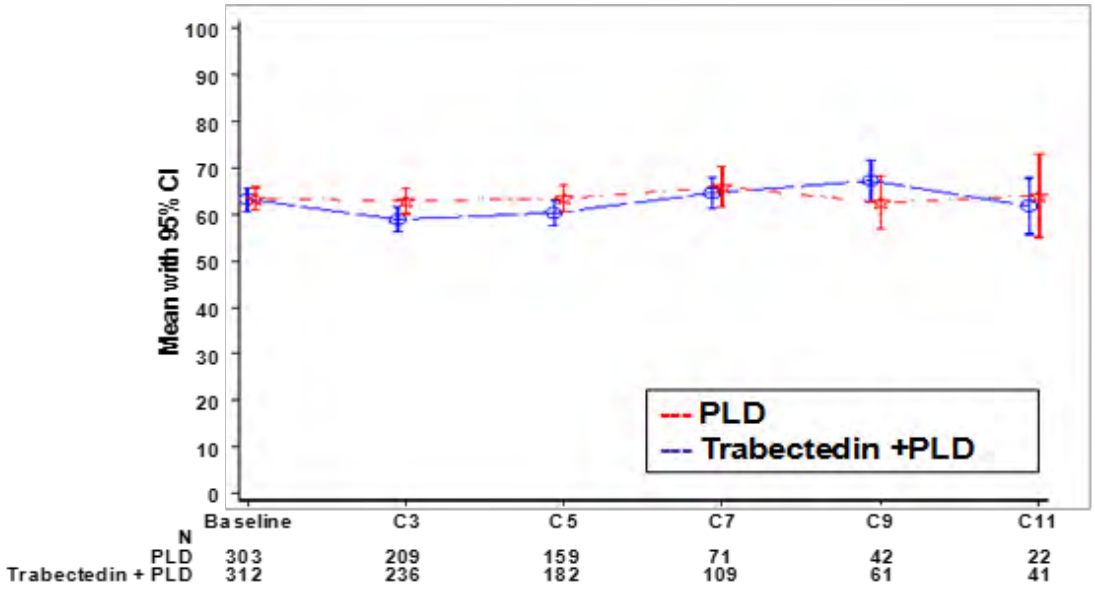
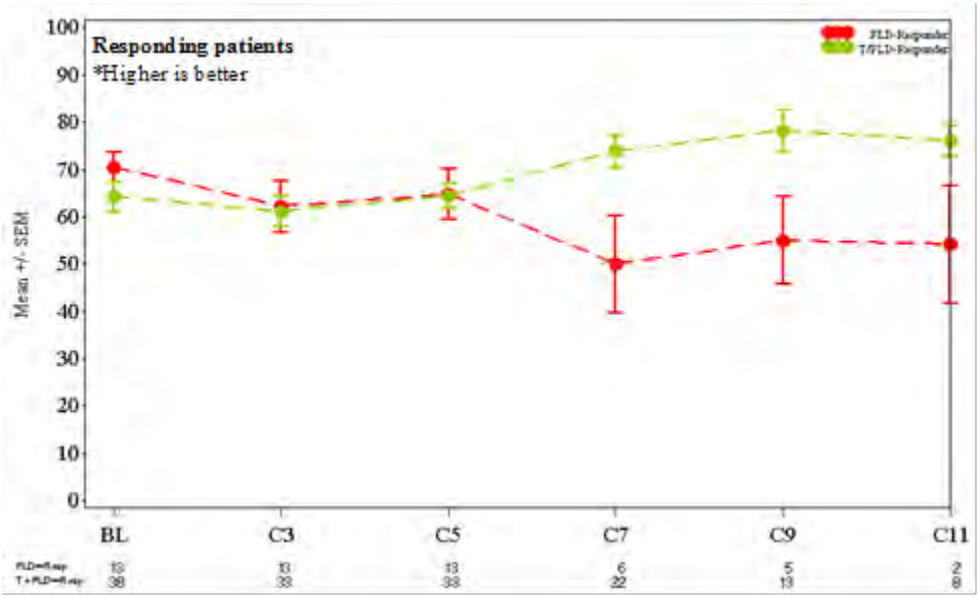


Figure 12. Mean QLQ-C30 global health status score over time for the partially platinum-sensitive subgroup (reproduced with permission from PharaMar's submission)



Topotecan versus paclitaxel

ten Bokkel Huinink *et al*. (1997)[21] evaluated QoL using the EORTC QOL-C30 questionnaire. It is reported that between 75% and 85% of patients enrolled in the study had evaluable QoL data. However, no results are reported in either of the two identified publications.[21;51] The authors comment that scores were similar between the groups and that neither paclitaxel nor topotecan was associated with any compromise of QoL.

Pegylated liposomal doxorubicin hydrochloride versus topotecan

Gordon *et al*. (2001)[48] report that quality of life was assessed using the EORTC QLQ-C30 questionnaire. All patients completed a QLQ-C30 questionnaire before study entry, during every cycle and 4 weeks after the last treatment dose. The full publication reports that about 82% of patients completed the questionnaire at baseline and that at study entry function and symptom scale scores were similar between the groups. At week 12, it is reported that there were no significant differences between the groups in any of the measured scores. No further details are reported in the full publication. Additional detail is reported in TA91, which is summarised here.

TA91 reports that only 50% of patients completed the questionnaire at 12 weeks.[13] At week 12, similar proportions of patients in the PLDH and topotecan groups had improved or stable global QoL scores, with no statistically significant difference identified between groups (68/239 [28.5%] with PLDH vs 55/235 [23.4%] with topotecan; Relative risk [RR] 0.82, 95% CI: 0.61 to 1.12). Proportion of patients who had a worsened global QoL score was also reported to be similar in the two treatment groups (49/239 [20.5%] with PLDH vs 48/235 [20.4%] with topotecan; RR 0.97, 95% CI: 0.70 to 1.42). Considering the subscales of the QLQ-C30, a statistically significant difference between PLDH and topotecan was identified for only the pain sub-scale score (RR 1.26, 95% CI: 1.08 to 1.50), which favoured topotecan (results from TA91 summarised in Table 59).

Table 59. Percentage of patients with a maintained or improved QoL score at 12 weeks' follow-up for PLDH versus topotecan (collated from Table 10 and Figure 7 in TA91[13])

QoL sub-scale	PLDH % (n/N)	Topotecan (n/N)	RR (95% CI)[a]
Physical	56% (66/118)	56% (61/107)	1.02 (0.81 to 1.28)
Role	65% (77/118)	58% (63/109)	0.89 (0.72 to 1.10)
Emotional	67% (80/119)	74% (80/108)	1.10 (0.93 to 1.31)
Cognitive	73% (87/119)	73% (79/108)	1.00 (0.85 to 1.17)
Social	69% (82/119)	64% (69/108)	0.93 (0.77 to 1.12)
Global QoL	58% (68/117)	52% (54/104)	0.89 (0.70 to 1.13)
Fatigue	57% (67/118)	56% (61/109)	0.99 (0.78 to 1.24)
Nausea/vomiting	72% (86/119)	71% (77/109)	0.98 (0.83 to 1.15)
Pain	64% (76/119)	81% (88/109)	1.26 (1.08 to 1.50)

[a] RR<1 favours PLDH.

Abbreviations used in table: PLDH, pegylated liposomal doxorubicin hydrochloride; QoL, quality of life; RR, relative risk.

Gemcitabine plus carboplatin versus carboplatin alone

Pfisterer *et al*.[49] evaluated QoL using the EORTC QLQ-C30 and QLQ-C28 (version 2) questionnaires. QoL was assessed 2 weeks before enrolment and before commencement of each treatment cycle. Questionnaire completion rate was high, with 85.4% (152/178) and 82.6% (147/178) of patients in the gemcitabine plus carboplatin and carboplatin alone groups, respectively, having completed a questionnaire at baseline and at least one post-baseline questionnaire. The authors report that there were no statistically significant differences between treatment groups for all scales/items at baseline or in changes in score from baseline to treatment discontinuation. No further details reported.

Paclitaxel plus carboplatin versus platinum-based therapy alone

The ICON4/AGO-OVAR2.2 investigators evaluated QoL using the EORTC QLQ-C30 questionnaire.[60] In total, 90% (482/536) of patients enrolled in centres following the MRC CTU ICON4 protocol completed the questionnaire at baseline, before receiving any study drug. The authors report that all scales were balanced across the two treatment groups at baseline and that most patients had little or no functional difficulties and few had moderate or severe symptoms at baseline (no further details reported). In the first 6 months after randomisation, patients receiving platinum monotherapy scored significantly worse on the nausea and vomiting symptom scale than did the paclitaxel plus platinum-based chemotherapy group ($p = 0.0014$ for worst score and $p = 0.005$ for AUC). However, this difference seemed to be transient and was observed for only the first 15 weeks after randomisation. All other worst scores or AUCs were reported to be similar between treatment groups for the remaining eight symptom scales, the five functional scales, and global health status of the QLQ-C30 (no further details reported).

Gonzalez-Martin *et al*.[47] also evaluated QoL using the QLQ-C30 questionnaire. The authors reported that there were no differences between treatments in the five functional components of the QLQ-C30. No other details were reported.

Paclitaxel plus carboplatin versus paclitaxel alone

Lortholary *et al*.[61] explored QoL using the EORTC QLQ-C30 and QLQ-OV28 questionnaires. Completion rate of questionnaires ranged between 40% and 70%, with questionnaires collected at baseline, and after 2, 4, and 6 cycles of treatment. Global health scores were stable over time and similar across treatment arms. Among symptom and functional scales, patients receiving weekly paclitaxel plus carboplatin experienced improvements in constipation, abdominal/gastrointestinal symptoms, appetite loss, pain, and emotional functioning. Patients treated with weekly paclitaxel experienced improvements in attitude to disease and insomnia, but worsening of dyspnoea and peripheral neuropathy. No further details reported.

Paclitaxel versus oxaliplatin

Piccart *et al*.[62] used the EORTC QLQ-C30 questionnaire and a specific checklist to evaluate QoL. Patients were to complete the questionnaires at least 8 days before their first treatment and, subsequent to start of treatment, every 6 weeks or every two visits. At baseline, completed questionnaires were available for 66 patients. However, at the end of the second treatment cycle (week 6), only 47 patients had completed their questionnaires, with a further drop to 31 completed questionnaires by the end of the fourth treatment cycle (12 weeks). The authors report that the mean QoL score increased by more than 10 points between baseline and cycle 4 for patients in the paclitaxel group, irrespective of study withdrawal. By contrast, in the oxaliplatin group, the mean QoL score decreased through cycle 2, but by less than 10 points, after which most patients' mean scores returned to baseline levels. The authors propose that the initial decrease in score in the oxaliplatin group is associated with peripheral neurotoxicity. No further details on scores reported.

Topotecan administered on 5 consecutive days (conventional regimen) versus topotecan administered weekly

Sehouli *et al*.[23] explored disease-specific QoL using the EORTC QLQ-OV28 questionnaire. Details on schedule of completion of questionnaire were not reported. Baseline data were available for 120 patients (65 treated with conventional topotecan group vs 55 treated with weekly topotecan). A second assessment was available for considerably fewer patients (39 treated with conventional topotecan group vs 20 treated with weekly topotecan), but it is unclear at what point in the trial the second questionnaire was completed. Patients with at least a completed baseline and at least one follow-up assessment reported an improvement in neuropathy scales, but a worsening in body image. The authors reported that there was no difference in scores between treatment groups. No further details reported.

4.2.2.5 Adverse events

Summary of results for adverse effects

Data for adverse effects for individual trials are reported in the main text. Within each trial, the most frequently reported adverse effects were as expected for the individual treatments based on the Summary of Product Characteristics (SmPC). Commonly occurring adverse effects were alopecia, nausea and vomiting, haematological toxicities (neutropenia, anaemia, thrombocytopenia, and leukopenia).

Based on expert clinical advice, the TAG restricted its comparison of adverse events to those considered most problematic for patients or most likely to consume substantial health care resource. The potential for an NMA was, therefore, investigated for the following severe (grade 3–4) adverse events: allergic reaction; alopecia; anaemia; fatigue; febrile neutropenia; nausea and vomiting; and neuropathy. The results of each investigation are presented in the main text. The results were mixed with most found to be non-significant or with chemotherapies having significant lower risk of one or

more adverse events but then being found to have significantly higher risks of others (e.g., PLDH plus carboplatin has significantly less risk of allergic reaction and alopecia but significantly higher risk of anaemia and nausea and vomiting when compared to paclitaxel plus carboplatin). In many cases, an NMA was not possible due to the lack of available data in the trials assessed. In these instances, the individual trial results are reported with the ORs and 95% confidence intervals calculated. Overall, no chemotherapy was consistently associated with either a lower risk or a higher risk of the severe adverse events assessed.

Pegylated liposomal doxorubicin hydrochloride plus carboplatin versus paclitaxel plus carboplatin

Bafaloukos *et al*.[29] based the safety analysis on the 177 patients who received at least one cycle of allocated treatment (84 in the PLDH plus carboplatin group vs 89 in the carboplatin plus paclitaxel group). A significantly larger proportion of patients in the paclitaxel plus carboplatin group discontinued treatment because of associated toxicity (13.5% with paclitaxel plus carboplatin vs 3% with PLDH plus carboplatin; p = 0.016).

Neutropenia (grade 3–4) was the most commonly observed severe toxicity, with a similar proportion of people between groups experiencing this adverse effect (30% with paclitaxel plus carboplatin vs 35% with PLDH plus carboplatin); the difference between groups did not reach statistical significance (p value not reported).

PLDH plus carboplatin was associated with a significantly higher rate of severe thrombocytopenia (Grade 3–4: 11% with PLDH plus carboplatin vs 2% with paclitaxel plus carboplatin; p = 0.016; Table 60) and PPE and skin toxicity (Grade 1–2; 38% with PLDH plus carboplatin vs 9% with paclitaxel plus carboplatin; p = 0.003). By contrast, paclitaxel plus carboplatin was associated with significantly higher rate of severe neurotoxicity (7% with paclitaxel plus carboplatin vs 0% PLDH plus carboplatin; p = 0.029) and alopecia (20% with paclitaxel plus carboplatin vs 5% PLDH plus carboplatin; p = 0.003).

Table 60. Adverse effects as reported by Bafaloukos *et al*.[29]

Event	PLDH plus carboplatin (N = 84)				Paclitaxel plus carboplatin (N = 89)			
Withdrawal due to haematological events	1[a]				6[b]			
Withdrawal due to hypersensitivity	2				3			
Withdrawal due to grade 3 skin toxicity	1				0			
	Grade 1	*Grade 2*	*Grade 3*	*Grade 4*	*Grade 1*	*Grade 2*	*Grade 3*	*Grade 4*
Neutropenia	13 (15%)	20 (24%)	23 (27%)	7 (8%)	14 (16%)	20 (22%)	18 (20%)	9 (10%)
Anaemia	27 (32%)	23 (27%)	7 (8%)	1 (1%)	29 (33%)	0	3 (3%)	0
Leukopenia	25 (30%)	30	4 (5%)	1 (1%)	24 (27%)	23 (26%)	5 (6%)	1 (1%)
Thrombocytopenia[c]	4 (5%)	7 (8%)	9 (10%)	1 (1%)	1 (1%)	6 (7%)	2 (2%)	0
Stomatitis	7 (8%)	5 (6%)	3 (3%)	0	–	1 (1%)	–	0
Nausea/vomiting	16 (19%)	12 (14%)	4 (5%)	0	18 (20%)	10 (11%)	1 (1%)	0
Diarrhoea	5 (6%)	1 (1%)	0	0	5 (6%)	1 (1%)	1 (1%)	0
Infection	3 (4%)	1 (1%)	1 (1%)	1 (1%)	1 (1%)	3 (3%)	–	0
Neurotoxicity[c]	19 (23%)	1 (1%)	0	0	24 (27%)	27 (30%)	5 (6%)	1 (1%)
Alopecia[c]	12 (14%)	5 (6%)	4 (5%)	0	1 (1%)	56 (63%)	18 (20%)	0
Allergy	4 (5%)	2 (2%)	1 (1%)	0	18 (20%)	9 (10%)	1 (1%)	0
Skin[c]	9 (11%)	12 (14%)	1 (1%)	0	6 (7%)	2 (2%)	0	0
Hand and foot	2 (2%)	8 (10%)	0	0	0	0	0	0
Fatigue	8 (10%)	6 (7%)	0	0	12 (13%)	6 (7%)	0	0
Fever	2 (2%)	4 (5%)	0	0	–	5 (6%)	0	0
Anorexia	5 (6%)	–	0	0	4 (4%)	2 (2%)	0	0
Cardiac	0	1 (1%)	0	0	0	0	0	0
Arthralgias/myalgias	6 (7%)	0	0	0	18 (20%)	8 (9%)	0	0

[a] Severe thrombocytopenia.

[b] Severe neutropenia.

[c] Rate of severe thrombocytopenia (Grade 3–4; p = 0.016) and of PPE and skin toxicity (Grade 1–2; p = 0.003) were statistically significantly higher in the PLDH plus carboplatin group. Rate of neurotoxicity (Grade 1–2; p = 0.0003; Grade 3–4 p = 0.029) and alopecia (p = 0.003) are significantly higher with paclitaxel plus carboplatin. All other differences are reported to be not statistically significant.

Abbreviation used in table: PLDH, pegylated liposomal doxorubicin hydrochloride; PPE, palmar–plantar erythrodysesthesia.

In the CALYPSO trial (Pujade-Lauraine *et al*.[31]), significantly fewer patients treated with PLDH plus carboplatin discontinued treatment early as a result of adverse effects compared with patients treated with paclitaxel plus carboplatin (6% with PLDH plus carboplatin vs 15% with paclitaxel plus carboplatin; $p < 0.001$). There were two treatment-related deaths in the PLDH plus carboplatin group (one attributed to cerebral haemorrhage and one to acute myeloid leukaemia).

Overall, severe (grade 3-4) non-haematological toxicity occurred significantly more frequently in the paclitaxel plus carboplatin group (36.8% with paclitaxel plus carboplatin vs 28.4% with PLDH plus carboplatin; $p = 0.001$). Incidence of anaemia and febrile neutropenia were similar between treatment groups. However, grade 3-4 neutropenia and thrombocytopenia were significantly more frequent in the paclitaxel plus carboplatin group (neutropenia: $p < 0.01$; thrombocytopenia: $p < 0.001$; Table 61).

Adverse events that occurred significantly more frequently in the paclitaxel plus carboplatin group than in the PLDH plus carboplatin group were grade 2 (complete or total hair loss) alopecia ($p < 0.001$), hypersensitivity reactions ($p < 0.001$), and sensory and motor neuropathy (sensory, $p < 0.001$; motor, $p = 0.002$; Table 61). By contrast, PLDH plus carboplatin was associated with a significantly higher incidence of hand-foot syndrome (grade 2-3; $p < 0.001$), nausea ($p < 0.001$), vomiting ($p < 0.001$), and mucositis ($p < 0.001$; Table 61).

Table 61. Adverse effects as reported by Pujade-Lauraine et al.[31]

Event	PLDH plus carboplatin (N = 466)	Paclitaxel plus carboplatin (N = 501)	p-value
Withdrawal due to hypersensitivity reaction	1%	6%	p <0.001
Treatment-related fatalities	3	1	Not reported
Grade 3–4			
Neutropenia	164 (35.2%)	229 (45.7%)	<0.01
Febrile neutropenia	12 (2.6%)	21 (4.2%)	0.171
Infection	12 (2.6%)	16 (3.2%)	0.723
Thrombocytopenia	74 (15.9%)	31 (6.2%)	<0.001
Anaemia	37 (7.9%)	27 (5.4%)	0.573
Bleeding	3 (0.6%)	0	0.718
Grade ≥2			
Alopecia	31 (7%)	419 (83.6%)	<0.001
Nausea	164 (35.2%)[a]	121 (24.2%)[a]	<0.001
Vomiting	105 (22.5%)[a]	78 (15.6%)[a]	<0.001
Constipation	100 (21.5%)	109 (21.8%)	0.6
Diarrhoea	25 (5.4%)[a]	41 (7.6%)[a]	<0.001
Fatigue	172 (36.9%)[a]	202 (40.3%)[a]	0.220
Mucositis	65 (13.9%)[a]	35 (7%)[a]	<0.001
Neuropathy (sensory)	23 (4.9%)[a]	135 (26.9%)	<0.001
Neuropathy (motor)	7 (1.5%)	22 (4.4%)[a]	0.002
Cardiovascular	10 (2.1%)[a]	17 (3.4%)	0.616
Allergic reaction	26 (5.6%)[a]	94 (18.8%)	<0.001
Hand foot syndrome	56 (12.0%)[a]	11 (2.2%)[a]	<0.001
Arthralgia/myalgia	19 (4.0%)[a]	96 (19.2%)[a]	<0.001
Any grade			
Alopecia[b]	158 (34%)	452 (90.2%)	–
Nausea	365 (78.3%)	354 (70.7%)	–
Vomiting	228 (48.9%)	181 (36.1%)	–
Constipation	258 (55.4%)	287 (57.5%)	–
Diarrhoea	108 (23.2%)	158 (31.6%)	–
Fatigue	363 (77.9%)	409 (81.6%)	–
Mucositis	182 (39.1%)	131 (26.1%)	–
Neuropathy (sensory)	186 (39.9%)	366 (73.1%)	–
Neuropathy (motor)	34 (7.3%)	67 (13.4%)	–
Cardiovascular	49 (10.5%)	57 (11.4%)	–
Allergic reaction	72 (15.5%)	165 (32.9%)	–
Hand foot syndrome	180 (38.6%)	51 (10.2%)	–
Arthralgia/myalgia	104 (22.3%)	250 (49.9%)	–

[a] Only grades 2 and 3, no Grade 4 reported.
[b] Graded as 1, partial hair loss, or 2, complete hair loss.
Abbreviation used in table: PLDH, pegylated liposomal doxorubicin hydrochloride.

Pegylated liposomal doxorubicin hydrochloride plus carboplatin versus carboplatin alone

Alberts *et al*.[28] reported that the most common grade 3 and grade 4 adverse events in the PLDH carboplatin group were haematological, with eight patients (26%) experiencing a grade 4 haematological adverse event (thrombocytopenia and neutropenia; Table 62). No patient in the PLDH plus carboplatin group had an allergic reaction compared with 9 patients treated with carboplatin alone.

Table 62. Adverse effects as reported by Alberts *et al*.[28]

Event	PLDH plus carboplatin (N = 31)			Carboplatin alone (N = 30)		
Withdrawal due to adverse events	15 (48%)[a]			7 (23%)[b]		
Grade 4 haematological adverse events	8 (26%)			0		
Grade	*≤2*	*3*	*4*	*≤2*	*3*	*4*
Abdominal pain/cramping	97%	3%	0%	100%	0%	0%
Allergy/hypersensitivity	100%	0%	0%	83%	13%	3%
Anaemia	84%	16%	0%	100%	0%	0%
Catheter-related infection	97%	3%	0%	100%	0%	0%
Constipation/bowel obstruction	94%	6%	0%	97%	3%	0%
Depression	100%	0%	0%	97%	3%	0%
Dyspnoea	94%	3%	0%	93%	3%	3%
Fatigue/malaise/lethargy	90%	10%	0%	93%	7%	0%
Febrile neutropenia	90%	10%	0%	100%	0%	0%
Hand-foot skin reaction	97%	3%	0%	100%	0%	0%
Hypomagnesaemia	97%	3%	0%	100%	0%	0%
Hyponatremia	97%	3%	0%	100%	0%	0%
Hypotension	100%	0%	0%	97%	3%	0%
Infection with grade 3–4 neutropenia	94%	6%	0%	100%	0%	0%
Leukopenia	71%	26%	3%	100%	0%	0%
Myalgia	100%	0%	0%	97%	3%	0%
Nausea	94%	6%	0%	100%	0%	0%
Neutropenia/granulocytopenia	52%	29%	19%	97%	3%	0%
PRBC transfusion	90%	10%	0%	100%	0%	0%
Platelet transfusion	94%	6%	0%	100%	0%	0%
Respiratory infection without neutropenia	97%	3%	0%	100%	0%	0%
Thrombocytopenia	61%	29%	10%	90%	10%	0%
Vomiting	97%	3%	0%	100%	0%	0%
Maximum grade any adverse event	29%	45%	26%	60%	37%	3%

[a] 10 of 15 events involved haematological toxicities and/or fatigue.
[b] All patients withdrew as a result of allergic reactions.
Abbreviation used in table: PLDH, pegylated liposomal doxorubicin hydrochloride.

Trabectedin plus PLDH versus PLDH alone

In OVA-301 (Monk *et al*. [2010][30]), safety was evaluated using NCI-CTC for adverse events and the safety analysis population included all randomly assigned patients who received one or more dose of trabectedin or PLDH. Deaths were summarized by treatment and primary cause. Nineteen patients died during treatment (8 in the PLDH group vs 11 in the trabectedin plus PLDH group). Twelve patients died (6 in each group) as a result of disease progression. One patient in the PLDH group and 5 patients in the trabectedin plus PLDH group died as a result of an adverse effect. The full publication presented the most common grade 3 to 4 adverse events, together with other adverse events of interest that were potentially related to treatment, which are presented in Table 63. Grade 3 and 4 haematologic adverse effects were more common in the trabectedin plus PLDH group compared with the PLDH alone group. The incidence of known toxicities associated with PLDH, such as hand-foot syndrome, stomatitis and mucosal inflammation, was lower in the trabectedin plus PLDH than the PLDH monotherapy arm, although the number of events was low in the combination group.

Table 63. Adverse effects as reported by Monk *et al*. (2010)[30]

Event	Trabectedin plus PLDH (N = 333)	PLDH alone (N = 330)
Death due to adverse event	5	1
Grade 4		
Haematologic		
Neutropenia	113 (33.9%)	28 (8.5%)
Leukopenia	28 (8.4%)	8 (2.4%)
Thrombocytopenia	27 (8.1%)	2 (0.6%)
Anaemia	10 (3.0%)	1 (0.3%)
Febrile neutropenia	8 (2.4%)	1 (0.3%)
Non-haematologic		
Hand foot syndrome	0	4 (1.2%)
Mucosal inflammation	0	0
Stomatitis	0	1 (0.3%)
Fatigue	1 (0.3%)	1 (0.3%)
Nausea	0	0
Vomiting	1 (0.3%)	0
AST increase	3 (0.9%)	1 (0.3%)
ALT increase	8 (2.4%)	0
Grade 3		
Haematologic		
Neutropenia	96 (28.8%)	46 (13.9%)
Leukopenia	82 (24.6%)	24 (7.3%)
Thrombocytopenia	34 (10.2%)	6 (1.8%)
Anaemia	31 (9.3%)	15 (4.5%)
Febrile neutropenia	15 (4.5%)	6 (1.8%)

Non-haematologic		
Hand foot syndrome	13 (3.9%)	61 (18.5%)
Mucosal inflammation	7 (2.1%)	19 (5.8%)
Stomatitis	3 (0.9%)	16 (4.8%)
Fatigue	19 (5.7%)	8 (2.4%)
Nausea	29 (8.7%)	8 (2.4%)
Vomiting	33 (9.9%)	7 (2.1%)
AST increase	21 (6.3%)	1 (0.3%)
ALT increase	95 (28.5%)	1 (0.3%)
Other events of interest (grade not stated)		
Alopecia	40 (12%)	44 (13%)
Alkaline phosphatase increase	68 (20%)	24 (7%)
Neuropathy	34 (10%)	24 (7%)
Bilirubin conjugated increase/ hyperbilirubinaemia	51 (15%)	18 (5%)
Abbreviations used in table: ALT, alanine transaminase; AST, aspartate transaminase; PLDH, pegylated liposomal doxorubicin hydrochloride.		

Pegylated liposomal doxorubicin hydrochloride versus topotecan

Gordon *et al*. (2001)[48] reported withdrawal rates due to adverse effects of 18% and 16% from the PLDH and topotecan groups, respectively. Almost all patients reported an adverse effect. The incidence of grade 1, 2, or 3 events was reported to be similar across the groups, but grade 4 events occurred more frequently in the topotecan group. Gordon *et al*.[48] note that the toxicity profiles of topotecan and PLDH were different, with PLDH associated with adverse effects of mild to moderate severity. The most common adverse effect in the PLDH group was severe PPE, with the difference between PLDH and topotecan reaching statistical significance ($p < 0.001$; Table 64). By contrast, incidence of severe (grade 3–4) haematologic toxicity was significantly higher with topotecan (neutropenia [$p < 0.001$] and leukopenia [$p < 0.001$]; Table 64).

TA91 presents additional data on adverse effects, reporting treatment-emergent adverse events that occurred in at least 10% of patients (Table 65).[13] TA91 identified statistically significant differences between PLDH and topotecan for various grade 3 events. Adverse effects that were significantly higher in the PLDH compared with the topotecan group were:

- mucous membrane disorder (RR 0.05, 95% CI: 0.006 to 0.56);
- stomatitis (RR 0.056, 95% CI: 0.01 to 0.31);
- PPE (RR 0.009, 95% CI: 0.001 to 0.087);
- rash (RR 0.11, 95% CI: 0.017 to 0.61).

By contrast, adverse effects that were significantly higher in the topotecan group compared with the PLDH group were:

- fever (RR 4.07, 95% CI: 1.00 to 16.82);
- anaemia (RR 4.62, 95% CI: 2.64, 8.16);
- leukopenia (RR 4.02, 95% CI: 2.6 to 6.27);
- neutropenia (RR 1.7, 95% CI: 1.04 to 3.00);
- thrombocytopenia (RR 13.56, 95% CI: 4.54 to 40.99);
- alopecia (RR 5.09, 95% CI: 1.60 to 16.27).

Although a larger proportion of patients treated with PLDH experienced grade 4 pain, stomatitis and PPE, the difference between PLDH and topotecan did not reach statistical significance for these outcomes.[13] By contrast, incidence of grade 4 fever, anaemia, leukopenia, neutropenia, and thrombocytopenia remained statistically significantly higher in the topotecan group compared with the PLDH group.

Table 64. Adverse effects as reported by Gordon *et al*. (2001)[48]

Event	**PLDH (N = 239)**		**Topotecan (N = 235)**	
Withdrawal due to PPE	9 (3.8%)		0	
Withdrawal due to sepsis	0		2 (0.8%)	
Withdrawal due to any adverse event	43 (18%)		37 (16%)	
Grade 4 adverse events	17.2%		71.1%	
	***All grades*[a]**	***Grade 3 or 4*[a]**	***All grades*[a]**	***Grade 3 or 4*[a]**
Neutropenia	84 (35%)	29 (12%)	191 (81%)	180 (77%)
Anaemia	85 (36%)	13 (5%)	169 (72%)	66 (28%)
Leukopenia	31 (13%)	24 (10%)	152 (65%)	117 (50%)
Thrombocytopenia	87 (36%)	3 (1%)	148 (63%)	80 (34%)
Alopecia	38 (16%)	3 (1%)	114 (49%)	14 (6%)
PPE	117 (49%)	55 (23%)	2 (1%)	0
Stomatitis	95 (40%)	20 (8%)	35 (15%)	1 (0.4%)

[a] For adverse effects reported by grade, p <0.001 for all effects, with the exception of grade 3–4 alopecia for which the p value is 0.007.

Abbreviations used in table: PLDH, pegylated liposomal doxorubicin hydrochloride; PPE, palmar–plantar erythrodysesthesia.

Table 65. Treatment-emergent adverse events that occurred in at least 10% of patients as reported in TA91[13]

Body system **Adverse event**	**PLDH** **(N = 239)**			**Topotecan** **(N = 235)**		
	All grades *n (%)*	*Grade 3* *n (%)*	*Grade 4* *n (%)*	*All grades* *n (%)*	*Grade 3* *n (%)*	*Grade 4* *n (%)*
Body as a whole						
Asthenia	96 (40.2%)	17 (7.1%)	0	121 (51.5%)	19 (8.1%)	0
Abdominal pain	80 (33.5%)	24 (10.0%)	1 (0.4%)	89 (37.9%)	19 (8.1%)	4 (1.7%)
Fever	51 (21.3%)	2 (0.8%)	0	72 (30.6%)	8 (3.4%)	5 (2.1%)
Pain	50 (20.9%)	4 (1.7%)	1 (0.4%)	40 (17.0%)	4 (1.7%)	0
Mucous membrane disorder	34 (14.2%)	9 (3.8%)	0	8 (3.4%)	0	0
Back pain	28 (11.7%)	4 (1.7%)	0	24 (10.2%)	2 (0.9%)	0
Infection	28 (11.7%)	5 (2.1%)	0	15 (6.4%)	2 (0.9%)	0
Headache	25 (10.5%)	2 (0.8%)	0	35 (14.9%)	0	0
Digestive system						
Nausea	110 (46.0%)	12 (5.0%)	1 (0.4%)	148 (63.0%)	16 (6.8%)	3 (1.3%)
Stomatitis	99 (41.4%)	19 (7.9%)	1 (0.4%)	36 (15.3%)	1 (0.4%)	0
Vomiting	78 (32.6%)	17 (7.1%)	2 (0.8%)	103 (43.8%)	18 (7.7%)	5 (2.1%)
Constipation	72 (30.1%)	6 (2.5%)	0	107 (45.5%)	11 (4.7%)	2 (0.9%)
Diarrhoea	50 (20.9%)	5 (2.1%)	1 (0.4%)	82 (34.9%)	9 (3.8%)	1 (0.4%)
Anorexia	48 (20.1%)	6 (2.5%)	0	51 (21.7%)	3 (1.3%)	0
Dyspepsia	29 (12.1%)	2 (0.8%)	0	33 (14.0%)	0	0
Intestinal obstruction	27 (11.3%)	19 (7.9%)	4 (1.7%)	26 (11.1%)	14 (6.0%)	7 (3.0%)
Haemic and lymphatic system						
Anaemia	96 (40.2%)	13 (5.4%)	1 (0.4%)	177 (75.3%)	59 (25.1%)	10 (4.3%)
Leukopenia	88 (36.8%)	21 (8.8%)	3 (1.3%)	151 (64.3%)	83 (35.3%)	36 (15.3%)
Neutropenia	84 (35.1%)	19 (7.9%)	10 (4.2%)	193 (82.1%)	33 (14.0%)	146 (62.1%)
Thrombocytopenia	31 (13.0%)	3 (1.3%)	0	153 (65.1%)	40 (17.0%)	40 (17.0%)
Metabolic/nutritional disorder						
Peripheral oedema	27 (11.3%)	5 (2.1%)	0	41 (17.4%)	6 (2.6%)	0
Nervous system						
Paresthesia	24 (10.0%)	0	0	21 (8.9%)	0	0
Dizziness	10 (4.2%)	0	0	24 (10.2%)	0	0
Respiratory system						
Pharyngitis	38 (15.9%)	0	0	42 (17.9%)	1 (0.4%)	0
Dyspnea	36 (15.1%)	8 (3.3%)	2 (0.8%)	55 (23.4%)	7 (3.0%)	3 (1.3%)
Cough increased	23 (9.6%)	0	0	27 (11.5%)	0	0
Skin and appendages						
PPE	121 (50.6%)	55 (23.0%)	2 (0.8%)	2 (0.9%)	0	0
Rash	68 (28.5%)	10 (4.2%)	0	29 (12.4%)	1 (0.4%)	
Alopecia[a]	46 (19.2%)	3 (1.3%)	0	123 (52.3%)	15 (6.4%)	0

[a] Grade 3 alopecia was reported. However, the NCI CTC lists criteria only for Grade1 and 2 alopecia.

Abbreviations used in table: PLDH, pegylated liposomal doxorubicin hydrochloride; PPE, palmar–plantar erythrodysesthesia.

Pegylated liposomal doxorubicin hydrochloride versus paclitaxel

TA91 reports that 16.7% (18/108) of patients in the PLDH group and 6.5% (7/108) of patients in the paclitaxel group discontinued treatment because of adverse effects.[13] The five most commonly reported treatment emergent adverse events associated with PLDH were nausea (51.9%), PPE (50.9%), stomatitis (48.1%), alopecia (43.5%), and asthenia (38.9%). In the paclitaxel group, the five most commonly reported adverse events were alopecia (87.0%), nausea (43.5%), paresthesia (43.5%), constipation (38.0%), and asthenia (33.3%).

The treatment emergent adverse events that occurred in at least 10% of participants in either treatment group for all grades, Grade 3 and Grade 4 are presented in Table 66. The incidence of Grade 4 events was low in each group, with neutropenia the only Grade 4 event occurring in both the PLDH and paclitaxel groups (0.9% with PLDH vs 2.8% with paclitaxel).

TA91 presented forest plots to illustrate the significance of the difference between groups. Grade 3 events occurring in a significantly smaller proportion of people in the paclitaxel group compared with the PLDH group to be (RR <1 indicates paclitaxel was associated with a lower rate of adverse event):

- PPE (0% with paclitaxel vs 14.8% with PLDH); RR 0.031 (95% CI: 0.003 to 0.297);
- stomatitis (0.9% with paclitaxel vs 10.2% with PLDH); RR 0.091 (95% CI: 0.02 to 0.53);

Alopecia was the only Grade 3 adverse effect occurring significantly more frequently with paclitaxel than with PLDH (18.5% with paclitaxel vs 2.8% PLDH; RR 6.67, 95% CI: 2.20 to 20.66; Table 66).

Table 66. Treatment-emergent adverse events in a least 10% of participants by preferred term for PLDH versus paclitaxel as reported in TA91

Adverse event classified by body system	PLDH			Paclitaxel		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
Asthenia	42 (38.9%)	4 (3.7%)	0	36 (33.3%)	6 (5.3%)	1 (0.9%)
Abdominal pain	34 (31.5%)	12 (11.1%)	0	35 (32.4%)	7 (6.5%)	0
Fever	28 (25.9%)	7 (6.5%)	0	8 (7.4%)	3 (2.8%)	0
Pain	24 (22.2%)	1 (0.9%)	0	24 (22.2%)	3 (2.8%)	0
Infection	23 (21.3%)	2 (1.9%)	1 (0.9%)	10 (9.3%)	1 (0.9%)	0
Headache	12 (11.1%)	1 (0.9%)	0	13 (12.0%)	2 (1.9%)	0
Ascites	11 (10.2%)	6 (5.6%)	0	8 (7.4%)	1 (0.9%)	0
Back pain	11 (10.2%)	1 (0.9%)	0	14 (13.0%)	1 (0.9%)	0
Cardiovascular system						
Vasodilation	5 (4.6%)	1 (0.9%)	0	13 (12.0%)	1 (0.9%)	0
Digestive system						
Nausea	56 (51.9%)	6 (5.6%)	1 (0.9%)	47 (43.5%)	2 (1.9%)	0
Stomatitis	52 (48.1%)	11 (10.2%)	0	12 (11.1%)	1 (0.9%)	0
Vomiting	37 (34.3%)	10 (9.3%)	2 (1.9%)	34 (32.5%)	4 (3.7%)	0
Constipation	30 (27.8%)	4 (3.7%)	0	41 (38.0%)	5 (4.6%)	0
Diarrhoea	23 (21.3%)	3 (2.8%)	0	24 (22.2%)	3 (2.8%)	0
Anorexia	18 (16.7%)	1 (0.9%)	0	11 (10.2%)	0	0
Dyspepsia	14 (13.0%)	1 (0.9%)	0	11 (10.2%)	0	0
Haemic and lymphatic system						
Neutropenia	18 (16.7%)	6 (5.6%)	1 (0.9%)	23 (21.3%)	10 (9.3%)	3 (2.8%)
Anaemia	17 (15.7%)	3 (2.8%)	0	23 (21.3%)	5 (4.6%)	0
Leukopenia	15 (13.9%)	5 (4.6%)	1 (0.9%)	21 (19.4%)	9 (8.3%)	0
Metabolic/nutritional disorder						
Peripheral oedema	14 (13.0%)	0	0	15 (13.9%)	1 (0.9%)	0
Musculoskeletal system						
Myalgia	4 (3.7%)	1 (0.9%)	0	31 (28.7%)	7 (6.5%)	0
Arthralgia	2 (1.9%)	0	0	23 (21.3%)	2 (1.9%)	0
Nervous system						
Paresthesia	15 (13.9%)	0	0	47 (43.5%)	4 (3.7%)	0
Somnolence	11 (10.3%)	3 (2.8%)	0	17 (15.7%)	2 (1.9%)	0
Respiratory system						
Dyspnea	18 (16.7%)	6 (5.6%)	1 (0.9%)	15 (13.9%)	1 (0.9%)	0
Pharyngitis	8 (7.4%)	0	0	18 (16.7%)	0	0
Skin and appendages						
PPE	55 (50.9%)	16 (14.8%)	1 (0.9%)	13 (12.0%)	0	0
Alopecia	47 (43.5%)	3 (2.8%)	0	94 (87.0%)	20 (18.5%)	1 (0.9%)
Rash	15 (13.9%)	2 (1.9%)	0	19 (17.6%)	1 (0.9%)	0

Abbreviations used in table: PLDH, pegylated liposomal doxorubicin hydrochloride; PPE, Palmar–plantar erythrodysesthesia.

Topotecan versus paclitaxel

ten Bokkel Huinink *et al*.[21] evaluated adverse effects according to the NCI-CTC. There were 2 treatment-related deaths in the topotecan group, which were attributed to topotecan-induced sepsis. There were no treatment-related deaths in the paclitaxel group. Ten patients (7 in the topotecan group vs 4 in the paclitaxel group) discontinued treatment as a result of an adverse effect. Febrile neutropenia, infection and sepsis were the causes of withdrawal from the topotecan group, whereas discontinuations from the paclitaxel group were as a result of neurotoxicity. Severe (grade 3–4) haematological adverse effects predominantly occurred more frequently in the topotecan group than in the paclitaxel group, with differences between groups in grade 4 leukopenia, neutropenia, and thrombocytopenia reaching statistical significance (Table 67). The only haematological adverse effect that occurred more frequently in paclitaxel-treated patients was grade 3 neutropenia (Table 67).

Most non-haematological adverse effects were mild to moderate in severity (grade 1–2). The most frequently reported adverse effects considered related or possibly related to treatment in both groups were alopecia and gastrointestinal disturbances, including nausea, vomiting, diarrhoea, and constipation (Table 67). A larger proportion of patients in the paclitaxel group experienced alopecia than in the topotecan group. Mild to moderate nausea, vomiting, and constipation occurred more frequently in the topotecan group. By contrast, more patients in the paclitaxel group experienced mild to moderate diarrhoea.

Table 67. Adverse effects as reported by ten Bokkel Huinink *et al*.[21]

Event	**Topotecan (N = 112)**		**Paclitaxel (N = 114)**	
Withdrawal for adverse event	7 (7%)		3 (4%)	
Death due to sepsis/ myelosuppression	2		0	
Haematological				
Grade 3–4				
	Grade 3 (%)	*Grade 4 (%)*	*Grade 3 (%)*	*Grade 4 (%)*
Leukopenia[a]	50.9%	33.6%	17.9%	2.7%
Neutropenia[a]	15.3%	79.3%	28.6%	23.2%
Thrombocytopenia[a]	24.3%	25.2%	0.9%	1.8%
Anaemia	36.9%	3.6%	3.6%	2.7%
Non-haematological[b]				
	Grade1–2 (%)	*Grade 3–4 (%)*	*Grade1–2 (%)*	*Grade 3–4 (%)*
Alopecia	75.9	0	92.1	0.9
Nausea	67.9	9.8	43.0	1.8
Vomiting	53.6	9.9	28.1	2.7
Fatigue	33.1	8.0	25.4	6.1
Constipation	37.5	5.4	30.7	0

Diarrhoea	33.9	6.3	37.8	0.9
Abdominal pain	21.5	5.4	36.0	3.5
Fever (excludes febrile neutropenia)	27.7	0.9	17.7	0
Stomatitis	23.2	0.9	14.0	0.9
Dyspnoea	17.8	6.3	13.2	5.3
Asthenia	17.0	5.4	9.6	3.5
Arthralgia	5.5	0.9	28.9	2.6
Myalgia	3.6	0	25.4	2.6
Neuropathy	0.9	0	15.8	0
Skeletal pain	4.5	0	11.4	5.3
Flushing	4.5	0	14.1	0
Paresthesia	0.9	0	29.0	0

[a] p <0.001 for grade 4 events.

[b] Reported non-haematological adverse effects are those categorised as related or possibly related to treatment and occurring in more than 10% of patients treated with topotecan or paclitaxel.

Gemcitabine plus carboplatin versus carboplatin alone

In the trial reported by Pfisterer *et al*.[49], grade 3-4 haematologic toxicities were significantly more frequent in the gemcitabine plus carboplatin group than in the carboplatin alone group, with neutropenia the predominant haematological toxicity (Table 68). The proportion of patients discontinuing treatment as a result of a haematological adverse event was small in each group (5.1% with gemcitabine plus carboplatin vs 4.0% with carboplatin alone). Grade 3-4 non-haematologic adverse events were infrequent in each group, with less than 5% of patients in each group experiencing a non-haematological toxicity reported in the full publication (Table 68). Grade 2 alopecia occurred in 14.3% patients treated with gemcitabine plus carboplatin patients compared with 2.3% of patients treated with of carboplatin alone (statistical significance of result not reported). Adverse events were graded according to the NCI-CTC guidance.

Table 68. Adverse effects as reported by Pfisterer *et al*.[49]

Event	Gemcitabine plus carboplatin (N = 175)		Carboplatin alone (N = 174)		p-value (grades 3 and 4 together)
	Grade 3	Grade 4	Grade 3	Grade 4	
Haematologic					
Anaemia	39 (22.3%)	9 (5.1%)	10 (5.7%)	4 (2.3%)	<0.001
Neutropenia	73 (41.7%)	50 (28.6%)	19 (10.9%)	2 (1.1%)	<0.001
Thrombocytopenia	53 (30.3%)	8 (4.6%)	18 (10.3%)	2 (1.1%)	<0.001
Non-haematologic					
Hypersensitivity	3 (1.7%)	1 (0.6%)	3 (1.7%)	2 (1.1%)	0.7503
Diarrhoea	3 (1.7%)	0	0	0	0.2479
Dyspnoea	2 (1.1%)	0	2 (1.1%)	1 (0.6%)	0.6848
Fatigue	3 (1.7%)	1 (0.6%)	3 (1.7%)	0	0.99
Febrile neutropenia	2 (1.1%)	0	0	0	0.4986
Infection without neutropenia	0	1 (0.6%)	0	0	0.99
Infection with neutropenia	0	0	0	0	–
Neuropathy (motor)	1 (0.6%)	0	0	0	0.99
Neuropathy (sensory)	2 (1.1%)	0	3 (1.7%)	0	0.6848
Vomiting	5 (2.9%)	0	2 (1.1%)	1 (0.6%)	0.7234
	Grade 1	Grade 2	Grade 1	Grade 2	
Haematologic					
Anaemia	32 (18.3%)	73 (41.7%)	71 (40.8%)	44 (25.3%)	–
Neutropenia	9 (5.1%)	27 (15.4%)	44 (25.3%)	33 (19.0%)	–
Thrombocytopenia	41 (23.4%)	36 (20.6%)	66 (37.9%)	14 (8.0%)	–
Non-haematologic					
Hypersensitivity	1 (0.6%)	4 (2.3%)	3 (1.7%)	2 (1.1%)	–
Diarrhoea	16 (9.1%)	7 (4.0%)	7 (4.0%)0	6 (3.4%)	–
Dyspnoea	1 (0.6%)	12 (6.9%)0	2 (1.1%)	4 (2.3%)	–
Fatigue	29 (16.6%)	35 (20.0%)	25 (14.4%)	23 (13.2%)	–
Febrile neutropenia	0	0	0	0	–
Infection without neutropenia	1 (0.6%)	1 (0.6%)	1 (0.6%)	1 (0.6%)	–
Infection with neutropenia	1 (0.6%)	0	0	1 (0.6%)	–
Neuropathy (motor)	9 (5.1%)	1 (0.6%)	6 (3.4%)	1 (0.6%)	–
Neuropathy (sensory)	43 (24.6%)	7 (4.0%)	38 (21.8%)	6 (3.4%)	–
Vomiting	41 (23.4%)	28 (16.0%)	32 (18.4%)	1 (0.6%)	–
Alopecia[a]	61 (34.9%)	25 (14.3%)	27 (15.5%)	23 (13.2%)	–

[a] Alopecia graded as 1 or 2 as authors comment that grade 3 or 4 is not recognised by NCI-CTC version 2.0 and later.

Paclitaxel plus carboplatin versus platinum-based therapy alone

In ICON4/AGO-OVAR2.2, paclitaxel plus platinum-based therapy was associated with higher rates of alopecia compared with conventional platinum-based therapy alone (322/392 [86%] with paclitaxel plus platinum-based chemotherapy vs 95/410 [25%] with conventional platinum-based therapy; Table 69).[60] Additionally, the proportion of patients experiencing a grade 2–4 neurological toxicity was higher in the paclitaxel plus platinum chemotherapy group (76/392 [20%]) compared with the conventional platinum-based therapy (4/410 [1%]). By contrast, incidence of moderate or severe (grade 2–4) haematological adverse effects was higher in the conventional platinum-based therapy group.

Table 69. Adverse effects as reported in ICON4/AGO-OVAR 2.2[60]

Event	Paclitaxel plus platinum chemotherapy (N = 392)	Conventional platinum-based chemotherapy (N = 410)
"Moderate or severe": neurological (grade 2–4)	76 (20%)	4 (1%)
Not yet known	15	31
Haematological	111 (29%)	182 (46%)
Not yet known	8	16
Infection	64 (17%)	53 (14%)
Not yet known	15	24
Renal	31 (8%)	37 (9%)
Not yet known	8	16
Mucositis (grade 2–3)	26 (7%)	21 (6%)
Not yet known	15	31
Nausea and vomiting (grade 2–4)	131 (35%)	153 (40%)
Not yet known	15	29
Alopecia (grade 2–4)	322 (86%)	95 (25%)
Not yet known	28	19

Gonzalez-Martin *et al*.[47] based the safety analysis on 78 patients who received at least one cycle of treatment. Adverse effects were graded according to NCI-CTC criteria. Grade 3–4 haematological toxicity was similar between the groups. Although severe neutropenia (grade 3–4) was more common in the paclitaxel plus carboplatin group, the difference between groups was not statistically significant ($p = 0.24$; Table 70). Treatment with paclitaxel plus carboplatin was associated with a higher incidence of grade 2–4 non-haematological adverse effects, with significantly higher incidences of alopecia, mucositis, myalgia/arthralgia and peripheral neuropathy compared with treatment with carboplatin alone (Table 70).

Table 70. Incidence of adverse effects in the trial reported by Gonzalez-Martin *et al*.[47]

Event	Carboplatin (N = 40)						Paclitaxel plus carboplatin (N = 38)						p-value
	NCI CTC Grade						NCI CTC Grade						
Haematological													
	0	*1*	*2*	*3*	*4*	*3–4*	*0*	*1*	*2*	*3*	*4*	*3–4*	
Leukopenia	17	16	6	1	–	1 (2.5)	19	11	6	2	–	2 (5.3)	0.93
Neutropenia	13	11	12	3	1	4 (10.0)	16	7	8	6	1	7 (18.4)	0.24
Thrombocytopenia	8	17	10	3	2	5 (12.5)	20	12	5	1	–	1 (2.6)	0.25
Anaemia	4	20	10	5	1	6 (15.0)	8	20	8	2	–	2 (5.3)	0.33
Non-haematological													
	0	*1*	*2*	*3*	*4*	*2–4*	*0*	*1*	*2*	*3*	*4*	*2–4*	
Allergy	33	4	3	1	–	4 (10)	28	4	2	3	1	6 (15.8)	–
Alopecia	30	3	7	–	–	7 (17.5)	5	–	11	22	–	33 (86.8)	0.001
Fever	36	4	–	–	–	–	34	2	2	–	–	2 (5.3)	
Infection	39	–	–	1	–	1 (2.5)	33	3	1	1	–	2 (5.3)	
Haemorrhage	36	4	–	–	–	–	36	2	–	–	–	–	
Nausea	13	15	12	–	–	12 (30.0)	17	15	6	–	–	6 (15.8)	
Vomiting	21	9	6	4	–	10 (25.0)	24	9	4	1	–	5 (13.2)	
Stomatitis/mucositis	37	3	–	–	–	–	27	4	7	–	–	7 (18.4)	0.004
Diarrhoea	34	5	1	–	–	1 (2.5)	35	2	1	–	–	1 (2.6)	
Constipation	27	10	3	–	–	3 (7.5)	25	10	3	–	–	3 (7.9)	
Creatinine	35	4	1	–	–	1 (2.5)	36	1	1	–	–	1 (2.6)	
Pulmonary (dyspnoea)	38	1	1	–	–	1 (2.5)	35	1	1	1	–	2 (5.3)	
Neurosensory	34	6	–	–	–	–	17	12	9	–	–	9 (23.7)	0.009
Myalgias/arthralgias	39	1	–	–	–	–	15	9	12	2	–	14 (36.8)	0.001
Mood depression	39	–	1	–	–	1 (2.5)	36	1	–	1	–	1 (2.6)	
Asthenia	20	10	10	–	–	10 (25.0)	16	11	9	2	–	11 (28.9)	
Anorexia	35	1	3	1	–	4 (10.0)	35	2	1	–	–	1 (2.6)	
Abbreviation used in table: NCI CTC, National Cancer Institute Common Toxicity Criteria.													

Paclitaxel plus carboplatin versus paclitaxel alone

In the trial reported by Lortholary *et al*.[61], one patient randomised to treatment with weekly paclitaxel did not receive a dose of study drug and was therefore not included in the safety analysis. No deaths were categorised as treatment-related. Non-haematological toxicity was similar between treatment

groups, with the exception of hypersensitivity reactions, which occurred more frequently with combination treatment compared with weekly paclitaxel alone (Table 71). A larger proportion of patients treated with weekly paclitaxel plus carboplatin experienced grade 3–4 leukopenia and neutropenia. Discontinuation rate because of adverse effects was also higher in the group receiving combination therapy (Table 71). No patient in the weekly paclitaxel group discontinued treatment because of haematological toxicity, whereas 14% in the weekly paclitaxel plus carboplatin group discontinued treatment for this reason.

Table 71. Adverse effects as reported by Lortholary *et al*.[61]

Event	Weekly paclitaxel plus carboplatin (N = 51)	Weekly paclitaxel (N = 57)
Withdrawal for toxicity	29%	2%
Withdrawal for haematological toxicity	14%	0
Grade 3–4		
Leukopenia	31%	7%
Neutropenia	54%	13%
Febrile neutropenia	4%	0
Anaemia	19%	6%
Thrombocytopenia	4%	2%
Grade 2–4		
Hypersensitivity	16%	2%
Peripheral neuropathy	20%	32%
Vomiting	20%	17%
Fatigue	61%	59%
Mucositis (Grade 2)	6%	7%
Alopecia (Grade 2)	46%	33%

Paclitaxel versus oxaliplatin

Piccart *et al*.[62] reported safety analysis based on all 86 patients randomised: all patients had received at least one treatment cycle and were assessable for the safety analysis. Only grade 3 and grade 4 adverse events were reported (presented in Table 72), with grade assigned according to NCI-CTC. Considering haematological toxicities, severe neutropenia (grade 3-4) occurred only in the paclitaxel group (9/41 [22%]), whereas grade 3 thrombocytopenia was reported only in the oxaliplatin group (2/45 [4%]). Severe anaemia was rare, and no episodes of febrile neutropenia were observed. Of the non-haematological adverse events reported, the number of patients experiencing an adverse event was low in each group. No episodes of grade 4 nausea and vomiting were reported. The most frequently reported non-haematological adverse effect was pain, with 12% (5/41) and 4% (2/45) of patients in the paclitaxel and oxaliplatin groups, respectively, experiencing a grade 3 pain event (Table 72). The proportion of patients experiencing a grade 3 neurosensory adverse event was similar between the two treatment groups (7% with paclitaxel vs 9% with oxaliplatin; Table 72).

Table 72. Adverse effects as reported by Piccart *et al*.[62]

Event	Paclitaxel (N = 41)		Oxaliplatin (N = 45)	
	Grade 3	*Grade 4*	*Grade 3*	*Grade 4*
Hematologic				
Neutropenia	6 (15%)	3 (7%)	—	—
Anaemia	—	1 (2%)	1 (2%)	—
Thrombocytopenia	—	—	2 (4%)	—
Liver function				
AST	—	—	—	—
ALT	2 (5%)	—	—	—
Gastrointestinal				
Nausea	1 (2%)	NA	2 (4%)	NA
Vomiting	1 (2%)	—	3 (7%)	—
Diarrhoea	—	—	2 (4%)	—
Neurosensory	3 (7%)	NA	4 (9%)	NA
Other				
Lethargy	3 (7%)	NA	3 (7%)	NA
Pain	5 (12%)	—	2 (4%)	—
Abbreviations used in table: ALT, alanine transaminase; AST, aspartate transaminase.				

Topotecan oral versus topotecan intravenous

Gore *et al*.[24] reported that neutropenia and leukopenia were the most common haematological toxicities occurring in both treatment groups, although the rate of both adverse events was higher in the group receiving topotecan intravenously rather than orally (Table 73). Seven deaths were attributed to haematological toxicity, two in the oral treatment group and five in the intravenous treatment group. A similar proportion of patients in each group developed Grade 3–4 thrombocytopenia or anaemia. Gastrointestinal disturbances were the most common non-haematological toxicity, with most events reported as mild to moderate in severity. Incidence of gastrointestinal adverse effects was higher in the oral topotecan group (Table 73). Grade 3–4 non-haematological toxicities generally occurred in less than 10% of patients. Incidence of grade 3–4 nausea, diarrhoea, vomiting, and fever was marginally higher in patients treated with oral topotecan compared with intravenous topotecan (Table 73).

Table 73. Adverse effects as reported by Gore *et al*.[24]

Event	Oral topotecan (N = 135)		Intravenous topotecan (N = 131)	
Deaths due to haematological toxicity	2		5	
Haematological				
	Grade 3	*Grade 4*	*Grade 3*	*Grade 4*
Patients				
Neutropenia	40 (30%)	67 (50%)	15 (11%)	110 (84%)
Anaemia	51 (38%)	5 (4%)	43 (33%)	10 (8%)
Leukopenia	59 (44%)	28 (21%)	78 (60%)	40 (31%)
Thrombocytopenia	30 (22%)	27 (20%)	27 (21%)	23 (18%)
Courses	N = 729		N = 778	
Neutropenia	190 (26%)	106 (15%)	249 (32%)	393 (51%)
Anaemia	163 (22%)	31 (4%)	371 (48%)	68 (9%)
Leukopenia	70 (10%)	42 (6%)	90 (12%)	29 (4%)
Thrombocytopenia	85 (12%)	7 (1%)	78 (10%)	10 (1%)
Non-haematological				
	All grades	*Grade 3–4*	*All grades*	*Grade 3–4*
Patients				
Nausea	92 (68%)	12 (9%)	80 (61%)	6 (5%)
Diarrhoea	76 (56%)	13 (10%)	40 (31%)	6 (5%)
Vomiting	74 (55%)	10 (7%)	52 (40%)	4 (3%)
Alopecia	72 (53%)	10 (7%)	68 (52%)	8 (6%)
Fatigue	50 (37%)	5 (4%)	50 (38%)	5 (4%)
Abdominal pain	49 (36%)	9 (7%)	39 (30%)	9 (7%)
Constipation	47 (35%)	4 (3%)	42 (32%)	7 (5%)
Fever	38 (28%)	14 (10%)	31 (24%)	7 (5%)

Topotecan administered on 5 consecutive days (conventional regimen) versus topotecan administered weekly

Sehouli *et al*.[23] report that, of the 194 patients randomised, five patients did not receive any dose of study drug, which differs slightly from the number reported in the CONSORT diagram (2 patients in each group). The methods state that all analyses are based on the ITT principle. However, it is unclear from the reporting of the adverse effects whether all patients have been analysed. It should be noted that, although the comparator is referred to as conventional topotecan, the dose administered in this group is 1.25 mg/m^2 for 5 consecutive days compared with the licensed dose of 1.5 mg/m^2.

Compared with the conventional dosing schedule, weekly topotecan was associated with significantly fewer episodes of severe (grade 3–4) haematological events (anaemia, leukopenia, neutropenia, and

thrombocytopenia; Table 74). Incidence of severe non-haematological events was low in each group, with no difference between groups reaching statistical significance (Table 74).

Table 74. Adverse effects as reported by Sehouli *et al*.[23]

Event	Topotecan weekly (N = 97)	Topotecan conventional (N = 97)	p-value
Grade 3–4			
Anaemia	7 (7.2%)	20 (20.6%)	0.007
Leukopenia	13 (13.4%)	56 (57.7%)	<0.001
Neutropenia	15 (15.5%)	39 (40.2%)	<0.001
Lymphopenia	1 (1.0%)	5 (5.2%)	0.097
Thrombocytopenia	5 (5.2%)	22 (22.7%)	<0.001
Febrile neutropenia	1 (1.0%)	4 (4.1%)	0.174
Fever	0	1 (1.0%)	0.316
Infection	5 (5.1%)	4 (4.1%)	0.733
Nausea	1 (1.0%)	5 (5.2%)	0.097
Vomiting	4 (4.1%)	3 (3.1%)	0.700
Diarrhoea	1 (1.0%)	1 (1.0%)	1.000
Constipation	2 (2.1%)	3 (3.1%)	0.650
Ileus	7 (7.2%)	7 (7.2%)	1.000
Fatigue	10 (10.3%)	6 (6.2%)	0.296
Motor neuropathy	1 (1.0%)	0	0.316
Sensory neuropathy	1 (1.0%)	0	0.316
Pain	12 (12.4%)	6 (6.2%)	0.138
Pleural effusion	2 (2.1%)	1 (1.0%)	0.561
Pneumonia	1 (1.0%)	1 (1.0%)	1.000
Dyspnoea	5 (5.2%)	2 (2.1%)	0.248

Paclitaxel high dose (250 mg/m^2) versus paclitaxel standard dose (175 mg/m^2)

Omura *et al*.[66] reported that febrile neutropenia was the most commonly observed severe toxicity. After the first cycle of therapy, the incidence of neutropenic fever did not differ significantly between:

- patients receiving paclitaxel 175 mg/m^2 (without filgrastim) and those assigned to paclitaxel 250 mg/m^2 with filgrastim (22% paclitaxel 175 mg/m^2 and no filgrastim vs 19% with paclitaxel 250 mg/m^2 and filgrastim; p value not reported);
- filgrastim 10 μg/kg and filgrastim 5 μg/kg among women receiving paclitaxel 250 mg/m^2 (19% with 5 μg/kg filgrastim vs 18% with 10 μg/kg filgrastim; 95% CI –11% to 13%, no point estimate reported).

Patients receiving the higher paclitaxel dose (250 mg/m^2) reported a numerically greater incidence of anaemia, thrombocytopenia, nausea and vomiting, neuropathy and myalgia/arthralgia than those receiving paclitaxel 175 mg/m^2. The difference between groups was statistically significant for thrombocytopenia (15% with 250 mg/m^2 vs 7% with 175 mg/m^2; p = 0.009), neuropathy (16% with

250 mg/m^2 vs 7% with 175 mg/m^2; p = 0.024) and myalgia/arthralgia (10% with 250 mg/m^2 vs 3% with 175 mg/m^2; p = 0.022). Adverse effects as reported in Omura *et al*.[66] are summarised in Table 75.

Table 75. Incidence of grade 3 or 4 toxicity other than neutropenia as reported in Omura *et al*.[66]

Adverse effect	Paclitaxel regimen		p-value
	175 mg/m^2 (%)	250 mg/m^2 + filgrastim (%)	
Anaemia	7	15	0.102
Thrombocytopenia	5	15	0.009
Nausea and vomiting	5	10	0.211
Neuropathy	7	16	0.024
Myalgia/arthralgia	3	10	0.022

Paclitaxel weekly versus paclitaxel every 3 weeks

Of the 208 patients randomised in the trial reported by Rosenberg *et al*.[59], 205 received at least one dose of paclitaxel and were included in the safety analysis. No treatment-related deaths occurred in the trial. Considering haematological adverse effects, paclitaxel given every 3 weeks was associated with a significantly higher incidence of severe neutropenia (grade 3–4) compared with the once weekly regimen (19/104 [18%] with paclitaxel weekly vs 45/101 [45%] with paclitaxel every 3 weeks; p = <0.001; Table 76). Of the other haematological adverse effects assessed, number of episodes of severe anaemia, leukopenia and thrombocytopenia were similar between the two treatment groups, with none of the differences between groups reaching statistical significance. However, assessment of haematological toxicities of grade 1–4 identified a statistically significantly higher incidence of anaemia in patients treated with paclitaxel weekly compared with every 3 weeks (81/104 [78%] with paclitaxel weekly vs 65/101 [64%] with paclitaxel every 3 weeks; p = 0.04; Table 76). The difference between groups in neutropenia remained significant and favoured paclitaxel weekly (i.e., smaller proportion of patients experienced an event; Table 76).

No grade 4 non-haematological adverse effects were reported. Grade 1–3 non-haematological adverse effects were common, with high incidences of neuropathy, alopecia and arthralgia/myalgia (Table 76). The difference between the two paclitaxel regimens in neuropathy and in alopecia was not statistically significant. However, paclitaxel every 3 weeks was associated with a significantly higher incidence of arthralgia/myalgia compared with the weekly regimen (61/104 [59%] with paclitaxel weekly vs 85/101 [84%] with paclitaxel every 3 weeks; p = 0.04; Table 76). A larger proportion of patients treated with weekly paclitaxel experienced problems with their nails (discolouration and/or loosening from the nail bed) compared with patients treated every 3 weeks (37/104 [36%] with paclitaxel weekly vs 2/101 [2%] with paclitaxel every 3 weeks; p <0.001; Table 76). Considering only grade 3 non-haematological events, episodes of grade 3 neuropathy and grade 3 alopecia were significantly

higher in the paclitaxel every 3 weeks regimen compared with the weekly regimen (Table 76). Problems with nail changes remained significantly more common in the paclitaxel weekly group. Incidence of nausea/vomiting and of arthralgia/myalgia was similar in each group, with no statistically significant difference between the two treatment groups (Table 76).

Table 76. Adverse effects as reported by Rosenberg *et al*.[59]

Event	Paclitaxel weekly (N = 104)	Paclitaxel 3 weekly (N = 101)	p-value
Withdrawals due to toxicity	1	4	Not reported
Haematological toxicity			
Grade 3–4			
Anaemia (haemoglobin)	4 (4%)	4 (4%)	1.0
Leukopenia (WBC)	17 (16%)	17 (17%)	1.0
Neutropenia (neutrophils)	19 (18%)	45 (45%)	<0.001
Thrombocytopenia (platelets)	0	1 (1%)	0.49
Grade 1–4			
Anaemia	81 (78%)	65 (64%)	0.04
Leukopenia	74 (71%)	79 (78%)	0.27
Neutropenia	63 (61%)	80 (79%)	<0.01
Thrombocytopenia	1 (1%)	5 (5%)	0.12
Non-haematological			
Grade 3			
Neuropathy	11 (11%)	29 (29%)	<0.001
Alopecia	48 (46%)	80 (79%)	<0.001
Arthralgia/myalgia	5 (5%)	8 (8%)	0.40
Nausea/vomiting	4 (4%)	3 (3%)	1.0
Nails	9 (9%)	0	<0.01
Grade 1–3			
Neuropathy	84 (81%)	86 (85%)	0.72
Alopecia	85 (82%)	91 (90%)	0.11
Arthralgia/myalgia	61 (59%)	85 (84%)	<0.001
Nausea/vomiting	48 (46%)	42 (42%)	0.57
Nails	37 (36%)	2 (2%)	*<0.001*
Abbreviation used in table: WBC, white blood count.			

Network meta-analysis

For the NMA, studies that reported combined grades of adverse events (e.g. grades 2–4, including grades 3 and 4) were excluded from the analysis. Where data were reported separately for vomiting and nausea in the same study, this was combined for the purposes of the analysis, as were data on neurosensory events. It is acknowledged that this might have led to double-counting. For trials that specified they would record all adverse events, events rates of zero were not imputed; only data reported in the papers were used to inform the analysis. Network diagrams for the adverse events analysed in the NMA are presented in Appendix 4.

To give focus to the evaluation of adverse events the TAG consulted with its expert clinical advisors and identified the following severe adverse events (grade 3–4) as those most problematic for patients or most likely to consume substantial health care resource:

- allergic reaction;
- alopecia;
- anaemia;
- fatigue;
- febrile neutropenia;
- nausea and vomiting;
- neuropathy.

The treatments evaluated for these serious adverse events are as follows:

- gemcitabine plus carboplatin;
- platinum monotherapy;
- PLDH monotherapy;
- PLDH plus carboplatin;
- paclitaxel monotherapy; that is, 175mg/m^2 or 200 mg/m^2 every 21 days;
- paclitaxel monotherapy (weekly); that is, paclitaxel 67 mg/m^2 every week for 21 days;
- topotecan monotherapy (IV); that is, topotecan 1.25 or 1.5 mg/m^2 daily for 5 days every 21 days;
- topotecan monotherapy (oral);
- topotecan monotherapy (IV, weekly); that is, topotecan 4.0 mg/m^2 (weekly) on days 1, 8, and 15 of a 28-day cycle.

Unlike the efficacy outcomes reported earlier, the evaluation of severe adverse events is based on the total population regardless of PFI. That is, it is not broken down by the various subgroups based on platinum sensitivity (or insensitivity). However, for consistency the baseline treatment for each network assessed are consistent with the efficacy analyses.

Allergic reaction

The absolute numbers for the RCTs included in the NMA evaluating allergic reaction in patients with recurrent ovarian cancer are reported in Section 4.1.7.2. Unfortunately, as described earlier, a single network could not be constructed out of the available trials. The two networks constructed for this outcome are depicted in Appendix 4.

The results from this NMA are presented in Table 77. Overall, only PLDH plus carboplatin was found to have significantly less risk of an allergic reaction (at the 5% level) than paclitaxel plus carboplatin. PLDH plus carboplatin is also associated with significantly less risk of allergic reaction than platinum

as monotherapy. No other comparison of chemotherapies was found to have a statistically significant difference.

As only one trial[61] provided data on this adverse event for network 2 it was not possible to conduct an NMA. Lortholary *et al.*[61] compared low dose paclitaxel (80 mg/m^2) with low dose paclitaxel (80 mg/m^2) plus carboplatin. Low dose paclitaxel was found to have significantly less risk of causing an allergic reaction than paclitaxel plus carboplatin (OR 0.114, 95% CI: 0.014 to 0.942).

Table 77. Results of the network meta-analysis for allergic reaction for people with recurrent ovarian cancer

Comparison	OR	95% CrI	
		Lower limit	Upper limit
Network 1			
Versus paclitaxel plus carboplatin (OR <1 favours comparator, OR >1 favours paclitaxel plus carboplatin)			
Platinum monotherapy	0.755	0.057	3.043
PLDH plus carboplatin	0.130	0.001	0.705
Gemcitabine plus carboplatin	0.757	0.030	3.798
Versus platinum as a monotherapy (OR <1 favours comparator, OR >1 favours gemcitabine plus carboplatin)			
PLDH plus carboplatin	0.213	0.004	0.965
Gemcitabine plus carboplatin	0.997	0.183	3.091
Versus PLDH plus carboplatin (OR <1 favours comparator, OR >1 favours PLDH plus carboplatin)			
Gemcitabine plus carboplatin	6.680	0.495	242.200
Abbreviations used in table: CrI, Credible Interval; OR, odds ratio; PLDH, pegylated liposomal doxorubicin hydrochloride.			

Alopecia

The absolute numbers for the RCTs included in the NMA evaluating alopecia in patients with recurrent ovarian cancer are reported in Section 4.1.7.2. Unfortunately, as described earlier, a single network could not be constructed out of the available trials. The two networks constructed for this outcome are depicted in Appendix 4.

As only one trial[29] provided data on this adverse event for network 1 it was not possible to conduct an NMA. Bafaloukos *et al.*[29] compared PLDH plus carboplatin to paclitaxel plus carboplatin. PLDH plus carboplatin was found to have significantly less risk of causing alopecia than paclitaxel plus carboplatin (OR 0.235, 95% CI: 0.077 to 0.724).

The results for the NMA of network 2 are presented in Table 78. Overall, all chemotherapies assessed were found to have a significantly higher risk of alopecia (at the 5% level) than PLDH monotherapy. Paclitaxel monotherapy was also found to have a significantly higher risk of alopecia than paclitaxel

monotherapy (weekly). No other comparison of chemotherapies was found to have a statistically significant difference.

Table 78. Results of the network meta-analysis for alopecia for people with recurrent ovarian cancer

Comparison	OR	95% CrI	
		Lower limit	Upper limit
Versus PLDH monotherapy (OR <1 favours comparator, OR >1 favours PLDH monotherapy)			
Topotecan monotherapy (IV)	6.099	1.578	18.780
Topotecan monotherapy (oral)	8.621	1.344	31.990
Paclitaxel monotherapy (weekly)	3.512	0.643	12.920
Paclitaxel monotherapy	15.160	3.444	52.790
Versus topotecan monotherapy (IV) (OR <1 favours comparator, OR >1 favours topotecan IV monotherapy (IV))			
Topotecan monotherapy (oral)	1.415	0.467	3.390
Paclitaxel monotherapy	0.841	0.081	3.584
Paclitaxel monotherapy (weekly)	3.623	0.409	14.760
Versus topotecan monotherapy (oral) (OR <1 favours comparator, OR >1 favours topotecan oral monotherapy (oral))			
Paclitaxel monotherapy	0.770	0.050	3.648
Paclitaxel monotherapy (weekly)	3.312	0.249	15.130
Versus paclitaxel monotherapy (OR <1 favours comparator, OR >1 favours paclitaxel monotherapy)			
Paclitaxel monotherapy (weekly)	4.766	2.467	8.489
Abbreviations used in table: CrI, Credible Interval; OR, odds ratio; PLDH, pegylated liposomal doxorubicin hydrochloride.			

Anaemia

The absolute numbers for the RCTs included in the NMA evaluating anaemia in patients with recurrent ovarian cancer are reported in Section 4.1.7.2. Unfortunately, as described earlier, a single network could not be constructed out of the available trials. The two networks constructed for this outcome are depicted in Appendix 4.

The results the NMA from Network 1 are presented in Table 79. Overall, PLDH plus carboplatin and gemcitabine plus carboplatin were found to have significantly higher risk of anaemia (at the 5% level) than paclitaxel plus carboplatin. Gemcitabine plus carboplatin was also found to have a significantly higher risk of anaemia than platinum monotherapy. No other comparison of chemotherapies was found to have a statistically significant difference.

The results the NMA from Network 2 are also presented in Table 79. Overall, topotecan monotherapy (IV), topotecan monotherapy (oral), and PLDH plus trabectedin were found to have significantly

higher risk of anaemia (at the 5% level) than PLDH monotherapy. PLDH plus trabectedin, paclitaxel monotherapy and topotecan monotherapy (IV, weekly) were also found to have significantly higher risk of anaemia than topotecan monotherapy (IV). Paclitaxel monotherapy was found to have significantly less risk than topotecan monotherapy (oral) and topotecan monotherapy (oral). No other comparison of chemotherapies was found to have a statistically significant difference.

One additional trial[61] provided data on this adverse event but it was not possible to include this in either network due to the atypical doses of paclitaxel compared. Lortholary *et al.*[61] compared low dose paclitaxel (80 mg/m^2) with low dose paclitaxel (80 mg/m^2) plus carboplatin. No significant difference in risk of anaemia was identified than paclitaxel plus carboplatin (OR 0.273, 95% CI: 0.071 to 1.048).

Table 79. Results of the network meta-analysis for anaemia for people with recurrent ovarian cancer

Comparison	OR	95% CrI	
		Lower limit	Upper limit
Network 1			
Versus paclitaxel plus carboplatin (OR <1 favours comparator, OR >1 favours paclitaxel plus carboplatin)			
Platinum monotherapy	1.255	0.305	3.479
PLDH plus carboplatin	1.926	1.164	3.039
Gemcitabine plus carboplatin	5.848	1.158	18.040
Versus platinum monotherapy (OR <1 favours comparator, OR >1 favours gemcitabine plus carboplatin)			
PLDH plus carboplatin	2.205	0.527	6.289
Gemcitabine plus carboplatin	4.664	2.366	8.600
Versus PLDH plus carboplatin (OR <1 favours comparator, OR >1 favours PLDH plus carboplatin)			
Gemcitabine plus carboplatin	3.152	0.609	9.880
Network 2			
Versus PLDH monotherapy (OR <1 favours comparator, OR >1 favours PLDH monotherapy)			
Topotecan monotherapy (IV)	7.374	3.775	13.590
Topotecan monotherapy (oral)	7.949	3.305	16.680
PLDH plus trabectedin	2.940	1.559	5.202
Paclitaxel monotherapy	0.742	0.209	1.848
Paclitaxel monotherapy (weekly)	2.551	0.407	9.425
Topotecan monotherapy (IV, weekly)	2.346	0.625	6.118
Versus topotecan monotherapy (IV) (OR <1 favours comparator, OR >1 favours topotecan monotherapy (IV))			
Topotecan monotherapy (oral)	1.078	0.640	1.714
PLDH plus trabectedin	0.443	0.166	0.958
Paclitaxel monotherapy	0.101	0.036	0.209
Paclitaxel monotherapy (weekly)	0.385	0.051	1.519
Topotecan monotherapy (IV, weekly)	0.318	0.107	0.704

Versus topotecan monotherapy (oral) (OR <1 favours comparator, OR >1 favours topotecan monotherapy (oral))			
PLDH plus trabectedin	0.438	0.140	1.044
Paclitaxel monotherapy	0.099	0.031	0.231
Paclitaxel monotherapy (weekly)	0.381	0.046	1.549
Topotecan monotherapy (IV, weekly)	0.314	0.091	0.765
Versus PLDH plus trabectedin (OR <1 favours comparator, OR >1 favours PLDH plus trabectedin)			
Paclitaxel monotherapy	0.277	0.064	0.766
Paclitaxel monotherapy (weekly)	0.951	0.128	3.676
Topotecan monotherapy (IV, weekly)	0.876	0.192	2.531
Versus paclitaxel monotherapy (OR <1 favours comparator, OR >1 favours paclitaxel monotherapy)			
Paclitaxel monotherapy (weekly)	4.701	0.445	20.380
Topotecan monotherapy (IV, weekly)	3.869	0.866	11.400
Versus paclitaxel monotherapy (weekly) (OR <1 favours comparator, OR >1 favours paclitaxel monotherapy (weekly))			
Topotecan monotherapy (IV, weekly)	1.749	0.149	7.204
Abbreviations used in table: CrI, Credible Interval; OR, odds ratio; PLDH, pegylated liposomal doxorubicin hydrochloride.			

Fatigue

The absolute numbers for the RCTs included in the NMA evaluating fatigue in patients with recurrent ovarian cancer are reported in Section 4.1.7.2. Unfortunately, as described earlier, a single network could not be constructed out of the available trials. The two networks constructed for this outcome are depicted in Appendix 4.

An NMA of Network 1 could not be performed due to zero events in a link in the network[29] and non-comparable doses and/or treatment regimen in the remaining available trials. Individual trial results are presented in Table 80.

The results the NMA from Network 2 are presented in Table 81. No comparison of chemotherapies was found to have a statistically significant difference (at the 5% level).

Table 80. Results of the individual trials for network 1 for fatigue for people with recurrent ovarian cancer

Comparison	OR	95% CI		Trial
		Lower limit	Upper limit	
PLDH plus carboplatin vs paclitaxel plus carboplatin	Infinity*	NA	NA	Bafaloukos *et al*.[29]
PLDH monotherapy (every 3 weeks) vs PLDH monotherapy (every 4 weeks)	0.454	0.204	1.012	Monk *et al*. (2010)[30]
Gemcitabine plus carboplatin vs platinum monotherapy	1.326	0.292	6.011	Pfisterer *et al*.[49]
Paclitaxel monotherapy vs paclitaxel plus carboplatin	1.031	0.555	1.917	Lortholary *et al*.[61]
PLDH plus carboplatin vs platinum monotherapy	1.452	0.226	9.309	Alberts *et al*.

				2008[28]

*Zero events in both groups.
Abbreviations used in table: CI, Confidence Interval; OR, odds ratio; NA, not applicable; PLDH, pegylated liposomal doxorubicin hydrochloride.

Table 81. Results of the network meta-analysis for fatigue for network 2 for people with recurrent ovarian cancer

Comparison	OR	95% CrI	
		Lower limit	Upper limit
Versus paclitaxel monotherapy (OR <1 favours comparator, OR >1 favours paclitaxel monotherapy)			
Topotecan monotherapy (IV)	1.570	0.479	3.978
Topotecan monotherapy (oral)	1.896	0.242	7.042
Topotecan monotherapy (IV, weekly)	3.334	0.548	11.390
Versus topotecan monotherapy (IV) (OR <1 favours comparator, OR >1 favours topotecan monotherapy (IV))			
Topotecan monotherapy (oral)	1.213	0.256	3.645
Topotecan monotherapy (IV, weekly)	2.123	0.627	5.573
Versus topotecan monotherapy (oral) (OR <1 favours comparator, OR >1 favours topotecan oral monotherapy (oral))			
Topotecan monotherapy (IV, weekly)	2.761	0.342	10.540
Abbreviations used in table: CrI, Credible Interval; OR, odds ratio.			

Febrile neutropenia

The absolute numbers for the RCTs included in the NMA evaluating febrile neutropenia in patients with recurrent ovarian cancer are reported in Section 4.1.7.2. Unfortunately, no NMA could be performed due to zero events in three of the available trials.[28][49][61] Individual trial results are presented in Table 82.

Table 82. Results of the individual trials for febrile neutropenia for people with recurrent ovarian cancer

Comparison	OR	95% CI		Trial
		Lower limit	Upper limit	
PLDH plus carboplatin vs platinum monotherapy	Infinity*	NA	NA	Alberts *et al*.[28]
PLDH plus carboplatin vs paclitaxel plus carboplatin	0.614	0.299	1.263	Pujade-Lauraine *et al*.[31]
PLDH plus trabectedin vs PLDH monotherapy	3.256	1.378	7.692	Monk *et al*. (2010)[30]
Gemcitabine plus carboplatin vs platinum monotherapy	Infinity[a]	NA	NA	Pfisterer *et al*.[49]
Paclitaxel plus carboplatin vs paclitaxel monotherapy	Infinity[b]	NA	NA	Lortholary 2011
Topotecan monotherapy vs topotecan monotherapy (weekly)	4.000	0.439	36.439	Sehouli *et al*.[23]

[a] Zero platinum monotherapy events
[b] Zero paclitaxel monotherapy events
Abbreviations used in table: CI, Confidence Interval; OR, odds ratio; PLDH, pegylated liposomal doxorubicin hydrochloride.

Nausea and vomiting

The absolute numbers for the RCTs included in the NMA evaluating nausea and vomiting in patients with recurrent ovarian cancer are reported in Section 4.1.7.2. Unfortunately, as described earlier, a single network could not be constructed out of the available trials. The two networks constructed for this outcome are depicted in Appendix 4.

The results the NMA from Network 1 are presented in Table 83. Overall, PLDH plus carboplatin was found to have significantly higher risk of nausea and vomiting (at the 5% level) than paclitaxel plus carboplatin. No other comparison of chemotherapies was found to have a statistically significant difference.

The results the NMA from Network 2 are also presented in Table 83. Overall, paclitaxel monotherapy was found to have significantly lower risk of nausea and vomiting (at the 5% level) than PLDH monotherapy. Topotecan monotherapy (oral) and PLDH plus trabectedin were found to have significantly higher risk of nausea and vomiting than PLDH monotherapy (and any of the other chemotherapies assessed). However, when compared with each other no significant difference was found. No other comparison of chemotherapies was found to have a statistically significant difference.

Table 83. Results of the individual trials for nausea and vomiting for people with recurrent ovarian cancer

Comparison	OR	95% CrI	
		Lower limit	Upper limit
Network 1			
Versus paclitaxel plus carboplatin (OR <1 favours comparator, OR >1 favours paclitaxel plus carboplatin)			
Platinum monotherapy	4.897	0.415	23.550
PLDH plus carboplatin	426.200	2.000	709.700
Versus platinum as a monotherapy (OR <1 favours comparator, OR >1 favours gemcitabine plus carboplatin)			
PLDH plus carboplatin	109.700	0.721	234.900
Network 2			
Versus PLDH monotherapy (OR <1 favours comparator, OR >1 favours PLDH monotherapy)			
Topotecan monotherapy (oral)	3.849	1.377	8.921
Topotecan monotherapy (IV)	1.460	0.886	2.294
PLDH plus trabectedin	5.291	2.866	9.342
Paclitaxel monotherapy (weekly)	0.554	0.061	2.237
Paclitaxel monotherapy	0.279	0.120	0.535
Topotecan monotherapy (IV, weekly)	1.023	0.219	2.915
Versus topotecan monotherapy (oral) (OR <1 favours comparator, OR >1 favours topotecan oral monotherapy (oral))			
Topotecan monotherapy (IV)	0.449	0.180	0.904
PLDH plus trabectedin	1.724	0.486	4.403

Paclitaxel monotherapy (weekly)	0.176	0.015	0.765
Paclitaxel monotherapy	0.089	0.024	0.223
Topotecan monotherapy (IV, weekly)	0.315	0.055	0.985
Versus topotecan monotherapy (IV) ***(OR <1 favours comparator, OR >1 favours topotecan IV monotherapy (IV))***			
PLDH plus trabectedin	3.840	1.698	7.673
Paclitaxel monotherapy (weekly)	0.392	0.043	1.596
Paclitaxel monotherapy	0.197	0.084	0.379
Topotecan monotherapy (IV, weekly)	0.701	0.166	1.869
Versus PLDH plus trabectedin ***(OR <1 favours comparator, OR >1 favours PLDH plus trabectedin)***			
Paclitaxel monotherapy (weekly)	0.114	0.011	0.484
Paclitaxel monotherapy	0.058	0.019	0.130
Topotecan monotherapy (IV, weekly)	0.211	0.038	0.655
Versus paclitaxel monotherapy (weekly) ***(OR <1 favours comparator, OR >1 favours paclitaxel monotherapy (weekly))***			
Paclitaxel monotherapy	1.029	0.134	3.613
Topotecan monotherapy (IV, weekly)	4.260	0.257	19.750
Versus paclitaxel monotherapy (every 3 weeks) ***(OR <1 favours comparator, OR >1 favours paclitaxel monotherapy (every 3 weeks))***			
Topotecan monotherapy (IV, weekly)	4.107	0.753	12.880
Abbreviations used in table: CrI, Credible Interval; OR, odds ratio; PLDH, pegylated liposomal doxorubicin hydrochloride.			

Neuropathy

The absolute numbers for the RCTs included in the NMA evaluating neuropathy in patients with recurrent ovarian cancer are reported in Section 4.1.7.2. Unfortunately, no NMA could be performed due to zero events in three of the available trials.[21][23][29][47] Individual trial results are presented in Table 84.

Table 84. Results of the individual trials for neuropathy for people with recurrent ovarian cancer

Comparison	OR	95% CI		Trial
		Lower limit	Upper limit	
PLDH plus carboplatin vs paclitaxel plus carboplatin	Infinity[a]	NA	NA	Bafaloukos *et al*.[29]
Platinum monotherapy vs paclitaxel plus carboplatin	Infinity[b]	NA	NA	Gonzalez Martin *et al*.[47]
Gemcitabine plus carboplatin vs platinum monotherapy	0.994	0.198	4.994	Pfisterer *et al*.[49]
PLDH plus trabectedin vs PLDH monotherapy	1.404	0.815	2.419	Monk *et al*. (2010)[30]
Paclitaxel monotherapy (weekly) vs paclitaxel monotherapy	0.368	0.175	0.777	Rosenberg *et al*.[59]
Topotecan monotherapy (IV) vs paclitaxel monotherapy	Infinity[b]	NA	NA	ten Bokkel Huinink *et al*. (1997)[21]
Topotecan monotherapy (IV) vs topotecan (IV, weekly) monotherapy	Infinity[c]	NA	NA	Sehouli *et al*.[23]

Paclitaxel monotherapy vs paclitaxel plus carboplatin	1.639	0.693	3.878	Lortholary *et al.*[61]

[a] Zero PLDH plus carboplatin events
[b] Zero events in both groups
[c] Zero topotecan monotherapy (IV) events
Abbreviations used in table: CI, Confidence Interval; OR, odds ratio; PLDH, pegylated liposomal doxorubicin hydrochloride.

4.3 Discussion

The population of ovarian cancer patients that are the focus of this MTA are those who have relapsed following first-line treatment with platinum-based therapy or have disease that is refractory to platinum-based chemotherapy. Diagnosis of recurrent disease varies in UK clinical practice, with diagnosis based on clinical examination, biochemical markers (CA125), or radiological confirmation, or any combination of these three. Clinical expert advice is that, typically, a patient is diagnosed as relapsed if they have a serial rise in CA125 or have developed clinical signs, such as ascites. Diagnosis is typically confirmed with radiological scans. If a patient has no clinical symptoms but does have a rise in CA125, although possibly classified as relapse, the patient might not start a new chemotherapeutic regimen until they go on to develop symptoms. Date of relapse by CA125 is likely to be about 4 months earlier than date of relapse based on radiological scans.

A patient's response to first-line platinum-based therapy is indicative of their response to second and subsequent lines of platinum-based treatment, with the length of the platinum-free interval (PFI) and the extent of relapse (site and number of tumours) particularly prognostic of response. However, most patients will develop resistance to platinum-based therapy over time, with decreasing length of PFI with increasing rounds of treatment. Platinum-resistant ovarian cancer has a particularly poor prognosis, with a reported median OS of less than 12 months.

The systematic review of clinical effectiveness evidence carried out to address the decision problem that is the focus of this MTA identified 16 randomised controlled trials (RCTs), evaluating 14 pair wise comparisons. Of the 16 RCTs identified, 5 evaluated the intervention and comparator within their licensed indication, and dose and route of administration. The remaining 11 RCTs evaluated the intervention or comparator outside the parameters specified in the licence. However, the scope of the evidence identified was insufficient to fully address the decision problem; therefore, where possible the TAG has carried out synthesis of the evidence within network meta-analyses (NMAs).

Based on clinical expert advice, the Technology Assessment Group (TAG) has focused on the clinical effectiveness of interventions in populations defined by degree of platinum-sensitivity (i.e., platinum-sensitive [i.e., recurrence ≥6 months after last platinum-based treatment] and platinum resistant [i.e., recurrence <6 months after last platinum-based treatment] or refractory [progression during platinum-based treatment]).

The identified RCTs facilitated the construction of three distinct networks for the outcomes of overall survival (OS) and progression-free survival (PFS), two of which considered patients with platinum sensitive disease; the remaining network considered patients with disease that is platinum-resistant/refractory. As the systematic review was conducted in such a way as to identify all trials with at least one intervention of interest, a wider selection of treatments were assessed, but unfortunately this did not uncover one or more trials that could link the disconnected networks in patients with platinum sensitive disease. Furthermore, due to time constraints, the decision was taken not to search for non-randomised trials.

The two networks, for OS and PFS, constructed in patients with platinum sensitive disease were, platinum sensitive – network 1, which compared regimens containing platinum, in particular: platinum plus paclitaxel, PLDH plus platinum, gemcitabine plus carboplatin, and platinum alone. Platinum sensitive – network 2, which compared non-platinum based therapies, in particular: PLDH, trabectedin plus PLDH, paclitaxel and topotecan.

4.3.1 Platinum sensitive patients

Overall survival (OS) and progression free survival (PFS) data were identified for eight and seven different head-to-head comparisons of interventions and comparators of interest, respectively. Of these, three reported a statistically significant difference in OS between the treatments considered. In particular, Parmar *et al*. reported a statistically significant difference in OS between paclitaxel plus platinum vs conventional platinum treatment (HR [95% CI]: 0.82 [0.69 to 0.97]), observed in the ICON4/AGO-OVAR trial. Gonzalez Martin *et al.* reported a statistically significant difference between paclitaxel plus carboplatin vs carboplatin alone (HR [95% CI]: 0.31 [0.14 to 0.68]) and Gordon *et al*. present a statistically significant difference between PLDH and topotecan (HR [95% CI]: 1.43 [1.07 to 1.92]). Six of the identified head-to-head comparisons identified a statistically significant difference in PFS. These were:

- CALYPSO: PLDH plus carboplatin vs paclitaxel plus carboplatin (HR [95% CI]: 0.82 [0.72 to 0.94]);
- ICON4/AGO-OVAR 2.2: Paclitaxel plus platinum vs conventional platinum treatment (HR [95% CI]: 0.76 [0.66 to 0.89]);
- Gonzalez Martin *et al*.: Paclitaxel plus carboplatin vs carboplatin alone (HR [95% CI]: 0.54 [0.32 to 0.92]);
- Alberts *et al*.: PLDH plus carboplatin vs carboplatin alone (HR [95% CI]: 0.54 [0.32 to 0.93]);
- OVA-301: Trabectedin plus PLDH vs PLDH (HR [95% CI]: 0.73 [0.56 to 0.95]);
- Pfisterer *et al*.: Gemcitabine plus carboplatin vs carboplatin alone (HR [95% CI]: 0.72 [0.58 to 0.90]).

In the NMA evaluating platinum-based chemotherapies, PLDH plus carboplatin and paclitaxel plus carboplatin were found to significantly improve OS compared with platinum monotherapy. However, no statistically significant differences in OS were identified between the remaining treatments considered in the network. When compared with platinum monotherapy, PFS was estimated to significantly improve in patients treated with paclitaxel plus carboplatin, gemcitabine plus carboplatin or PLDH plus carboplatin. In addition a statistically significant difference in PFS was estimated for paclitaxel plus carboplatin vs PLDH plus carboplatin.

However, the TAG consider it important to note that examination of the baseline characteristics of trials included in NMAs of platinum-based therapies, revealed an imbalance in baseline performance score (ECOG) within one of the included trials. In particular, the trial carried out by Gonzalez-Martin *et al*., in which paclitaxel plus carboplatin is compared with platinum monotherapy; the proportion of patients with a baseline ECOG score of 2 that were randomised to treatment with platinum monotherapy was 17.9% vs 5.6% of patients randomised to treatment with paclitaxel plus carboplatin. The TAG notes that this imbalance is likely to result in an overestimation of the relative treatment effect of paclitaxel plus carboplatin vs platinum monotherapy.

Furthermore, the TAG notes the presence of clinical heterogeneity in the duration of PFI between trials. In particular, patients enrolled in the ICON-4 trial had a comparably longer PFI than patients enrolled in the other trials included in NMA of OS and PFS data. Similarly, a comparatively high proportion of patients enrolled in the trial carried out by Gonzalez-Martin *et al*. were diagnosed as recurrent based on assessment of CA125 levels; therefore these patients are likely to be more susceptible to platinum therapy than patients enrolled in the other included trials. However, the TAG notes that although patients in ICON-4 and Gonzalez-Martin *et al*. may be expected to experience greater benefit than patients enrolled in the other trials, the magnitude of this difference is unlikely to affect estimates of the relative effect of treatment.

NMA of non-platinum based therapies indicated that PLDH monotherapy and trabectedin plus PLDH are both significantly more effective at prolonging OS than topotecan monotherapy. No other significant OS differences were identified. Analysis of non-platinum-based regimens indicates that trabectedin plus PLDH statistically significantly improves PFS compared with PLDH, paclitaxel and topotecan when given as monotherapies. No statistically significant differences in PFS were identified among the monotherapies evaluated (PLDH, topotecan, and paclitaxel). However, as a result of the use of subgroup data to inform these analyses, assessment of the presence of clinical heterogeneity was not possible. In addition, the TAG considers it import to highlight that subgroup data from the included trials were not sufficiently powered to detect a difference in OS or PFS.

Overall response rate was reported for eleven different head-to-head comparisons of interventions and comparators of interest. Of these, only two were statistically significant: trabectedin plus PLDH vs PLDH from OVA-301 (OR [95% CI]: 1.57 [1.04 to 2.35]); gemcitabine plus carboplatin vs carboplatin alone from Pfisterer *et al*. (OR [95% CI]: 1.527 [1.025 to 2.275]).

Based on the trials identified, it was not possible to construct a complete network informing ORR. Akin to analyses of OS and PFS, two discrete networks were generated, one evaluating platinum-based therapies (paclitaxel plus carboplatin, gemcitabine plus carboplatin, PLDH plus carboplatin and platinum monotherapy) and the second comparing non-platinum-based regimens (PLDH, trabectedin plus PLDH, topotecan (intravenous), paclitaxel (every 3 weeks), topotecan (oral) and paclitaxel weekly).

In the NMA evaluating platinum-based chemotherapies, paclitaxel plus carboplatin and gemcitabine plus carboplatin were found to have a significantly higher ORR than platinum monotherapy. There was no significant difference between PLDH plus carboplatin vs any of the chemotherapeutic treatments assessed. Analysis of non-platinum-based regimens indicates that trabectedin plus PLDH significantly improves ORR compared with PLDH, and oral topotecan. Compared with oral topotecan, intravenous topotecan was found to be associated with a significant increase in the proportion of patients achieving CR or PR. No other statistically significant differences were identified.

4.3.2 Platinum resistant/refractory patients

OS and PFS data were reported for five and four different head-to-head comparisons in PRR patients, respectively. Two RCTs enrolled only patients with PRR, with the remaining RCTs reporting results from a subgroup of patients within the trial. None of the trials identified a significant difference in OS or PFS between the two treatment groups evaluated. Furthermore, no statistically significant differences in ORR were reported in the eight different head-to-head comparisons involving PRR patients. Similarly, no statistically significant differences in OS or PFS were identified in NMA of treatment with paclitaxel, PLDH and topotecan. However, NMA of ORR estimated that PLDH significantly increased ORR compared with paclitaxel (175 mg/m^2) every 21 days and with an alternative regimen in which paclitaxel was given weekly at a dose of 67 mg/m^2. PLDH monotherapy was also significantly more effective than an unconventional regimen of topotecan in which topotecan was administered weekly at a dose of 4 mg/m^2. As a result of the use of subgroup data to inform these analyses, the TAG notes that the individual trial data may have been underpowered to detect a difference in OS, PFS or ORR. Furthermore, as baseline characteristics were not reported for the subgroups, an assessment of the presence of clinical heterogeneity was not possible.

4.3.3 Health related quality of life

Treatments for newly diagnosed ovarian cancer are given with curative intent; however, for women with advanced, recurrent disease, second and subsequent line chemotherapies are typically given with palliative rather than curative intent, with the aim of alleviating symptoms and prolonging survival. Thus, key considerations in the choice of treatment at these stages in the pathway are maintaining the patient's quality of life. Of the 16 RCTs identified, 10 reported some level of data on QoL. However, reporting of results was generally limited, with few trials reporting scores generated from responses to the questionnaires. The most commonly used scale in the identified trials is the EORTC QLQ-C30 questionnaire, which was developed to assess the QoL of cancer patients and can be supplemented with disease-specific modules for individual cancers, including ovarian cancer. For many comparisons, scores on QoL scales were comparable between treatments. Differences in QoL include:

- for PLDH plus platinum vs paclitaxel plus platinum, at 3 months, PLDH plus platinum was associated with a significant improvement in global health compared with paclitaxel plus platinum. However, this benefit was not maintained at 6 months;
- for paclitaxel plus platinum vs platinum-based therapy patients receiving platinum monotherapy scored significantly worse on the nausea and vomiting symptom scale than did the paclitaxel plus platinum-based chemotherapy group. However, this difference seemed to be transient and was observed for only the first 15 weeks after randomisation;
- for trabectedin plus PLDH vs PLDH in the subgroup of patients with partially platinum sensitive ovarian cancer, it is indicated that there exist a difference in global health status score among responding patients beyond cycle 5, with patients in the trabectedin plus PLDH group having a higher score than those receiving PLDH alone (higher score is favourable);
- for PLDH vs topotecan was associated with a significantly more favourable rating on the pain sub-scale of the EORTC QLQ-C30;
- for paclitaxel plus platinum vs paclitaxel patients receiving weekly paclitaxel plus platinum experienced improvements in constipation, abdominal/gastrointestinal symptoms, appetite loss, pain, and emotional functioning. Patients treated with weekly paclitaxel alone experienced improvements in attitude to disease and insomnia, but worsening of dyspnoea and peripheral neuropathy.
- for paclitaxel vs oxaliplatin, mean QoL score on the EORTC QLQ-C30 increased by more than 10 points between baseline and cycle 4 for patients in the paclitaxel group, irrespective of study withdrawal. By contrast, in the oxaliplatin group, the mean QoL score decreased through cycle 2, but by less than 10 points, after which most patients' mean scores returned to baseline levels.

4.3.4 Adverse events

An important consideration in the choice of second-line treatment is the adverse effect of neurotoxicity, which is commonly associated with paclitaxel and also with carboplatin. Neurotoxicity can persist for up to 2 years after the end of treatment. Patients who relapse after first-line treatment with paclitaxel–platinum combination therapy and are subsequently re-challenged with the same regimen within 12 months (i.e., those who are partially platinum-sensitive) are at an increased risk of developing neurotoxicity. However, despite the associated increased risk of neurotoxicity, paclitaxel plus carboplatin is generally the preferred second-line treatment in UK practice in recurrent platinum-sensitive cancer, particularly for patients who relapse >12 months after completion of first-line chemotherapy. Carboplatin is chosen over cisplatin because of its more favourable adverse effect profile.

Within each of the identified trials, the most frequently reported adverse effects were as expected for the individual treatments based on the Summary of Product Characteristics (SmPC). Commonly occurring adverse effects were alopecia, nausea and vomiting, haematological toxicities (neutropenia, anaemia, thrombocytopenia, and leukopenia). Based on expert clinical advice the TAG restricted its comparison of adverse events to those considered most problematic for patients or most likely to consume substantial health care resource.

The potential for an NMA was, therefore, investigated for the following severe (grade 3–4) adverse events: allergic reaction, alopecia, anaemia, fatigue, febrile neutropenia, nausea and vomiting, and neuropathy. In many cases an NMA was not possible due to the lack of available data in the trials assessed. In these instances, the individual trial results are reported with the ORs and 95% confidence intervals were calculated. The majority of NMA results, supplemented by the individual trial results where an NMA 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 plus platinum, PLDH plus 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 severe adverse events assessed.

5 ASSESSMENT OF COST-EFFECTIVENESS

5.1 Review of existing cost-effectiveness evidence

This section provides a review of the existing cost-effectiveness evidence, both published and presented within manufacturer submissions, for treatments in recurrent ovarian cancer covered in the scope of this MTA:[38]

- Section 5.1.1 summarises the cost-effectiveness evidence presented within TA91 and TA222;
- Section 5.1.2 presents findings from the Technology Assessment Group systematic review of cost-effectiveness evidence;
- Section 5.1.3 provides a description and critique of manufacturer submitted evidence;
- Section 5.1.45.1.4 summarises the available evidence and draws conclusions about the published and submitted assessments of cost-effectiveness.

5.1.1 Review of TA91 and TA222 cost-effectiveness evidence

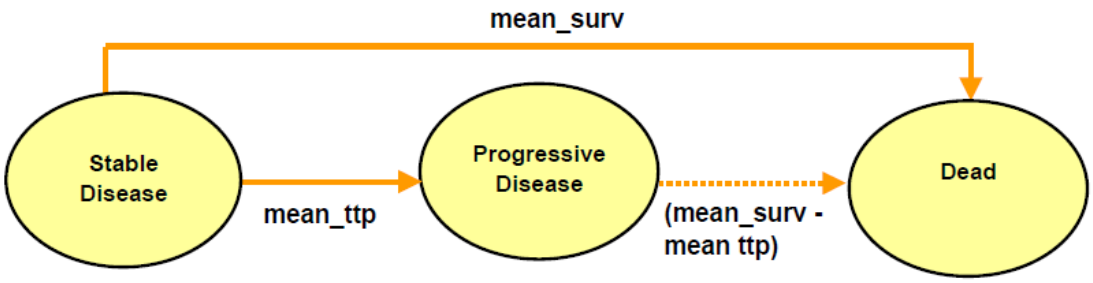
This MTA is, in part, a review and update of TA91 (paclitaxel, PLDH and topotecan for second-line or subsequent treatment of advanced ovarian cancer) and TA222 (trabectedin for the treatment of relapsed ovarian cancer).[10;79] The economic evidence presented within TA91 and TA222 was therefore considered to be a relevant source of information, and the cost-effectiveness analyses presented within both technology appraisals are summarised below.

5.1.1.1 Multiple Technology Appraisal No 91: paclitaxel, PLDH and topotecan for second-line or subsequent treatment of advanced ovarian cancer

Three manufacturers submitted cost-effectiveness evidence for consideration in TA91; GlaxoSmithKline [topotecan], Schering-Plough Ltd [PLDH] and Bristol-Myers Squibb Ltd. [paclitaxel]. GlaxoSmithKline and Schering-Plough Ltd. submitted cost-minimisation analyses comparing topotecan with PLDH. Bristol-Myers Squibb Ltd. submitted a cost-effectiveness analysis which estimated the incremental cost per life year gained (LYG) of paclitaxel, paclitaxel in combination with platinum, PLDH, and topotecan. In addition to the submitted analyses, the Technology Assessment Group (TAG) for TA91 identified four economic evaluations from the published literature; Smith *et al.*, Ojeda *et al.*, Capri *et al.* and Prasad *et al.*[80-83] Smith *et al.*, Ojeda *et al.*, and Capri *et al.* were cost-minimisation analyses which compared topotecan with PLDH.[80-82] Prasad *et al.* reported the costs and effects associated with topotecan and gemcitabine, but did not carry out a formal economic evaluation.[83] The TAG for TA91 concluded that the limitations of the submitted and published cost-effectiveness evidence were such that it was not possible to make a reliable comparison of the relative cost-effectiveness of the treatments considered in the scope of TA91. Therefore, to facilitate a comparison of the relative cost-effectiveness of the treatments

considered, the TAG developed a new decision analytic model. The model developed by the TAG was a semi-Markov cost-utility analysis, formed of three health states: stable disease, progressive disease, and death (Figure 13). The model evaluated overall survival in relation to the mean time to progression, and the time from progression to death (estimated as mean overall survival minus mean time to progression).

Figure 13. Structure of the economic model developed for TA91 (reproduced from TA91 Assessment Report p179[13])



Key:

mean_ttp = mean time to progression
mean_surv = mean (overall) survival time

Two analyses were carried out by the TAG for TA91; the main analysis considered a population of patients with refractory, resistant (platinum free interval [PFI] < 6 months), or platinum-sensitive (PFI ≥ 6 months) disease (full population), and the second analysis considered people with platinum-sensitive disease only.

For the main analysis, treatment effects in the form of hazard ratios were extracted from two published RCTs; the first of which compared paclitaxel monotherapy with topotecan (ten Bokkel *et al.*[51]), and the second of which compared topotecan with PLDH (data submitted for TA91[13]). Baseline estimates of PFS and OS were derived for the common comparator, topotecan, to which hazard ratios from the two identified RCTs were applied to estimate PFS and OS for paclitaxel monotherapy and PLDH. In sensitivity analysis, of the main analysis, a third RCT was included which compared paclitaxel with PLDH (Trial 30-57[84]). This RCT was excluded from the base case analysis, as the trial was terminated early, and therefore the results were likely to be preliminary. In the sensitivity analysis, data from the three identified RCTs were combined via a network meta-analysis (NMA) to estimate hazard ratios for each treatment vs topotecan. Hazard ratios were then applied to the baseline estimates of PFS and OS for patients treated with topotecan.

For the second analysis (people with platinum-sensitive disease) a further two RCTs were identified which were considered relevant; Cantu *et al.* (paclitaxel vs cyclophosphamide plus doxorubicin plus

cisplatin [CAP]) and ICON4 (paclitaxel plus platinum vs platinum).[50;85] ICON4 could not be connected to the network due to a lack of a common comparator; therefore, for the analysis, the TAG estimated the relative treatment effect associated with paclitaxel plus platinum using "an exponential approximation to estimate the absolute hazard associated with paclitaxel combination and topotecan respectively, and then take the ratio of these to provide the relative treatment effect" (Assessment Report, p190).[13] This relative treatment effect was then included in an NMA, establishing a network of five RCTs in total. As before, hazard ratios calculated from this NMA were applied to a baseline estimate of PFS and OS for patients treated with topotecan, resulting in estimates of PFS and OS for topotecan, paclitaxel monotherapy, PLDH, paclitaxel plus platinum combination therapy, platinum monotherapy, and CAP.

The costs included in the analysis comprised the costs of study drugs, pre-medication, monitoring, drug administration and the cost of managing adverse events. Long term costs, including subsequent chemotherapy costs, were excluded from the model as a result of the lack of data. Sources of cost data included the BNF for drug costs (BNF 47, cost year 2004), data submitted by manufacturers (cost year 1999/2000) and national cost sources (Unit Costs of Health and Social Care, cost year 2000).[86] [87]

Quality adjusted life years (QALYs) were estimated by applying health state utility values to the mean time spent in the stable disease and the progressed disease health states. The utility associated with stable disease (0.63, applied to the mean time spent by patients in the health state of stable disease) was sourced from a study by Tengs and Wallace, identified in a systematic search of the literature carried out by the TAG for TA91.[88] However, no estimate of utility for progressed disease was identified. Therefore, the TAG used a proxy measure of utility in progressed disease from breast cancer patients presented in a study by Brown and Hutton.[89] Although the TAG recognised the importance of the impact of treatment related toxicity on quality of life, no suitable or relevant quality of life data were identified or submitted that could inform the disutility associated with the treatments considered.

Results were presented for the full population with recurrent ovarian cancer, and also separately for people with platinum-sensitive disease. For the full population, topotecan was extendedly dominated by PLDH, and a cost-effectiveness estimate of £24,606 per additional QALY was estimated for PLDH compared with paclitaxel. For the platinum-sensitive population; topotecan, paclitaxel and PLDH were dominated by platinum monotherapy, CAP was extendedly dominated, and a cost-effectiveness estimate of £3,561 per additional QALY was estimated for paclitaxel plus platinum vs platinum monotherapy (Table 85).

Table 85. Results of the Technology Assessment Group main analysis from TA91 (adapted from Technology Assessment Group report p206)[13]

Treatment	PFS (weeks)	OS (weeks)	Quality adjusted survival (weeks)	Cost	ICER (incremental cost per additional QALY)	Probability of being cost-effectiveness at a maximum WTP of £30,000
Full population						
Topotecan	24.5	86.0	34.2	£8,448	Extendedly dominated	2%
Paclitaxel	20.1	79.7	30.9	£4,146	–	37%
PLDH	27.5	104.8	40.9	£8,902	£24,606	61%
Platinum-sensitive population (PFI ≥ 6 months)						
Topotecan	33.1	101.4	41.7	£8.330	Dominated	0%
Paclitaxel	28.0	105.1	41.2	£4,066	Dominated	0%
PLDH	43.0	145.8	58.5	£8,851	Dominated	1%
Paclitaxel plus platinum	82.0	178.8	81.2	£6,828	£3,561	60%
Platinum monotherapy	63.5	149.7	66.3	£3,383	–	1%
CAP	47.9	176.7	69.5	£3,512	Extendedly dominated	38%
Abbreviations used in table: CAP, cyclophosphamide plus doxorubicin plus cisplatin; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression free survival; PFI, platinum free interval; PLDH, pegylated liposomal doxorubicin hydrochloride; QALY, quality adjusted life year; WTP, willingness-to pay.						

The TAG also presented results for the full population in which data from an early terminated trial comparing paclitaxel with PLDH were incorporated.[69] For this analysis, topotecan was strictly dominated by paclitaxel, and PLDH vs paclitaxel was associated with an ICER of £58,475. The results of this analysis are presented in Table 86.

Table 86. Results of the Technology Assessment Group sensitivity analysis from TA91 incorporating additional data for the full population (adapted from Technology Assessment Group report p213)[13]

Treatment	PFS (weeks)	OS (weeks)	Quality adjusted survival (weeks)	Cost	ICER (incremental cost per additional QALY)	Probability of being cost-effectiveness at a maximum WTP of £30,000
Full population						
Topotecan	24.5	86.0	34.2	£8,448	Dominated	1%
Paclitaxel	20.1	92.1	34.6	£4,146	–	81%
PLDH	27.5	98.1	38.9	£8,902	£58,475	18%
Abbreviations used in table: ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression free survival; PLDH, pegylated liposomal doxorubicin hydrochloride; QALY, quality adjusted life year; WTP, willingness-to pay.						

5.1.1.2 Single Technology Appraisal No.222: trabectedin for the treatment of relapsed ovarian cancer

TA222 was a Single Technology Appraisal of trabectedin for the treatment of relapsed ovarian cancer. The manufacturer presented a cost utility analysis based on the model developed by the TAG for TA91. Results were presented separately for the platinum-sensitive population (PFI ≥ 6 months), the partially platinum-sensitive (PFI of 6-12 months) and the fully platinum-sensitive (PFI > 12 months) populations.

Estimates of mean overall survival and mean time to progression were derived by replicating the NMA used in TA91 for the platinum sensitive population for topotecan, paclitaxel and PLDH (i.e. excluding CAP, paclitaxel plus platinum and platinum monotherapy) with the addition of data from OVA-301, a clinical trial for trabectedin plus PLDH vs PLDH in the recurrent setting. It was not clear within the manufacturer's submission whether the early terminated trial (30-57[(84)]) was included within this analysis. The ERG for TA222 commented that "the manufacturer stated that three trials were included in the MTC [mixed treatment comparison] analysis: 039 [ten Bokkel *et al.*[(51)]; Gore *et al.*[(24)]] 30-49 [Schering-Plough; Gordon *et al.*[(13;53)]] and OVA-301 [Monk *et al.*[(30;63)]]. The ERG believes that trial 30-57 [[(84)]] was also included in the MTC for OS in order to provide the paclitaxel and PLDH comparison in the network of evidence" (ERG report for TA222, page 85[(90)]).

For PLDH monotherapy, the manufacturer estimated mean PFS and OS to which hazard ratios, estimated from the NMA, were applied thereby providing estimates of mean PFS and OS for topotecan, paclitaxel and trabectedin in combination with PLDH. Baseline estimates of PFS and OS for PLDH monotherapy were obtained by assuming that survival data for both interventions considered within OVA-301 were represented by exponential distributions; however, the Evidence Review Group (ERG) considering the evidence submitted in TA222 noted that exponential distributions were not the most appropriate fit to the patient-level data.

The costs included in the analysis comprised the costs of study drugs, pre-medication, monitoring, drug administration and the cost of managing adverse events. Following a clarification request from the ERG for TA222, the manufacturer also included an estimate of the cost of palliative care. Sources of cost data included the BNF for drug costs (BNF 58, cost year 2009), and national cost databases (National Tariff 2010/11; NHS Reference Costs 2007/08).[(91;92)]

QALYs were estimated by applying health state utility values to the mean time spent in each health state (i.e., stable disease, progressed disease and death). Utility values were estimated from EQ-5D data collected within OVA-301 and were presented by health state: stable disease mean estimate, 0.718; progressive disease mean estimate, 0.649; death, assumed to be 0.

The manufacturer presented results for the entire platinum-sensitive (relapse ≥ 6 months following previous platinum therapy) population and the partially platinum-sensitive (relapse within 6-12 months of previous platinum therapy) patients separately. Results from the manufacturer analyses are presented in Table 87.

Table 87. Results of the manufacturer's analysis from TA222 (adapted from the manufacturer's submission p165 and p179[93])

Population	Treatment	Total cost	Total QALYs	ICER (incremental cost per additional QALY, deterministic)
Platinum sensitive (PFI ≥ 6 months)	Paclitaxel	£4,738	1.17	–
	PLDH	£9,355	1.54	£12,680
	Topotecan	£15,726	1.27	Dominated
	Trabectedin plus PLDH	£26,389	1.81	£62,619
Partially platinum sensitive (PFI 6 to 12 months)	PLDH	£9,350	1.34	–
	Trabectedin plus PLDH	£26,349	1.78	£38,668
Abbreviations used in table: ICER, incremental cost-effectiveness ratio; PFI, platinum free interval; PLDH, pegylated liposomal doxorubicin hydrochloride; QALY, quality adjusted life year.				

The ERG for TA222 considered the comparison of trabectedin in combination with PLDH vs PLDH in people with partially platinum-sensitive disease to be the most pertinent decision problem. This was because PLDH was not listed as a comparator of interest in the NICE scope for people with fully platinum sensitive (PFI >12 months) disease. The ERG therefore did not present any results for the fully platinum sensitive population within their report; instead, the ERG focused on results for the partially platinum sensitive population (PFI 6-12 months). The ERG for TA222 investigated a number of changes to the model for partially platinum-sensitive patients, including amending the parametric distribution used to calculate the mean progression free survival and overall survival time for PLDH. The ERG concluded that "the most plausible ICER for trabectedin in combination with PLDH vs PLDH alone in women who relapse between 6 to 12 months after initial platinum-based chemotherapy ranges between £46,503 and £54,607" (TA222 ERG report, p127).[90]

5.1.2 Technology Assessment Group systematic review of existing cost-effectiveness evidence

A systematic review was carried out in December 2012 to identify relevant published economic evaluations to support the development of this MTA. The following databases were searched:

- MEDLINE (Ovid);
- EMBASE (Ovid);
- HTA database (HTA);
- NHS Economic Evaluations Database (NHS EED).

The search strategy for MEDLINE and EMBASE combined terms capturing the interventions and comparators of interest (topotecan, PLDH, paclitaxel, trabectedin, gemcitabine, best supportive care, bevacizumab, carboplatin, cisplatin, and etoposide); the target condition (ovarian cancer); and terms to capture economic evaluations. As this MTA is in part an update of TA91, in which a systematic review was carried out (search date of April 2004) to evaluate the cost-effectiveness of topotecan, PLDH, and paclitaxel; searches for these interventions were carried out with a date limit of 2004. Databases were searched from inception for gemcitabine and trabectedin. The search strategy for HTA and NHS EED combined terms for the target condition (ovarian cancer) with no further limits. Full details of the search terms are presented in Appendix 5.

In addition to searches of the above databases the following sources of potentially relevant publications were explored:

- experts in the field were contacted with a request for details of relevant published and unpublished studies of which they may have knowledge;
- the NICE website was searched for any recently published Technology Appraisals in ovarian cancer that had not already been identified via the database searches;
- reference lists of key identified studies were reviewed for any potentially relevant studies.

No restrictions on language or setting were applied to any of the searches. The titles and abstracts of papers identified through the searches were independently assessed for inclusion by two health economists using the criteria outlined in Table 88.

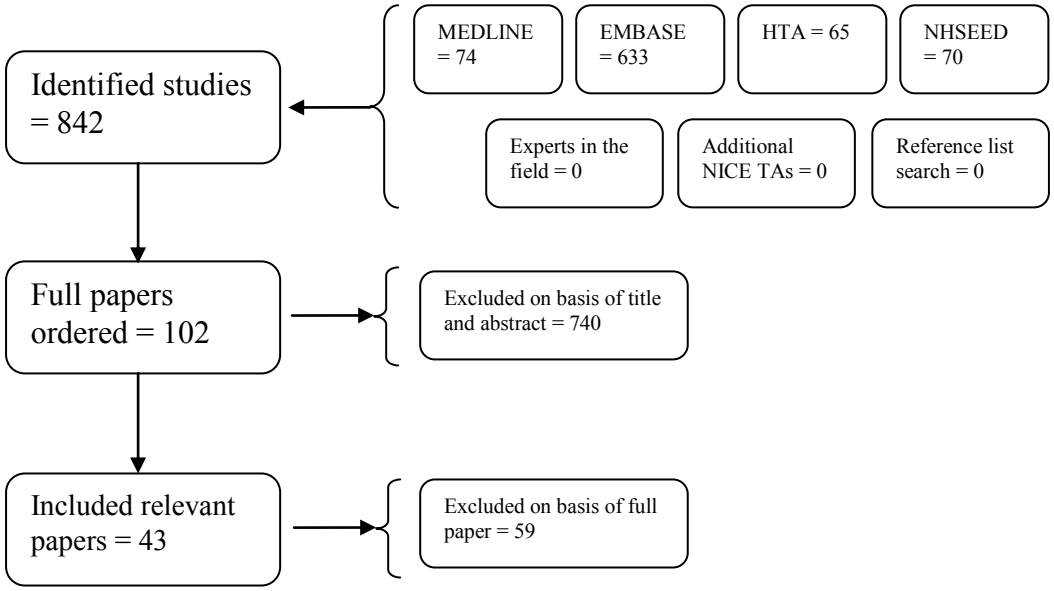
Table 88. Inclusion and exclusion criteria for the economic evaluation systematic review

Inclusion criteria	Exclusion criteria
• all full economic evaluations (cost-effectiveness, cost-benefit, cost-consequence or cost minimisation) • any setting (to be as inclusive as possible) • at least one of the interventions or comparators as per the final scope	• abstracts with insufficient methodological details • systematic reviews

The systematic review was updated in May 2013 whilst the report was under peer review. The search strategy remained the same as outlined above; however, results were limited from December 4th 2012 to May 21st 2013 in order to identify only additional relevant studies.

A total of 842 papers were identified from the December 2012 search (Figure 14). Of these papers, 740 were excluded on the basis of title and abstract. A total of 102 papers were therefore identified as potentially relevant and were ordered for full review. Of the 102 ordered papers, 59 were excluded following review of the full paper. For a description of the reason for exclusion of the ordered papers, see Appendix 6. A total of 43 papers were identified as economic evaluations from the December 2012 search.

Figure 14. Identified economic evaluation studies, December 2012 search



A further 91 papers were identified from the updated search in May 2013. Of these, 90 were excluded on the basis of title and abstract, with one paper identified as potentially relevant and ordered for full review. Additionally, two relevant NICE TAs were identified from the NICE website and were reviewed in full; TA284 and TA285.[11;15]

Of the 46 economic evaluation studies identified from the December 2012 (43 papers) and May 2013 (three papers) searches, 21 related specifically to recurrent ovarian cancer (Table 89). These 21 studies were considered by the TAG to be the most relevant to this MTA, and were extracted in full (Appendix 7); the remaining included papers are presented as short summaries (Appendix 7).

Table 89. Summary of included studies relating to recurrent ovarian cancer

	Identified in TA91	Related to TA91	Related to TA222	Additional studies
Study	Capri and Cattaneo *et al.*	Griffin *et al.*	NICE 2011	Forbes *et al.*
				TA285
			Papaioannou *et al.*	Chan *et al.*
	Ojeda *et al.*	Main *et al.*		Havrilesky *et al.*
			Papaioannou *et al.*	Lesnock *et al.*
				Lesnock *et al.*
	Smith *et al.*	NICE 2005	Gore *et al.*	Case *et al.*
				Havrilesky *et al.*
			Montalar *et al.*	Rocconi *et al.*
				Lee *et al.*

Of the 21 economic evaluations identified in patients with recurrent ovarian cancer, four studies (Capri and Cattaneo,[82] Ojeda *et al.*,[81] Forbes *et al.*,[94] and Smith *et al.*[80]) were published prior to

2004 and describe cost minimisation analyses comparing PLDH with topotecan. These studies were carried out from the perspective of Italy (Capri and Cattaneo[82]), Spain (Ojeda *et al.*[81]), the UK (Forbes *et al.*,[94] Smith *et al.*[80]), and the USA (Smith *et al.*[80]). Three of these studies (Capri and Cattaneo,[82] Ojeda *et al.*,[81] and Smith *et al.*[80]) were identified from the literature search for economic evaluations carried out in TA91, and are reviewed in detail within the TA91 Technology Assessment Report.[13]

Three of the 21 identified studies (NICE 2011,[79] Papaionannou *et al.*,[95] Papaioannou *et al.*[90]) were directly related to TA222 of which this MTA is in part a review and update (see Section 5.1.1 for a description of TA222). A further two studies, Gore *et al.*[96] and Montalar *et al.*[97] were published subsequent to TA222; Gore *et al.*[96] is a poster describing a cost-utility analysis of trabectedin in combination with PLDH compared with PLDH using more recent estimates of survival (Monk *et al. 2012*[63]*)*. Montalar *et al.*[97] is a cost-utility analysis carried out from the perspective of Spain comparing trabectedin in combination with PLDH vs PLDH monotherapy; the analysis was based upon the model developed for TA91. A further three identified studies (Griffin *et al.*,[98] Main *et al.*,[99] NICE 2005[10]) were related to TA91, of which this MTA is also in part a review and update. A description of the analysis carried out in TA91 is presented in Section 5.1.1.

Of the remaining nine economic evaluations identified, one was carried out from the perspective of the UK (TA285[15]); and was an STA considering the cost-effectiveness of bevacizumab in recurrent ovarian cancer. The model developed by the manufacturer for this STA was a semi-Markov model based upon the model structure outlined in TA91 (i.e. stable disease, progressed disease and death).

Of the remaining eight economic evaluations, seven were from the perspective of the US (Chan *et al.*,[100] Havrilesky *et al.*,[101] Lesnock *et al.*,[102] Lesnock *et al.*,[103] Case *et al.*,[104] Havrilesky *et al.*,[105] Rocconi *et al.*[106]) and one was from the perspective of Korea (Lee *et al.*[107]). Four of the eight economic evaluations were cost-utility analyses, i.e. assessed the incremental cost per additional QALY (Lesnock *et al.*,[103] Lesnock *et al.*,[102] Havrilesky *et al.*,[101] Lee *et al.*,[107]). Of these cost-utility analyses, Lesnock *et al.*[103] developed a Markov model with equivalent health states to those used in the TA91 TAG model: PFS; recurrence; and death. Havrilesky *et al*.[101] developed a Markov model with health states including no evidence of disease, and progressed disease; in addition, adverse events (specifically neurotoxicity), were accounted for within the model structure. Two studies, Lee *et al*.[107] and Lesnock *et al*.,[102] were presented as abstracts; Lee *et al*.[107] described the health states included within the model as: responsive; progressive; clinical remission; and death. Lesnock *et al*.[102] did not describe the model structure in sufficient detail to enable reporting of the health states.

All studies identified within recurrent ovarian cancer with the exception of the three studies appraised within TA91 (Capri and Cattaneo,[82] Ojeda *et al*.,[81] and Smith *et al.*[80]) were quality assessed against the NICE reference case, and Philips checklist (Appendix 8).[108]

5.1.3 Description and critique of manufacturer submitted evidence

Two manufacturers (Eli Lilly and Company Limited [gemcitabine]; PharmaMar [trabectedin]) submitted evidence for consideration for this MTA. Of these, one manufacturer (PharmaMar) submitted cost-effectiveness evidence. PharmaMar did not carry out a systematic review of the existing cost-effectiveness evidence; instead, the manufacturer developed an economic analysis based upon the model developed for TA91. The analysis and results are described below.

5.1.3.1 Trabectedin (Yondelis®) for the treatment of patients with relapsed platinum-sensitive ovarian cancer

The manufacturer developed an economic analysis based upon the model developed within TA91. With this model, the manufacturer evaluated the cost-effectiveness of trabectedin (1.1 mg/m^2) in combination with PLDH (30 mg/m^2) administered every three weeks, vs PLDH monotherapy (50 mg/m^2) administered every four weeks, for the treatment of patients with relapsed platinum-sensitive ovarian cancer. The TAG's appraisal of the manufacturer's economic evaluation against the requirements set out in the NICE reference case checklist for a base case analysis, and appraisal of the quality of the manufacturer's economic evaluation using the Philips checklist, are summarised in Appendix 8.[108]

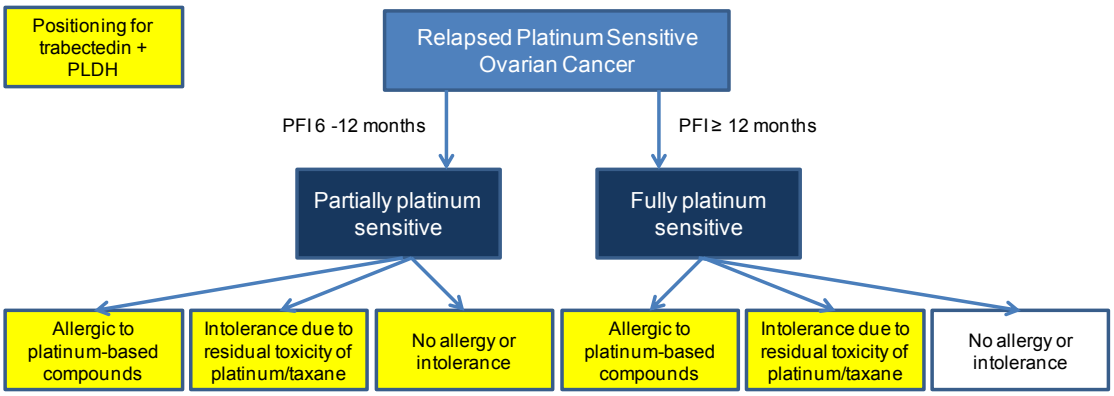
Patient population

Trabectedin, in combination with PLDH, is indicated for the treatment of patients with relapsed platinum-sensitive (PFI $\geq$ 6 months) ovarian cancer. The patient population for whom the manufacturer is requesting consideration within this MTA comprises a subset of this indication, specifically:

- people who are not suitable for, or not best managed with, platinum-based chemotherapy because of an allergy, or an intolerance due to residual toxicities; **and**
- people with partially platinum sensitive disease (PFI of 6 to 12 months).

The manufacturer illustrated this group of patients diagrammatically within the MS (Figure 15).

Figure 15. Patient population for which the manufacturer is positioning trabectedin (reproduced from MS, Figure 2.1, page 7)



Abbreviations using in figure: MS, manufacturer's submission; PFI, platinum free interval; PLDH, pegylated liposomal doxorubicin hydrochloride.

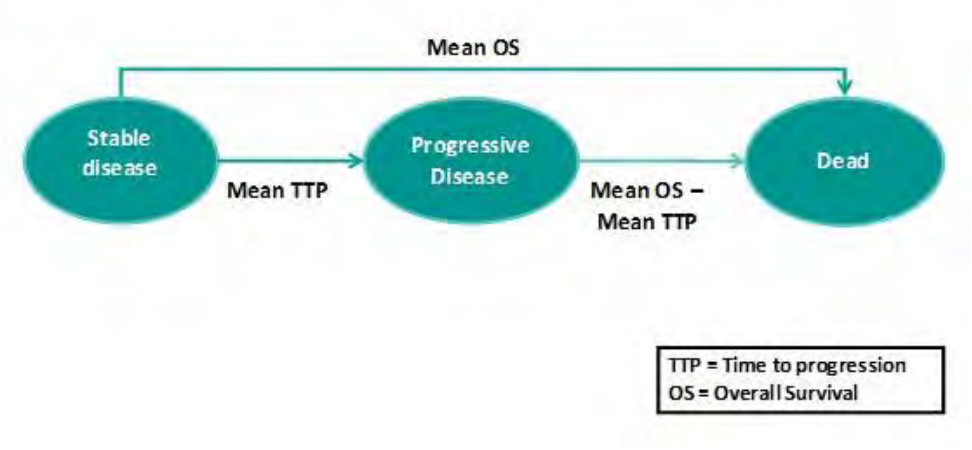
The manufacturer justified the choice of patient population by stating: "this patient population represents a restricted subgroup of the licensed platinum-sensitive population, and is chosen to align with the inclusion criteria of the OVA-301 trial and the clinical unmet need for non-platinum alternatives in these populations" (MS, page 30).

The TAG reviewed the inclusion criteria for OVA-301 supplied by the manufacturer within the submission and notes that OVA-301 included patients with platinum resistant, platinum refractory and platinum sensitive disease; the licence for trabectedin in combination with PLDH is for patients with platinum sensitive disease only. In addition, the TAG notes that the patients enrolled were those who "were not expected to benefit from or who were ineligible for or were not willing to receive retreatment with platinum-based chemotherapy" (MS, page 30 and MS, Appendix 2). The TAG notes that it is unclear from the MS what proportion of patients included within OVA-301 were allergic or intolerant to platinum therapy vs those who were not. However, following discussion with clinical experts, the TAG notes that the efficacy of non-platinum based treatments (such as trabectedin and/or PLDH) is unlikely to differ between people with an allergy or intolerance to platinum therapy vs people without. Therefore, the TAG considers that results are unlikely to differ between patients with or without the presence of allergy or intolerance.

Model structure

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 16). 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.

Figure 16. Model structure used in the PharmaMar submission



The TAG considers that the model structure employed by the manufacturer was generally appropriate and in line with previous published model structures identified from the TAG systematic review of the cost-effectiveness literature (Section 5.1.2). However, the TAG notes a key critique of the same model structure provided by the ERG for TA222: "the ERG believes that there are potential limitations to this simplicity, which can impose constraints regarding the assignment of costs, utilities and discounting" (ERG report for TA222, page 93).[(90)]

Comparators

The relevant comparators listed in the NICE scope for patients with platinum-sensitive ovarian cancer were:[(38)]

- paclitaxel monotherapy;
- paclitaxel in combination with platinum therapy;
- PLDH monotherapy;
- PLDH in combination with platinum therapy;
- gemcitabine in combination with carboplatin;
- topotecan;
- platinum-based monotherapy.

Additionally, the relevant comparators listed in the scope for patients with an allergy to platinum-based compounds were:

- paclitaxel monotherapy;
- PLDH monotherapy;
- topotecan;
- etoposide;
- best supportive care.

The comparator therapy assessed by the manufacturer was PLDH monotherapy. This represented one comparator listed within the NICE scope.

The manufacturer did not compare trabectedin in combination with PLDH with platinum-based regimens because data from the key clinical trial OVA-301 was restricted to patients who, upon enrolment, "were not expected to benefit from or who were ineligible for or were not willing to receive retreatment with platinum-based chemotherapy" (MS, page 30). However, the TAG notes that the patient group for which the manufacturer is seeking a recommendation includes partially platinum sensitive patients with no allergy or intolerance to platinum based chemotherapy, but who were not expected to benefit from platinum therapy. Following discussion with clinical experts, the TAG considers that partially platinum-sensitive patients may be treated with a platinum agent in clinical practice. The TAG acknowledges that patients with a PFI close to 6 months would be less likely to receive platinum; however, platinum therapy remains an important treatment option for this group of patients.

Nonetheless, the TAG notes that whilst a comparison of trabectedin in combination with PLDH vs a platinum agent is desirable, the clinical systematic review carried out by the TAG found no comparative clinical data linking (either directly or indirectly) trabectedin plus PLDH with a platinum agent administered either as monotherapy or in combination with another therapy. This issue and the importance of future research in this area are discussed in greater detail in Section 8.1.

In addition, the manufacturer did not compare trabectedin in combination with PLDH with paclitaxel or topotecan. The TAG notes that the manufacturer's rationale for omitting these comparisons was based on conclusions reached by the ERG responsible for assessing for TA222 (Box 1).

Box 1. Manufacturer's rationale for not including topotecan and paclitaxel as comparators within the economic evaluation (reproduced from MS page 30)

Non platinum-based regimens including paclitaxel, PLDH and topotecan were previously evaluated as comparators to trabectedin plus PLDH during the NICE STA. A MTC [mixed treatment comparison] including paclitaxel, PLDH and topotecan as comparators was presented during the submission. However, it was concluded by both the Appraisal Committee and the NICE ERG (Sheffield University) that when compared with paclitaxel or topotecan monotherapy:

"PLDH is the most clinically and cost-effective treatment within the platinum-sensitive population. As PLDH is the recommended second-line therapy, and trabectedin plus PLDH cannot be used where PLDH is contraindicated, the relative cost-effectiveness of trabectedin plus PLDH compared to paclitaxel or topotecan monotherapy is not needed, since there would never be a choice between these interventions. As such, a direct comparison of trabectedin plus PLDH is sufficient to address the decision problem."

Since no additional evidence has become available for PLDH, topotecan or paclitaxel since 2009 (see Section 3), in line with NICE and ERG guidance (from TA222), we have not considered paclitaxel and topotecan as comparators for trabectedin plus PLDH.

Abbreviations used in box: ERG, evidence review group; MS, manufacturer's submission; MTC, mixed treatment comparison; NICE, National Institute for Health and Care Excellence; PLDH, pegylated liposomal doxorubicin hydrochloride; STA, single technology appraisal.

The TAG acknowledges that based upon the network meta-analysis (NMA, referred to as a mixed treatment comparison within Box 1) and economic analysis carried out for TA91, for people with platinum sensitive disease, PLDH extendedly dominated topotecan, and resulted in an incremental cost per additional QALY vs paclitaxel at a value below £20,000. The TAG also notes that the manufacturer updated the clinical systematic review undertaken, in 2009, as part of TA222 and found two additional studies; both of which were related to OVA-301. The results from the clinical systematic review carried out by the TAG accorded with this. The TAG therefore acknowledges the rationale for restriction by the manufacturer; however, for completeness, have carried out a full NMA including paclitaxel and topotecan and included these comparisons within the TAG economic model (Section 5.2). This is to ensure that the most up-to-date information on clinical practice, costs, quality of life, and the most mature survival data from OVA-301 have been used to inform the decision problem that is the focus of this MTA.

Finally, the manufacturer did not compare trabectedin in combination with PLDH with etoposide or best supportive care because no comparative clinical evidence was found by the manufacturer to enable such a comparison. The TAG acknowledges that, similarly to the manufacturer, no comparative data between trabectedin plus PLDH and etoposide or best supportive care were found during the TAG systematic review of the clinical literature. This lack of data makes a robust comparison with etoposide or best supportive care unfeasible. The TAG explores this issue further in Section 5.2.12.

Effectiveness data (PFS and OS)

Estimates of mean PFS and OS were calculated from Kaplan-Meier data obtained from the OVA-301 clinical trial; an RCT providing head-to-head data for trabectedin in combination with PLDH vs PLDH monotherapy in patients with relapsed ovarian cancer. Specifically, the manufacturer fitted a variety of parametric curves (exponential, Weibull, Gompertz, log-logistic and log-normal) to OS and PFS Kaplan-Meier data for patients with platinum sensitive disease. These curves were fitted separately by treatment arm; i.e. treatment was not included as a covariate; the manufacturer did not provide a rationale within the submission for this methodology. In addition, the manufacturer used explanatory variables to control for the following baseline characteristics:

- age (continuous);

- race (categorical);
- PFI (continuous);
- CA-125 (categorical);
- liver or lung involvement (binary);
- prior taxane use (binary).

The manufacturer used the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) associated with each survival distribution to select the preferred distribution for PFS and OS. The Weibull distribution was selected to inform mean PFS for both trabectedin in combination with PLDH and PLDH monotherapy. The log-logistic distribution was selected to inform mean OS for both trabectedin in combination with PLDH and PLDH monotherapy. The results are summarised in Figures 17 and 18 and Table 90.

Figure 17. Survival distribution and Kaplan Meier plots for PFS (reproduced from MS, page 35)

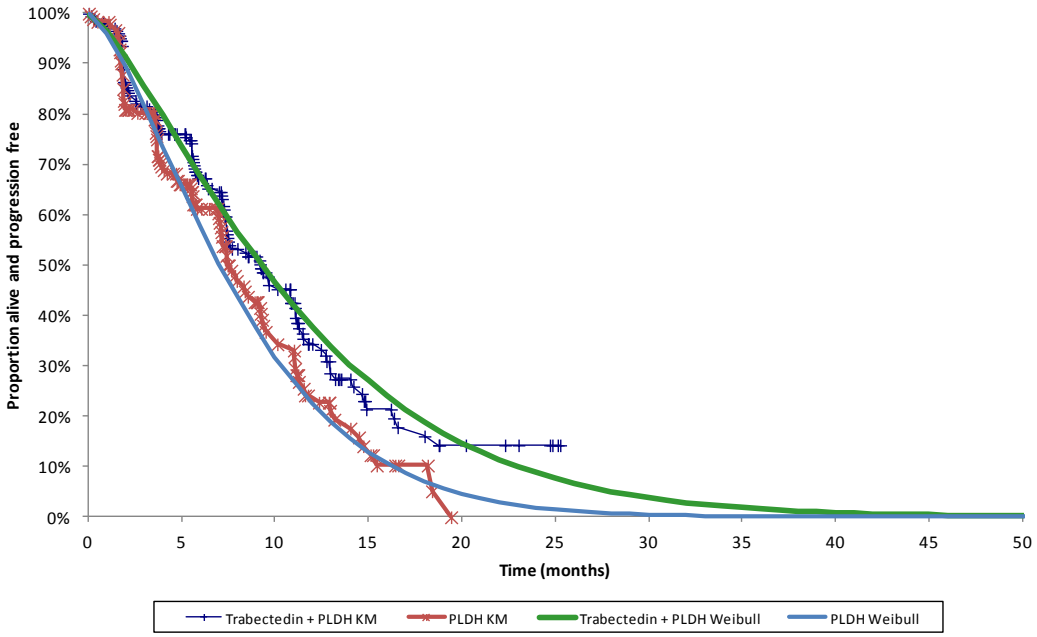


Figure 18. Survival distribution and Kaplan Meier plots for OS (reproduced from MS, page 35)

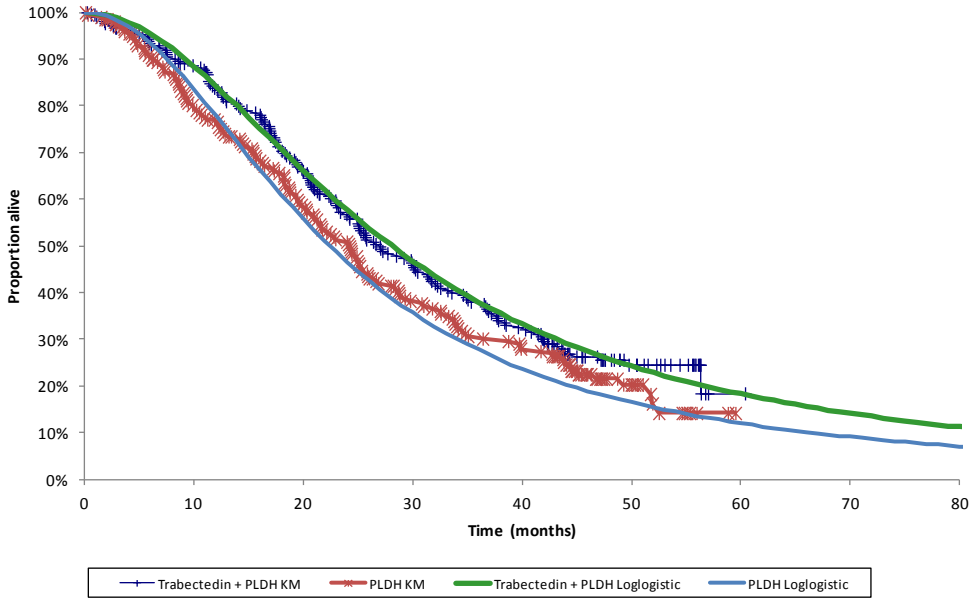


Table 90. Mean time to progression and mean overall survival estimated by the manufacturer from fitted curves

	Trabectedin in combination with PLDH	PLDH monotherapy
Mean time to progression	11.26 months	8.25 months
Mean overall survival	44.69 months	34.97 months
Abbreviation used in table: PLDH, pegylated liposomal doxorubicin hydrochloride.		

The PFS and OS data used within the manufacturer's economic model were obtained from the full platinum sensitive patient population of OVA-301; i.e. including both patients with partially (PFI 6 to 12 months) or fully (PFI > 12 months) platinum sensitive disease. The manufacturer's rationale for using these data was that OVA-301 was not powered for post-hoc analysis of subgroups within the platinum-sensitive stratum.

The TAG notes that within the analysis of PFS and OS, the manufacturer controlled for PFI (as a continuous variable). The TAG recognises that PFI is considered to be a prognostic factor for patients with relapsed ovarian cancer; patients with a longer PFI typically have an improved prognosis when compared with patients with a shorter PFI. The TAG also acknowledges that, when PFI is considered as a continuous rather than categorical variable, there exists a baseline imbalance in the PFI between patients in the PLDH plus trabectedin vs PLDH arms of OVA-301 (Table 91). The manufacturer calculated that the mean PFI for the two treatment arms was statistically significantly different (mean 13.3 months for PLDH monotherapy, and mean 10.6 months for trabectedin plus PLDH, p=0.009) Moreover, clinical opinion supports the manufacturer's use of a continuous, rather than categorical

variable to control for PFI. Consequently, the TAG considers the analysis carried out by the manufacturer to be appropriate, and recognises that the manufacturer explored the impact of controlling for PFI upon the ICER in sensitivity analysis. However, the TAG notes that the assessment of a statistical significant difference in PFI was estimated based on the full population (i.e. including platinum resistant/refractory patients) rather than for platinum sensitive patients alone.

Table 91. Reported mean PFI by treatment arm within the MS

	Trabectedin in combination with PLDH	PLDH monotherapy
Mean PFI (for all patients within OVA-301)	10.6 months	13.3 months
Mean PFI (for platinum sensitive patients within OVA-301)	14.3 months	19.0 months
Abbreviations used in table: MS, manufacturer's submission; PFI, platinum free interval; PLDH, pegylated liposomal doxorubicin hydrochloride.		

However, the TAG has one key area of concern around the extrapolated PFS and OS data used within the manufacturer's model; the degree of censoring observed within the PFS and OS data.

The PFS data used by the manufacturer within the economic model was subject to a high degree of censoring; for the full population (i.e. platinum sensitive and platinum resistant/refractory) within 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 within the MS, nor did the manufacturer provide an explanation for the quantity of censoring encountered. Moreover, the manufacturer did not provide detail around censoring for the platinum sensitive subgroup separately. The manufacturer reported that a total of 189 patients were censored in the final PFS analysis for platinum sensitive patients (approximately 45%); however, it is unclear for what reasons, and in which arm these patients were when censored.

In addition, limited details around censoring within the OS analysis have been presented within the MS. The manufacturer reports that a total of 114 patients were censored in the final OS analysis for platinum sensitive patients (approximately 27%); however, it is unclear for what reasons, and in which arm these patients were when censored.

The TAG requested the CSR for OVA-301 to explore this issue of censoring in both the PFS and OS analyses in further detail; however, [redacted]. Nevertheless, the number of people with platinum sensitive disease censored in the PFS and OS analyses by treatment arm was presented within the CSR. These are summarised in Table 92 and Table 93. The TAG notes that the degree of censoring for PFS in people with platinum sensitive

disease was approximately [redacted] in both arms, and the degree of censoring for OS in people with platinum sensitive disease was approximately [redacted].

Table 92. PFS for people with platinum sensitive disease, based upon the independent radiologist review data, all measureable subjects (adapted from MS CSR page 771)

	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
[redacted]		

Table 93. OS for people with platinum sensitive disease, based upon all randomised subjects analysis set (adapted from MS CSR [final efficacy update] page 18)

	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
[redacted]		

As a result of the high degree of censoring, and the lack of information provided around the reasons for censoring, the TAG notes that censoring within this analysis may be informative. The TAG notes that the presence of informative censoring may reduce the validity of the Kaplan Meier data presented and used within the model. The TAG does note, however, that censoring is [redacted] (in terms of both number of patients and proportion of patients) between the two arms of the study on aggregate, although it is unclear at what time points censoring occurred.

Adverse event incidence

The manufacturer included adverse events of Grade 3 or 4 (or those associated with a notable cost) within the model. Table 94 summarises the adverse event incidence used in the economic model.

Table 94. Adverse event incidence applied within the manufacturer's economic model (adapted from MS, Table 7.1, page 36)

Women with platinum-sensitive disease (n=425)		Grade 3 AE	Grade 4 AE
PLDH	Neutropenia	20.0%	11.2%
	Neutropenia Febrile	1.4%	0.5%
	Neutropenic Infection	-	-
	Neutropenic Sepsis	-	-
	Platelets*	2.4%	2.4%
	Haemoglobin*	4.9%	2.0%
	Nausea/ Vomiting	1.9%	-
	Diarrhoea	1.9%	-
	Palmar-Plantar Erythrodysaesthesia Syndrome	20.2%	0.5%
	Stomatitis	4.3%	-
Trabectedin/PLDH	Neutropenia	31.8%	41.0%
	Neutropenia Febrile	4.1%	1.8%
	Neutropenic Infection	0.5%	-
	Neutropenic Sepsis	0.5%	-
	Platelets*	11.5%	9.7%
	Haemoglobin*	13.8%	4.1%
	Nausea/Vomiting	14.3%	0.5%
	Diarrhoea	2.8%	-
	Palmar-Plantar Erythrodysaesthesia Syndrome	3.7%	-
	Stomatitis	1.4%	-

*Based on clinical laboratory values
Abbreviations used in table: AE, adverse event; PLDH, pegylated liposomal doxorubicin hydrochloride.

Quality of life

The manufacturer did not carry out a systematic search of the utilities literature; instead, the manufacturer used EQ-5D data derived from the OVA-301 trial for the health states described within the economic model (stable disease, and progressive disease). Mean utility in the stable and progressed health states were estimated to be 0.718 and 0.649, respectively. Although not reported, the TAG considers it likely that the estimates of HRQoL were derived from the full population included within the OVA-301 trial; i.e. both platinum-sensitive patients and platinum resistant patients. The manufacturer undertook a number of sensitivity analyses using HRQoL data by platinum sensitivity and treatment arm. 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.

The TAG notes that the HRQoL data used by the manufacturer is in line with the NICE Guide to the Methods of Technology Appraisal in which it is stated that EQ-5D is the preferred measure of HRQoL in adults.[109]

Resource use and costs

The manufacturer included the following costs within the economic analysis: treatment, administration and preparation, management of disease, and treatment of adverse events. Costs by treatment arm are summarised in Table 95.

Table 95. Costs by treatment arm used in PharmaMar economic model

Cost	Trabectedin in combination with PLDH	PLDH monotherapy	Stated source
Drug cost per cycle (based upon a BSA of 1.72 m^2) and assuming no vial sharing	£3,167	£1,425	BNF 2013
Drug administration costs	£334 per attendance £440 one off cost of central venous line insertion	£203 per attendance	NHS Reference Costs 2011/12
Medical management	Stable period: one outpatient visit per month (£121) and one CT scan every two months (£125) Progressed period: estimated £6,667 annual cost		NHS Reference Costs 2011/12 Guest 2006
Adverse events, total cost per patient	£398	£147	NHS Reference Costs 2011/12
Abbreviations used in table: BNF, British National Formulary; BSA, body surface area; CT, computed tomography; PLDH, pegylated liposomal doxorubicin hydrochloride.			

Subsequent to initial submission, the manufacturer submitted a proposed patient access scheme (PAS) affecting the total chemotherapy costs associated with trabectedin in combination with PLDH. For the PAS, the manufacturer proposes that the NHS pays for the first 5 cycles of chemotherapy, after which acquisition costs would be met by the manufacturer. To reflect this within the economic model, the manufacturer assumed that patients would receive a lower number of cycles (and therefore a lower cost – efficacy is not affected by this assumption) of therapy with trabectedin plus PLDH; without the PAS patients received 6.86 cycles of trabectedin on average and 4.28 cycles on average with the PAS. In addition, the manufacturer included implementation/administrative costs associated with the PAS and estimated that the total discounted implementation cost of the PAS would be £560.74.

Results

The manufacturer presented discounted, deterministic and probabilistic results from the analysis within the MS. The manufacturer presented results both without the PAS (Table 96), and subsequently following an updated submission, results including the PAS (Table 97).

Without the PAS, the manufacturer estimated an incremental cost per additional QALY for trabectedin in combination with PLDH vs PLDH monotherapy to be £39,306 in the deterministic base case and £39,447 in the probabilistic base case. The TAG notes that in the base case, probabilistic and deterministic results are comparable.

With the PAS, the manufacturer estimated an incremental cost per additional QALY for trabectedin in combination with PLDH vs PLDH monotherapy to be £27,573 in the deterministic base case and £27,761 in the probabilistic base case.

Table 96. Manufacturer estimates of base case results (adapted from MS, Table 7.9, page 41 and Table 7.12, page 43) without PAS

Treatment	Total costs (£)	Total LYG	Total QALYs	Inc costs (£)	Inc LYG	Inc QALYs	ICER (£)
Deterministic results							
Trabectedin plus PLDH	43,907	3.72	2.33	–	–	–	–
PLDH	24,809	2.91	1.85	19,098	0.81	0.49	39,306
Probabilistic results							
Trabectedin plus PLDH	44,203	3.724	2.35	–	–	–	–
PLDH	24,931	2.914	1.86	19,273	0.810	0.49	39,447
Abbreviations used in table: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PLDH, pegylated liposomal doxorubicin hydrochloride; QALYs, quality-adjusted life years.							

Table 97. Manufacturer estimates of base case results (adapted from PAS submission Table 8 page 24, and Table 9 page 27) with PAS

Treatment	Total costs (£)	Total LYG	Total QALYs	Inc costs (£)	Inc LYG	Inc QALYs	ICER (£)
Deterministic results							
Trabectedin plus PLDH	38,206	3.72	2.33	–	–	–	–
PLDH	24,809	2.91	1.85	13,397	0.81	0.49	27,573
Probabilistic results							
Trabectedin plus PLDH	38,206	3.724	2.35	–	–	–	–
PLDH	24,931	2.914	1.86	13,563	0.810	0.49	27,761
Abbreviations used in table: ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; PLDH, pegylated liposomal doxorubicin hydrochloride; QALYs, quality-adjusted life years.							

Sensitivity analysis

The manufacturer carried out a number of sensitivity analyses both deterministic (one-way sensitivity analysis, scenario analyses) and probabilistic for results with and without the PAS.

In one-way sensitivity analysis, the ten variables that the cost-effectiveness results were most sensitive to were presented in a tornado plot. Cost-effectiveness results were most sensitive to estimates of OS. The TAG notes that, although not reported, the manufacturer varied OS between an upper and lower 20% of the base case figure. For the analyses without the PAS, the TAG notes that the x-axis on the tornado diagram was limited to £107,000 when the result using the low value for trabectedin in combination with PLDH for overall survival within the economic model was in fact

£266,114 (without PAS). The TAG updated the tornado diagram presented within the manufacturer's model to reflect this (Figure 19, without PAS). Figure 20 presents results of the one-way sensitivity analysis for the results with PAS.

Figure 19. Results from the manufacturer's one-way sensitivity analysis updated by the TAG to reflect the full range of ICERs; without PAS

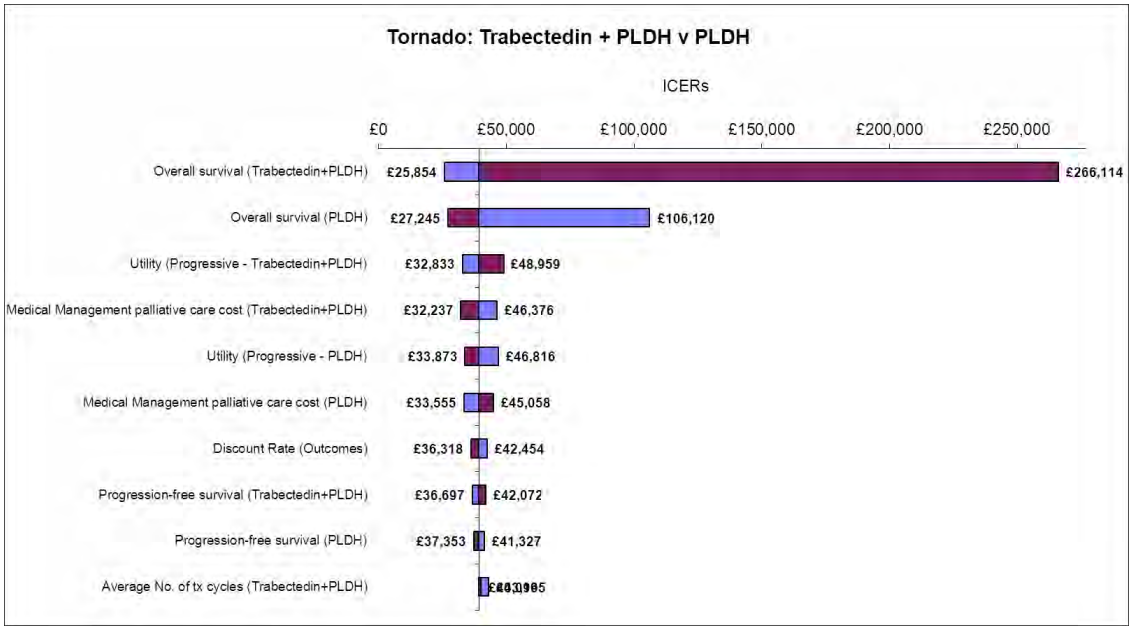
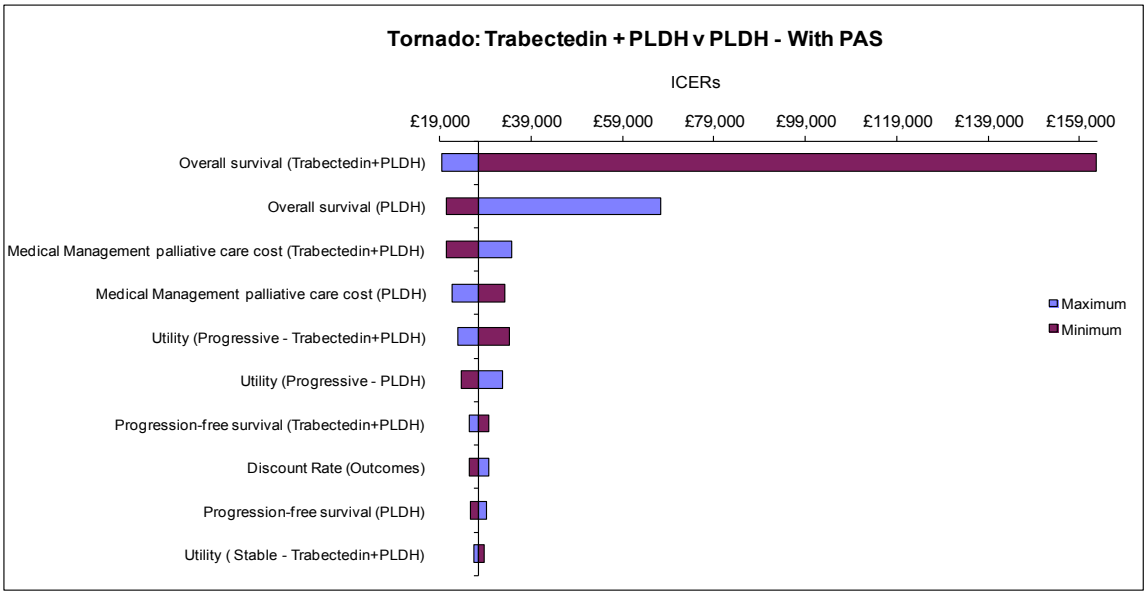


Figure 20. Results from the manufacturer's one-way sensitivity analysis; with PAS (reproduced from PAS submission page 25)



A number of scenario analyses were presented within the MS; results with and without the PAS are summarised in Table 98, Table 99 and Table 100.

Table 98. Scenario analyses presented by the manufacturer relating to PFS and OS (adapted from MS, Table 7.10, page 42 and PAS submission, Table 10, page 29)

Scenario	Trabectedin plus PLDH (PFS)	PLDH (PFS)	Trabectedin plus PLDH (OS)	PLDH (OS)	ICER without PAS (£)	ICER with PAS (£)
Base case	**Weibull AIC = 451.2**	**Weibull AIC = 380.9**	**Log-logistic AIC = 508.0**	**Log-logistic AIC = 472.7**	**39,306**	**27,573**
Distribution 1	Gompertz AIC = 457.7	Gompertz AIC = 384.0	Log-logistic AIC = 508.0	Log-logistic AIC = 472.7	39,320	27,572
Distribution 2	Weibull AIC = 451.2	Weibull AIC = 380.9	Weibull AIC = 508.1	Weibull AIC = 478.6	52,589	35,485
Distribution 3	Gompertz AIC = 457.7	Gompertz AIC = 384.0	Weibull AIC = 508.1	Weibull AIC = 478.6	52,611	35,485
Base case distribution (no PFI adjustment)	Weibull AIC = 456.3	Weibull AIC = 385.8	Log-logistic AIC = 514.3	Log-logistic AIC = 504.7	109,892	70,222

Abbreviations used in table: AIC; Akaike Information Criterion; ICER, incremental cost-effectiveness ratio; OS, overall survival; PAS, patient access scheme; PFI, platinum free interval; PFS, progression free survival; PLDH, pegylated liposomal doxorubicin hydrochloride.

Table 99. Additional scenario analyses presented by the manufacturer (adapted from MS, Table 7.11, page 42) without PAS

Scenario	Trabectedin + PLDH		PLDH		Incremental analysis	
	Total Cost	**Total QALYs**	**Total Cost**	**Total QALYs**	**ICER**	**Difference**
Base Case	**£43,907**	**2.33**	**£24,809**	**1.85**	**£39,306**	**–**
Treatment and platinum-sensitive specific utilities	£43,907	2.46	£24,809	1.98	£39,975	£669
Neutropenia *Grade 3 (base case: £0, alternative scenario: £122.31) Grade 4 (base case: £0, alternative scenario: £2,346.49)*	£44,901	2.33	£25,094	1.85	£40,766	£1,460
Neutropenic infection *Grade 3 and 4 (base case: £2,346, alternative scenario: £2,108)*	£43,906	2.33	£24,809	1.85	£39,304	-£2
Neutropenic sepsis *Grade 3 and 4 (base case: £2,346, alternative scenario: £2,108)*	£43,906	2.33	£24,809	1.85	£39,304	-£2

Abbreviations used in table: ICER, incremental cost-effectiveness ratio; MS, manufacturer's submission; PAS, patient access scheme; PLDH, pegylated liposomal doxorubicin hydrochloride; QALYs, quality-adjusted life years.

Table 100. Additional scenario analyses presented by the manufacturer (adapted from MS, Table 7.11, page 42) with PAS

Scenario	Trabectedin + PLDH		PLDH		Incremental analysis	
	Total Cost	Total QALYs	Total Cost	Total QALYs	ICER	Difference
Base Case	£38,206	2.33	£24,809	1.85	£27,573	–
Treatment and platinum-sensitive specific utilities	£38,206	2.46	£24,809	1.98	£28,042	£469
Neutropenia *Grade 3 (base case: £0, alternative scenario: £122.31) Grade 4 (base case: £0, alternative scenario: £2,346.49)*	£39,200	2.33	£25,094	1.85	£29,033	£1,460
Neutropenic infection *Grade 3 and 4 (base case: £2,346, alternative scenario: £2,108)*	£38,205	2.33	£24,809	1.85	£27,571	-£2
Neutropenic sepsis *Grade 3 and 4 (base case: £2,346, alternative scenario: £2,108)*	£38,205	2.33	£24,809	1.85	£27,571	-£2

Abbreviations used in table: ICER, incremental cost-effectiveness ratio; MS, manufacturer's submission; PAS, patient access scheme; PLDH, pegylated liposomal doxorubicin hydrochloride; QALYs, quality-adjusted life years.

The manufacturer also presented results from probabilistic analysis; both through plots upon the cost-effectiveness plane (Figure 21, Figure 23), and cost-effectiveness acceptability curves (CEACs, Figure 22 and Figure 24). According to the manufacturer's analysis, at a willingness-to-pay (WTP) threshold of £20,000, the probability that trabectedin in combination with PLDH is cost-effective vs PLDH monotherapy is 11% and 10% with and without the PAS, respectively. At a WTP threshold of £30,000, the probability of cost-effectiveness increases to 53% with the PAS and 20% without the PAS.

Figure 21. Cost-effectiveness plane presented by the manufacturer summarising the results of probabilistic analysis (reproduced from MS, Figure 7.7, page 43) without PAS

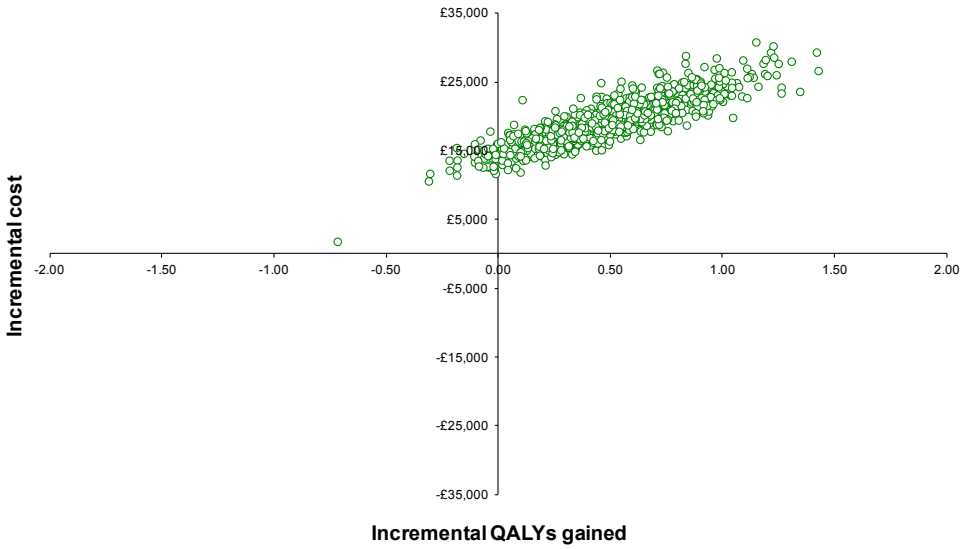


Figure 22. Cost-effectiveness acceptability curve presented by the manufacturer summarising the results of probabilistic analysis (reproduced from MS, Figure 7.8, page 43) without PAS

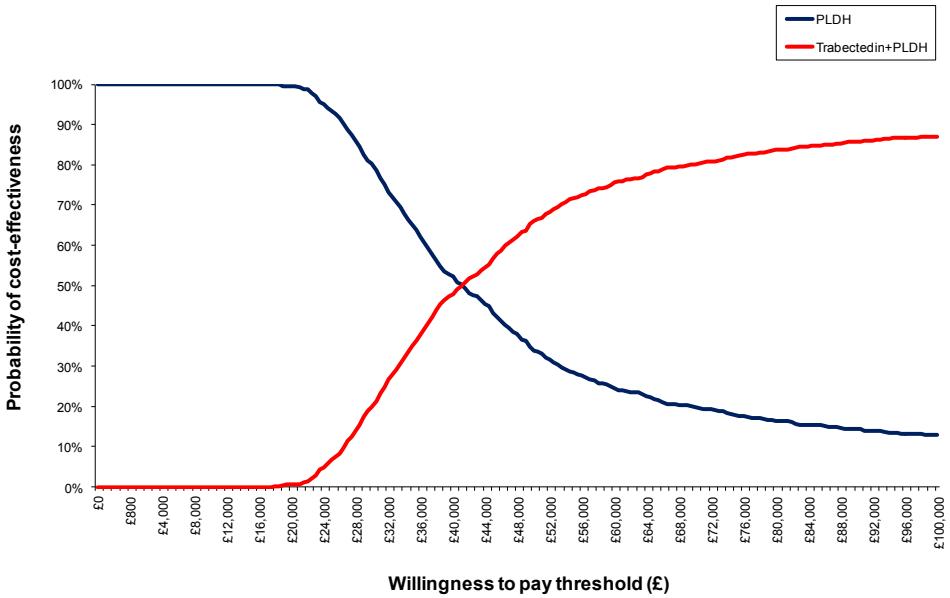


Figure 23. Cost-effectiveness plane presented by the manufacturer summarising the results of probabilistic analysis (reproduced from PAS submission Figure 6 page 28) with PAS

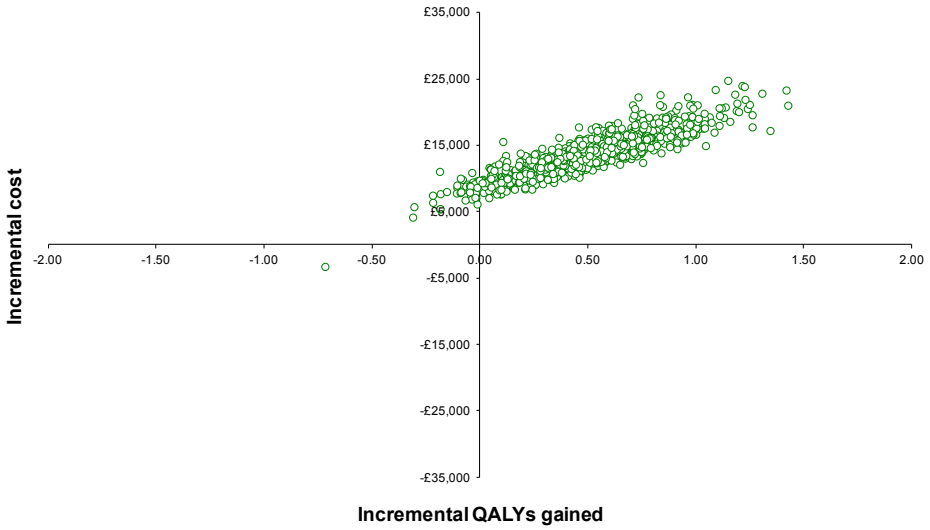
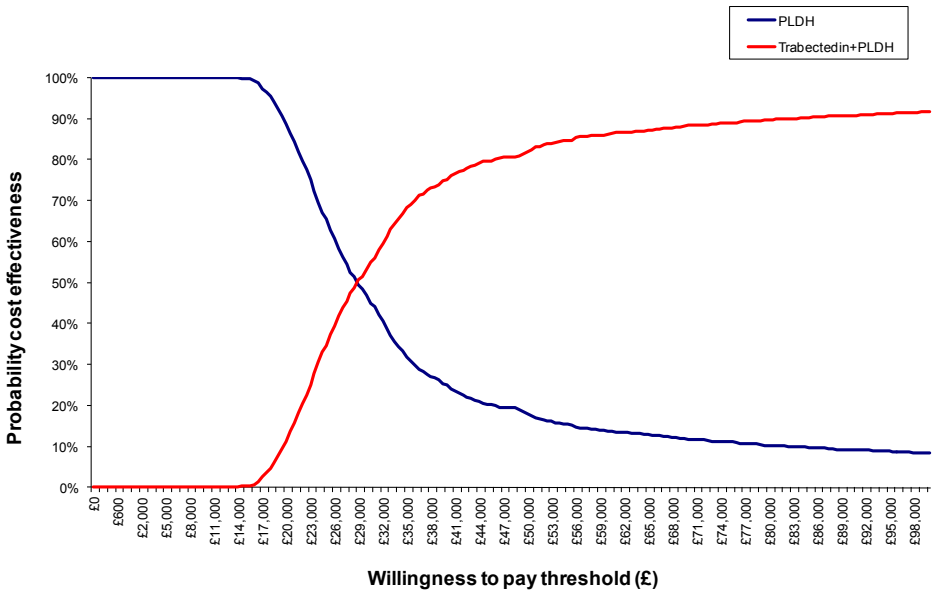


Figure 24. Cost-effectiveness acceptability curve presented by the manufacturer summarising the results of probabilistic analysis (reproduced from PAS submission Figure 7 page 28) with PAS



The TAG considers that the sensitivity analyses presented by the manufacturer identified estimates of OS as the key driver of model results and the main accumulator of QALYs. In particular, through changes in the functional form, and through controlling for PFI in the extrapolated estimates of OS.

Without the PAS, the manufacturer concluded that "the ICER of £39,306 per QALY could be considered cost-effective in the UK setting despite it being above the traditional NICE threshold

values of £20,000 to £30,000 per QALY as a consequence of trabectedin plus PLDH being a candidate for end of life criteria" (MS, page 43). The manufacturer's rationale for claiming that trabectedin in combination with PLDH is a candidate for end of life is outlined in Table 101. End of life is discussed in greater detail in Section 6.16.1 however, the TAG considers it important to note that whilst median OS for PLDH was estimated by the manufacturer to be 19.4 months in the platinum-sensitive population (after controlling for PFI and other prognostic factors), mean OS for PLDH was estimated to be 35 months. Therefore, baseline life expectancy, as indicated by mean overall survival for patients treated with PLDH, is likely to be greater than 24 months.

Table 101. Manufacturer rationale for claiming consideration under end of life criteria (reproduced from MS Appendix 5)

NICE End of Life Criteria	Eligibility of trabectedin for consideration under end of life
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Trabectedin plus PLDH is indicated for patients with a life expectancy expected to be less than 2 years without treatment. The final analysis showed that median overall survival in the platinum-sensitive and partially-platinum sensitive populations were 24.1 months and 16.4 months for patients treated with PLDH. Accounting for the imbalance in PFI and other prognostic factors in the platinum-sensitive population reduced the median to 19.4 months.
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment	For patients 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, which is well in excess of the 3 months required. Estimated mean survival suggests this extension of life could be in excess of 9 months.
No alternative treatment with comparable benefits is available through the NHS.	For the population considered (i.e. relapsed ovarian cancer patients who are unsuitable to platinum-based compounds and who would otherwise be treated with PLDH) no alternative treatment has shown comparable benefits.
The treatment is licensed or otherwise indicated, for small patient populations	It is estimated that there are 2,617 patients with relapsed platinum-sensitive ovarian cancer in England and Wales. In this submission, only relapsed platinum-sensitive ovarian cancer patients who are unsuitable for treatment with platinum-based chemotherapy because of allergy or intolerance due to residual toxicities or because they have partially platinum-sensitive disease will be considered for treatment with trabectedin plus PLDH. It is estimated that approximately 491 patients will fall into this group in 2014.
The estimates of the extension to life are robust and can be shown or reasonably inferred from either progression free survival or overall survival	Extension of life can be seen by the difference in both median and mean survival when considering OS adjusted for prognostic factors including PFI. Even when the PFI imbalance is not accounted for (which biases OS results in favour of PLDH), the platinum-sensitive population is associated with a 2.9 month survival gain and the partially platinum-sensitive population is associated with a 6 month survival gain.
The assumptions used in the reference case economic modelling are plausible objective and robust	Adjusting for imbalances in pre-specified prognostic factors which significantly affect OS and PFS reduces bias and has been performed by ERGs previously (NICE TA222)
Abbreviations used in table: ERG, evidence review group; MS, manufacturer's submission; OS, overall survival; PFI, platinum free interval; PLDH, pegylated liposomal doxorubicin hydrochloride.	

Budget impact

The manufacturer submitted a budget impact analysis for trabectedin use. The manufacturer estimated that the total budget impact of introducing trabectedin in combination with PLDH would be £3,284,036 in 2014 (491 patients), increasing to £4,359,077 in 2018 (506 patients). The TAG notes that these costs were based upon the submission without PAS. The manufacturer did not provide an updated budget impact analysis within the PAS submission. However, the TAG notes that within the submitted budget impact model, estimates with PAS were presented. With PAS, the manufacturer estimated a total budget impact of £1,439,204 in 2014 (491 patients), increasing to £1,910,333 in 2018 (506 patients).

The calculations used by the manufacturer to estimate the population are summarised in Table 102. The figures relate to the population for which the manufacturer has requested consideration; i.e. people who are not suitable for, or not best managed with, platinum-based chemotherapy because of an allergy, or an intolerance due to residual toxicities; and people with partially platinum sensitive disease (PFI of 6 to 12 months).

Table 102. Manufacturer estimates of patient numbers (reproduced from MS, page 44)

	2014	**2018**
Population England and Wales	56,839,104	58,679,898
Percentage women	51%	51%
Female population England and Wales	**28,419,552**	**29,339,949**
Incidence cases per 100,000 of the population per year	20.9	20.9
Total Incident Cases per year	**6,058**	**6,255**
Proportion of ovarian cancer that is epithelial	90%	90%
Number with epithelial ovarian cancer	**5,453**	**5,629**
Proportion of ovarian cancer diagnosed at stages III/IV	75%	75%
Number with epithelial stage III/IV ovarian cancer	**4,089**	**4,222**
Proportion of ovarian cancer cases that are recurrent	80%	80%
Number of patients with recurrent epithelial stage III/V ovarian cancer	**3,272**	**3,378**
Proportion of patients with recurrent stage III/IV ovarian cancer that are platinum-sensitive	80%	80%
Number of patients with recurrent stage III/IV ovarian cancer that are platinum-sensitive	**2,617**	**2,702**
Proportion of platinum-sensitive patients that are partially platinum-sensitive (6-12 months)	30%	30%
Proportion of partially sensitive patients unsuitable for platinum-based therapy	50%	50%
Number of partially platinum-sensitive patients that are unsuitable for platinum-based therapy (6-12 months)	**393**	**405**

Proportion of fully platinum-sensitive patients (>12 months) with hypersensitive reactions	20%	20%
Proportion of fully platinum-sensitive patients with severe hypersensitivity reactions	47%	47%
Proportion of fully platinum-sensitive patients with severe allergies whom abandon platinum treatment	25%	25%
Number of fully platinum-sensitive patients (>12 months) unsuitable for treatment with platinum-based therapy due to allergies	**43**	**44**
Proportion of fully platinum-sensitive patients with occurrence of neuropathy	20%	20%
Persistent neurological toxicity among fully platinum-sensitive patients and intolerant to be retreated with platinum at 1 year after the end of therapy	15%	15%
Number of fully platinum-sensitive patients unsuitable for treatment with platinum-based therapy due to intolerance	**55**	**57**
Total incidence patients eligible for treatment	**491**	**506**

The TAG notes that the calculations, used to estimate the eligible population, were based solely around incident patients. The TAG considers that the budget impact would increase should prevalent patients who experience further relapses and have not previously been treated with trabectedin be included within the calculations. The TAG estimated that based upon an incidence of 6,058 patients per year, and a death rate of 4,295 (Section 2.2.1), the remaining prevalent patients with ovarian cancer would be 1,763. Using the manufacturer's calculations for the year 2014 results in an estimate of the total number of patients eligible for treatment of 633.

5.1.4 Summary and conclusions of available cost-effectiveness evidence

No single cost-effectiveness analysis considering the full range of interventions and comparators relevant for this MTA was identified in the TAG systematic review (Section 5.1.2). The existing published UK cost-effectiveness evidence in recurrent ovarian cancer related largely to TA222 (NICE 2011,[79] Papaionannou *et al.,*[95] Papaioannou *et al.*[90]) and TA91 (Griffin *et al.,*[98] Main *et al.,*[99] NICE 2005[10]). In addition, three further studies (TA285,[15] Forbes *et al.,*[94] Smith *et al.*[80]) considering the UK perspective were identified; the manufacturer for TA285 built a model based upon the model used in TA91 and TA222, and the remaining two studies were cost-minimisation analyses published prior to 2004.

The majority of the published UK evidence, therefore, evaluated the cost-effectiveness of treatments in recurrent ovarian cancer based upon the model developed for TA91. This model was comprised of three health states: the stable disease period, the progressive disease period, and death. Other recently published cost-utility models in recurrent ovarian cancer also considered similar health states

(Lesnock *et al.*,[103] Havrilesky *et al.*,[101] Lee *et al.*[107]) from the perspective of the US (Lesnock *et al.*,[103] Havrilesky *et al.*[101]) and Korea (Lee *et al.*[107]).

One manufacturer submission was received that included economic evidence (PharmaMar). The manufacturer employed the TA91 model structure, and used Weibull and log-logistic distributions to estimate the mean time spent in each health state (stable disease, progressed disease and death). Clinical data from a single head-to-head comparison of trabectedin in combination with PLDH vs PLDH monotherapy (OVA-301) was used to inform the parametric distributions used.

As such, whilst there exist studies which compare the cost-effectiveness of the treatments relevant to the scope of this MTA, there does not exist a simultaneous comparison of all the interventions of interest. A *de novo* decision analytic model was therefore developed to address this issue, and was based upon the model structure developed within TA91 (Section 5.2.4). The model structure developed within TA91 was considered to be the most appropriate for this decision problem. This is because the structure has been widely used within recurrent ovarian cancer, and because the health states within this model capture clinically important aspects relating to the treatment of recurrent ovarian cancer; both extending survival, but also extending the stable, progression free, period.

5.2 Independent economic assessment

5.2.1 Overview

As no single published study, or manufacturer's submission, simultaneously compared the cost-effectiveness of treatments relevant to the scope of this MTA, the Technology Assessment Group (TAG) carried out an independent assessment and developed a *de novo* economic analysis. The methodology employed, and the results from this analysis are described and presented within this section (Table 103).

Table 103. Overview of the TAG's economic analysis

Element of the analysis	Section
Comparison of the *de novo* analysis to the final NICE scope	5.2.2
Population characteristics	5.2.3
Model structure	5.2.4
Interventions and comparators	5.2.5
Overview of model parameters, sources and key assumptions	5.2.6
Treatment effectiveness	5.2.7
Adverse event incidence	5.2.8
Health-related quality of life data	5.2.9
Costs	5.2.10
Approach to uncertainty	5.2.11
Results	5.2.12 and 5.2.13
Summary	5.2.14
Abbreviations used in table: NICE, National Institute for Health and Care Excellence; TAG, Technology	

Assessment Group.

5.2.2 Comparison to scope

The summary of the final scope issued by NICE for this MTA is presented below in Table 104, alongside a commentary detailing to what extent the *de novo* analysis carried out by the TAG satisfies the scope.

Table 104. Comparison of the Technology 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.	Yes For people with platinum sensitive ovarian cancer all interventions of interest were considered; however, due to the data available from the literature, two independent networks were constructed.
	For people with platinum-resistant or platinum-refractory ovarian cancer: • paclitaxel alone or in combination with platinum chemotherapy; • pegylated liposomal doxorubicin hydrochloride; • topotecan.	Partially Data for paclitaxel in combination with platinum was not available from the literature. Therefore, this intervention was omitted from the base case analysis.
	For people who are allergic to platinum-based compounds: • paclitaxel; • pegylated liposomal doxorubicin hydrochloride; • trabectedin in combination with pegylated liposomal doxorubicin hydrochloride; • topotecan.	Yes Based upon expert clinical advice it was considered that response to therapy was independent of presence or absence of platinum allergy. It was therefore assumed that results from non-platinum based regimens for the platinum sensitive and platinum resistant/refractory populations were applicable to people allergic to platinum based compounds.
Population(s)	People with ovarian cancer that has recurred after first-line (or subsequent) platinum-based chemotherapy or is refractory to platinum-based chemotherapy	Yes
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.	Yes 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.	Partially 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.
	For people who are allergic to platinum-based compounds: • the interventions listed above in comparison with each other; • etoposide; • best supportive care.	Partially Based upon expert clinical advice, it was considered that response to therapy was independent of presence or absence of platinum allergy. It was therefore assumed that results from non-platinum based regiments for the platinum sensitive and platinum resistant/refractory regimens were applicable to people allergic to platinum based compounds.
Outcomes	The outcome measures to be considered include: • overall survival; • progression-free survival; • response rate; • adverse effects of treatment; • health-related quality of life.	Partially Response rate was not utilised in the economic analysis; this outcome was considered in the clinical review.
Economic analysis	The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	Yes
Other considerations	If the evidence allows the following subgroups will be considered: • subgroups according to duration of response to first-line platinum-based chemotherapy; • people who are not suitable for platinum based chemotherapy because of allergy or intolerance. Guidance will only be issued in accordance	Partially Data for people with partially platinum sensitive and fully platinum sensitive disease was not sufficient to carry out a full economic analysis.

	with the marketing authorisation.	
Abbreviations used in table: NICE, National Institute for Health and Care Excellence; TAG, Technology Assessment Group.		

5.2.3 Population

The population of interest for this MTA is people with ovarian cancer that has recurred after first-line (or subsequent) platinum-based chemotherapy or is refractory to platinum-based chemotherapy. Specifically, the following subgroups are described:

- people with platinum-sensitive ovarian cancer (cancer which responds to initial chemotherapy but recurs 6 months or more after completion of the regimen), i.e., platinum free interval (PFI) $\geq$ 6 months;
- people with platinum-resistant (cancer which responds to initial chemotherapy but recurs within 6 months after completion of the regimen) and platinum-refractory cancer (cancer does not respond to initial therapy), i.e. PFI < 6 months;
- people who are allergic to platinum-based compounds.

Following consultation with clinical experts, it was noted that the duration of the platinum free interval is a key prognostic factor. Moreover, it was noted that platinum sensitivity (as indicated by the PFI), is a continuum, rather than a categorical variable. That is, patients' response to treatment would be expected to gradually decline with decreasing PFI. Furthermore, clinical experts fed back that, in conjunction with factors such as neuropathy and patient preference, the duration of PFI would affect the treatment options considered. (Section 3).

Furthermore, the TAG notes that clinical effectiveness data (identified in the TAG's clinical effectiveness review, Section 4.2), is presented by categories of platinum sensitivity. Most frequently, for patients with platinum sensitive disease (PFI $\geq$ 6 months) and patients with platinum resistant/refractory disease (PFI < 6 months).

Therefore, based on expert clinical opinion, and on the data available to inform the analysis, the TAG considers that disaggregation of the results by platinum sensitivity is more clinically relevant than presentation of the results in the full population (i.e., people with platinum resistant, refractory or sensitive disease). Consequently, results from the platinum resistant/refractory subgroup and the platinum sensitive subgroup are presented separately, with no explicit analysis of the full population (Section 5.2.12).

The TAG notes that some data were available for patients with fully platinum sensitive (PFI >12 months) and partially platinum sensitive (PFI 6-12 months) disease (Section 4.2). However, these data were insufficient to inform robust cost-effectiveness analysis. Therefore consideration of the cost-

effectiveness of treatments in patients with partially or fully platinum sensitive disease has been considered in sensitivity rather than base case analysis.

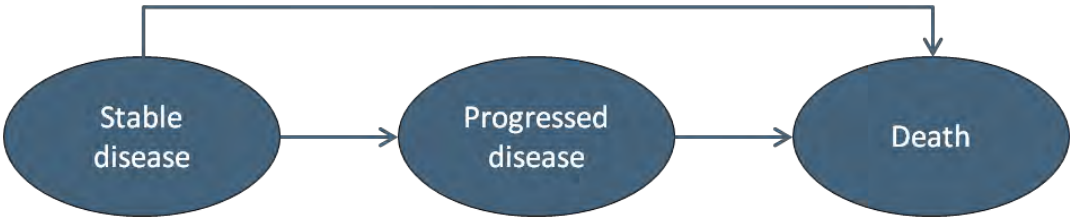
Additionally, the TAG sought clinical advice around expected response to treatment for patients with an allergy to platinum-based compounds compared to those without an allergy. It was noted by clinical experts that response to non-platinum based therapies would be expected to be consistent between patients with or without an allergy or intolerance to platinum based therapy. The TAG therefore considers it appropriate to include platinum allergic patients in the platinum sensitive and platinum refractory subgroups. Therefore, a separate analysis of platinum allergic patients has not been carried out; however, treatment options for platinum allergic patients are assumed to exclude platinum-based therapies.

5.2.4 Model structure

The model structure employed by the TAG, to facilitate a comparison of the cost-effectiveness of the interventions and comparators outlined for this MTA, is derived from the cohort model developed in TA91 (Figure 25).

The TAG elected to use a cohort model approach rather than individual patient modelling. This approach was considered to be the most appropriate because, with the exception of PFI, there is limited evidence of the effect of individual patient characteristics/history on disease course. Furthermore, data were not available at a sufficiently disaggregated level in order to model at the individual level.

Figure 25. Model structure for the Technology Assessment Group's *de novo* economic evaluation



As evidenced from the systematic review of the cost-effectiveness literature carried out by the TAG (Section 5.1.2), this model structure has previously been used to assess interventions for recurrent ovarian cancer. Moreover, the health states within this model capture clinically important aspects relating to the treatment of recurrent ovarian cancer; both extending survival, but also extending the stable, progression free, period. In TA285, a recent STA considering bevacizumab use in recurrent advanced ovarian cancer, the importance of PFS was highlighted.[15] Specifically, patient experts stated that, "increasing PFS gives additional time to deal with the physical, emotional and psychological effects of ovarian cancer and its treatment, and allows patients and their families to

come to terms with the implications of relapse" and that "this additional period of time is extremely important in helping them to recover from the shock of relapse, and enables them to use the period of wellbeing to make the most of their lives." The model structure developed within TA91, which incorporated both overall and progression free survival, was therefore considered to be the most appropriate for this decision problem.

Within TA91, the manufacturer's submission for TA222, and the submission from PharmaMar for this MTA, the time spent in each health state is based upon 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). For this MTA, a similar methodology (the partition method) has been used to estimate the proportion of patients in each health state; however, full survival curves rather than mean estimates, have been derived from the clinical data for each therapy. This ensures that time is appropriately captured within the economic model, and facilitates the assignment of costs, utilities and discounting. As highlighted by the ERG for TA222, models constructed around mean time estimates may be constrained in the application of costs, utilities and discounting.[90] This is described in greater detail in Section 5.2.7.

To capture the full costs and benefits associated with therapies for recurrent ovarian cancer, a lifetime time horizon was considered to be appropriate. In the base case analysis this is set as 15 years, because at this time point, over 99.9% of patients within the model have died. Furthermore, as per the NICE reference case, costs and benefits are discounted at a rate of 3.5% per annum, and an NHS and PSS perspective was considered.[109] The time horizon and discount rates used have been varied in sensitivity analysis (Section 5.2.11).

5.2.5 Interventions and comparators

The interventions and comparators of interest for this MTA, for both the platinum sensitive and platinum resistant/refractory subgroups outlined in Section 5.2.3, are presented in Table 105. In addition, the treatment options for patients considered platinum allergic are presented.

Table 105. Interventions and comparators of interest, by patient population, for this MTA

Therapy		Platinum sensitive	Platinum resistant/ refractory	Platinum allergic
Interventions	Paclitaxel plus platinum	✓	✓	N/A
	PLDH plus platinum	✓	N/A	N/A
	Gemcitabine plus carboplatin	✓	N/A	N/A
	PLDH	✓	✓	✓
	Paclitaxel	✓	✓	✓
	Trabectedin plus PLDH	✓	N/A	✓
	Topotecan	✓	✓	✓
Comparators	Platinum	✓	N/A	N/A
	Etoposide	N/A	✓	✓
	Etoposide plus platinum	N/A	✓	N/A
	Best supportive care	N/A	✓	✓
Abbreviations used in table: MTA, multiple technology appraisal; N/A, not applicable; PLDH, pegylated liposomal doxorubicin hydrochloride.				

In order to assess the relative cost-effectiveness of these therapies, relative clinical effectiveness data, with respect to PFS and OS, were required. However, as reported in Section 4.1, a paucity of comparative clinical data was identified in the clinical systematic review, therefore, the full range of desirable comparisons as outlined in Table 105 is not possible. Instead, Table 106 summarises, by population, the comparisons that are possible based on the availability of relative clinical data.

Table 106. Comparisons of interest, by patient population, for which (direct or indirect) clinical data were available (a cross indicates where a comparison was required, but data were not available)

Therapy	Paclitaxel plus platinum	PLDH plus platinum	Gemcitabine plus carboplatin	PLDH	Paclitaxel	Trabectedin plus PLDH	Topotecan	Platinum	Etoposide	Etoposide plus platinum	Best supportive care
Platinum sensitive											
Paclitaxel plus platinum		✓	✓	✗	✗	✗	✗	✓			
PLDH plus platinum	✓		✓	✗	✗	✗	✗	✓			
Gemcitabine plus carboplatin	✓	✓		✗	✗	✗	✗	✓			
PLDH	✗	✗	✗		✓	✓	✓	✗			
Paclitaxel	✗	✗	✗	✓		✓	✓	✗			
Trabectedin plus PLDH	✗	✗	✗	✓	✓		✓	✗			
Topotecan	✗	✗	✗	✓	✓	✓		✗			
Platinum resistant/refractory											
Paclitaxel	✗				✓		✓		✗	✗	✗
Paclitaxel plus platinum				✗	✗		✗		✗	✗	✗
PLDH	✗			✓			✓		✗	✗	✗
Topotecan	✗			✓	✓				✗	✗	✗
Platinum allergic											
Paclitaxel					✓	✓	✓		✗		✗
PLDH				✓		✓	✓		✗		✗
Trabectedin plus PLDH				✓	✓		✓		✗		✗
Topotecan				✓	✓	✓			✗		✗
Abbreviation used in table: PLDH, pegylated liposomal doxorubicin hydrochloride.											

For patients with platinum sensitive disease, clinical data were retrieved for each of the interventions and comparators outlined within Table 105. However, as a result of the trials available (Table 106), it was not possible to construct a single complete network comparing all interventions with all comparisons and with one another. Instead, two separate, disconnected networks formed the basis of the clinical analysis in the platinum sensitive subgroup (See clinical Section 4.1.5):

- network one comprises paclitaxel plus platinum, PLDH plus platinum, gemcitabine plus carboplatin, and platinum (hereafter referred to as "PS, network 1");
- network two comprises, PLDH, paclitaxel, PLDH plus trabectedin, and topotecan (hereafter referred to as "PS, network 2").

The use of two distinct networks to inform the relative clinical effectiveness of treatments for patients with platinum sensitive disease necessitated the disaggregation of the economic analysis in this patient population. Therefore, the incremental cost-effectiveness of treatments in PS, network 1 is considered separate to the incremental cost-effectiveness of treatments in PS, network 2. The TAG notes that the ICERs estimated from these two networks are not comparable with each other and should be interpreted as independent analyses. This is discussed in more detail in Section 5.2.15.

For the platinum resistant/refractory subgroup, clinical effectiveness data were available for PLDH, paclitaxel, paclitaxel plus platinum, and topotecan. However, the comparisons available (Table 106) resulted in a network limited to PLDH, paclitaxel, and topotecan. No data were found for etoposide, either as monotherapy or in combination with a platinum agent, and no data regarding best supportive care were identified. However, following clinical advice that the prognosis of patients with platinum resistant/refractory disease is often poor across available treatment options, a sensitivity analysis assuming equivalent efficacy between all treatments was carried out. The results of this sensitivity analysis are presented in Section 5.2.13.

For each of the interventions and comparators investigated within the *de novo* economic analysis, the treatment regimens modelled are those most representative of UK clinical practice (Table 107). Specification of the treatment regimens has been obtained through review of each relevant Summary of Product Characteristics (SmPC), followed by clinical expert verification to ensure accurate reflection of UK clinical practice. Etoposide is not licensed within ovarian cancer and therefore expert advice was sought to inform the doses used within the analysis. The TAG notes that the expert advice indicated that there is variation in clinical practice with regards to etoposide regimens used. However, as consideration of treatment with etoposide is limited to sensitivity analysis, the TAG does not expect this uncertainty to impact on the base case cost-effectiveness results.

Table 107. Chemotherapy regimens modelled within the Technology Assessment Group's *de novo* economic analysis (italic text indicates regimens used in sensitivity analysis only)

Chemotherapy	Regimen description
Paclitaxel	For platinum resistant/refractory disease: paclitaxel 80 mg/m^2 weekly for 18 weeks or until progression For platinum sensitive disease: paclitaxel 175 mg/m^2 day 1 every 21 day cycle (maximum six cycles)
Paclitaxel plus platinum	*For platinum resistant/refractory disease*: paclitaxel 80mg/m^2 plus carboplatin AUC three, weekly for 18 weeks or until progression* For platinum sensitive disease: paclitaxel 175 mg/m^2 and carboplatin AUC five, day 1 every 21 day cycle (maximum six cycles)
PLDH	40 mg/m^2 day 1 every 28 day cycle (maximum six cycles)
PLDH plus platinum	PLDH 30 mg/m^2; carboplatin target AUC of five, day 1 every 28 day cycle (maximum six cycles)
Gemcitabine plus carboplatin	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 (maximum six cycles)
Trabectedin plus PLDH	Trabectedin 1.1 mg/m^2; PLDH 30 mg/m^2, day 1 every 21 day cycle (maximum six cycles)
Topotecan	1.5 mg/m^2, day 1-5 every 21 day cycle (maximum six cycles)
Platinum monotherapy	Carboplatin target AUC of five, day 1 every 21 day cycle (maximum six cycles)
*Etoposide**	*50 mg (oral) days 1-21 every 28 days (maximum six cycles)*
*Etoposide plus platinum**	*Etoposide 50 mg (oral) days 1-21 every 28 days plus cisplatin IV 50 mg/m^2 day 1, 8 and 15 every 28 days (maximum six cycles)*
*Best supportive care**	*No chemotherapeutic regimen modelled; interventions associated with supporting patients for example, in their control of pain, nausea, vomiting, or constipation*
* Sensitivity analysis only Abbreviations used in table: AUC, area under the curve; m, metre; mg, milligram; PLDH, pegylated liposomal doxorubicin hydrochloride.	

5.2.6 Overview of model parameters, sources and assumptions

Table 108. Overview of parameters used within the Technology Assessment Group base-case economic analysis

Parameter	Mean value	Variance	Source	Section
Progression free survival (PS network 1)				
PFS survival distribution used for the baseline treatment, paclitaxel plus platinum	*Weibull distribution*: Intercept = 2.546 Log_Scale = -0.656	*Cholesky matrix* (Intercept) Log(scale) (Intercept) 0.026 0.000 Log(scale) -0.006 0.038	Analysis of CALYPSO data[31] using methods outlined in Hoyle[110]	Section 5.2.7
HR for PLDH plus platinum vs paclitaxel plus platinum	0.817	95% CrI; 0.717, 0.927	TAG NMA	
HR for gemcitabine plus carboplatin vs paclitaxel plus platinum	0.985	95% CrI; 0.748, 1.273	TAG NMA	
HR for platinum vs paclitaxel plus platinum	1.361	95% CrI; 1.182, 1.559	TAG NMA	
Progression free survival (PS network 2)				
PFS survival distribution used for the baseline treatment, PLDH	Kaplan-Meier data	N/A	Manufacturer submission	Section 5.2.7
HR for paclitaxel vs PLDH	1.615	95% CrI; 0.939, 2.586	TAG NMA	
HR for trabectedin plus PLDH vs PLDH	0.736	95% CrI; 0.560, 0.949	TAG NMA	
HR for topotecan vs PLDH	1.298	95% CrI; 0.979, 1.688	TAG NMA	
Progression free survival (platinum resistant/refractory)				
PFS survival distribution used for the baseline treatment, PLDH	*Weibull distribution:* Intercept = 1.665 Log_Scale = -0.345	*Cholesky matrix* (Intercept) Log(scale) (Intercept) 0.081 0.000 Log(scale) -0.013 0.080	Analysis of OVA-301 data[30] using methods outlined in Hoyle[110]	Section 5.2.7
HR for paclitaxel vs PLDH	1.360	95% CrI; 0.817, 2.123	TAG NMA	
HR for topotecan vs PLDH	0.998	95% CrI; 0.767, 1.277	TAG NMA	

Overall survival (PS network 1)				
OS survival distribution used for the b aseline treatment, paclitaxel plus platinum	*Weibull distribution:* Intercept = 3.750 Log_Scale = -0.534	*Cholesky matrix* (Intercept) Log(scale) (Intercept) 0.032 0.000 Log(scale) 0.004 0.046	Analysis of CALYPSO data[55] using methods outlined in Hoyle[110]	Section 5.2.7
HR for PLDH plus platinum vs paclitaxel plus platinum	1.023	95% CrI; 0.889, 1.172	TAG NMA	
HR for gemcitabine plus carboplatin vs paclitaxel plus platinum	1.247	95% CrI; 0.921, 1.652	TAG NMA	
HR for platinum vs paclitaxel plus platinum	1.290	95% CrI; 1.096, 1.509	TAG NMA	
Overall survival (PS network 2)				
OS survival distribution used for the baseline treatment, PLDH	*Weibull distribution:* Intercept = 3.449 Log_Scale = -0.304	*Cholesky matrix* (Intercept) Log(scale) (Intercept) 0.057 0.000 Log(scale) -0.008 0.066	Analysis of manufacturer KM data using methods outlined in Hoyle[110]	Section 5.2.7
HR for paclitaxel vs PLDH	1.219	95% CrI; 0.850, 1.690	TAG NMA	
HR for trabectedin plus PLDH vs PLDH	0.835	95% CrI; 0.667, 1.032	TAG NMA	
HR for topotecan vs PLDH	1.367	95% CrI; 1.035, 1.770	TAG NMA	
Overall survival (platinum resistant/refractory)				
OS survival distribution used for the baseline treatment, PLDH	*Weibull distribution:* Intercept = [redacted] Log_Scale = [redacted]	Cholesky matrix (Intercept) Log(scale) (Intercept) [redacted] [redacted] Log(scale) [redacted] [redacted]	Analysis of manufacturer CSR data using methods outlined in Hoyle[110]	Section 5.2.7
HR for paclitaxel vs PLDH	1.053	95% CrI; 0.783, 1.382	TAG NMA	
HR for topotecan vs PLDH	0.973	95% CrI; 0.764, 1.221	TAG NMA	

Probability of allergic reaction				
Paclitaxel	20.0%	Estimated 95% CI; 11%, 31%	Clinical opinion	Section 5.2.8
Paclitaxel plus platinum	3.9%	Estimated 95% CI; 2.2%, 6.1%	Weighted average of Bafaloukos[29] (1 event, 89 patients) and Gonzalez-Martin[47] (4 events, 38 patients)	
PLDH	5.0%	Estimated 95% CI; (3%, 8%)	Clinical opinion	
PLDH plus platinum	0.5%	Estimate based upon the odds ratio vs paclitaxel plus platinum (OR 0.130 95% CrI 0.001, 0.705)	TAG NMA	
Gemcitabine plus carboplatin	3.9%	Set equal to paclitaxel plus platinum	TAG NMA	
Trabectedin plus PLDH	5.0%	Estimated 95% CI; (3%, 8%)	Clinical opinion	
Topotecan	0.0%	N/A	Clinical opinion	
Platinum	3.9%	Set equal to paclitaxel plus platinum	TAG NMA	
Probability of anaemia				
Paclitaxel	4.7%	Set equal to PLDH	TAG NMA	Section 5.2.8
Paclitaxel plus platinum	5.1%	Estimated 95% CI; 2.9%, 7.9%	Weighted average of Bafaloukos[29] (3 events, 89 patients), Gonzalez-Martin[47] (2 events, 38 patients), and CALYPSO data[31] (27 events, 501 patients)	
PLDH	4.7%	Estimated 95% CI; 2.7%, 7.3%	Weighted average of Schering-Plough submission (trial 30-57) from TA91[13] (3 events, 108 patients), Gordon[48] (13 events, 239 patients), and OVA-301 data[30] (16 events, 330 patients)	
PLDH plus platinum	9.4%	Estimate based upon the odds ratio vs paclitaxel plus platinum (OR 1.926 95% CrI 1.164, 3.039)	TAG NMA	
Gemcitabine plus carboplatin	23.9%	Estimate based upon the odds ratio vs paclitaxel plus platinum (OR 5.848 95% CrI 1.158, 18.040)	TAG NMA	
Trabectedin plus PLDH	12.7%	Estimate based upon the odds ratio vs PLDH (OR 2.940 95% CrI 1.559, 5.202)	TAG NMA	
Topotecan	26.8%	Estimate based upon the odds ratio vs PLDH (OR 7.374 95% CrI 3.775, 13.590)	TAG NMA	
Platinum	5.1%	Set equal to paclitaxel plus platinum	TAG NMA	

Probability of febrile neutropenia				
Paclitaxel	5.0%	Estimated 95% CI; 2.8%, 7.7%	Clinical opinion	Section 5.2.8
Paclitaxel plus platinum	4.2%	Estimated 95% CI; 2.4%, 6.5%	CALYPSO data[31] (21 events, 501 patients)	
PLDH	2.1%	Estimated 95% CI; 1.2%, 3.3%	OVA-301 data[30] (7 events, 330 patients)	
PLDH plus platinum	4.2%	Set equal to paclitaxel plus platinum	TAG NMA	
Gemcitabine plus carboplatin	4.2%	Set equal to paclitaxel plus platinum	Clinical opinion	
Trabectedin plus PLDH	6.6%	Estimate based upon the odds ratio vs PLDH (OR 3.256 95% CrI 1.378, 7.692)	TAG NMA	
Topotecan	5.0%	Estimated 95% CI; 2.8%, 7.7%	Clinical opinion	
Platinum	0.0%	N/A	Clinical opinion	
Probability of nausea and vomiting				
Paclitaxel	2.9%	Estimate based upon the odds ratio vs PLDH (OR 0.279 95% CrI 0.120, 0.535)	TAG NMA	Section 5.2.8
Paclitaxel plus platinum	1.6%	Estimated 95% CI; 0.9%, 2.4%	Weighted average of Bafaloukos[29] (1 event, 89 patients) and Gonzalez-Martin[47] (1 event, 38 patients)	
PLDH	9.8%	Estimated 95% CI; 5.5%, 15.0%	Weighted average of OVA-301 data[30] (15 events, 330 patients), Schering-Plough submission (30-57 trial) from TA91[13] (19 events, 108 patients), and Gordon[48] (32 events, 239 patients)	
PLDH plus platinum	3.2%	Estimate based upon the odds ratio vs paclitaxel plus platinum (OR 2.055 95% CrI 1.598, 2.608)	TAG NMA, based upon all grades adverse events (Section 5.2.8)	
Gemcitabine plus carboplatin	3.2%	Set equal to PLDH plus platinum	Clinical opinion	
Trabectedin plus PLDH	36.4%	Estimate based upon the odds ratio vs PLDH (OR 5.291 95% CrI 2.866, 9.342)	TAG NMA	
Topotecan	9.8%	Set equal to PLDH	TAG NMA	
Platinum	1.6%	Set equal to paclitaxel plus platinum	TAG NMA	

Chemotherapy cost per cycle				
Paclitaxel 80mg/m^2 weekly (cycle) for 18 weeks or until progression (plus dexamethasone pre-treatment)	£306	Paclitaxel mean £302, standard error £2.03	Standard error around the mean estimates for the individual patient data from Sacco *et al.*[111]	Section 5.2.10
Paclitaxel 175 mg/m^2 day 1 every 21 day cycle (plus dexamethasone pre-treatment)	£638	Paclitaxel mean £634, standard error £3.87		
Paclitaxel 80mg/m^2 plus carboplatin AUC three, weekly for 18 weeks or until progression (plus dexamethasone pre-treatment)	£442	Paclitaxel mean £302, standard error £2.03 Carboplatin mean £136, standard error £1.59		
Paclitaxel 175 mg/m^2 and carboplatin AUC five, day 1 every 21 day cycle	£855	Paclitaxel mean £634, standard error £3.87 Carboplatin mean £217, standard error £2.63		
PLDH 40 mg/m^2 day 1 every 28 day cycle	£1,211	Standard error £9.62		
PLDH 30 mg/m^2; carboplatin target AUC of five, day 1 every 28 day cycle	£1,137	PLDH mean £920, standard error £9.95 Carboplatin mean £217, standard error £2.63		
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	Gemcitabine mean £265, standard error £1.68 Carboplatin mean £177, standard error £2.07		
Trabectedin 1.1 mg/m^2; PLDH 30 mg/m^2, day 1 every 21 day cycle	£3,679	Trabectedin mean £2,759, standard error £15.40 PLDH mean £920, standard error £9.95		
Topotecan 1.5 mg/m^2, day 1-5 every 21 days	£1,305	Topotecan mean £261, standard error £0.38		
Carboplatin target AUC5, day 1 every 21 days	£217	Carboplatin mean £217, standard error £2.63		
Administration cost				
Minutes pharmacy preparation required per single chemotherapy agent	20	Estimated 95% CI; 10.2, 29.8	Clinical opinion	Section 5.2.10
Cost per hour of pharmacist time	£47	Estimated 95% CI; £26,86, £72.67	Unit Costs of Health and Social Care 2012[112]	

Deliver complex Chemotherapy, including prolonged infusional treatment at first attendance (SB14Z)	£331	Estimated 95% CI; £230, £388	NHS Reference Costs 2011/12[113]	
Deliver more complex parenteral chemotherapy at First Attendance (SB13Z)	£249	Estimated 95% CI; £177, £301	NHS Reference Costs 2011/12[113]	
Deliver simple Parenteral Chemotherapy at first attendance (SB12Z)	£200	Estimated 95% CI; £128, £241	NHS Reference Costs 2011/12[113]	
Deliver subsequent elements of a chemotherapy cycle (SB15Z)	£270	Estimated 95% CI; £192, £326	NHS Reference Costs 2011/12[113]	
Health state cost				
Cost of outpatient visit; gynaecologic oncology	£135	Estimated 95% CI; £91, £172	NHS Reference Costs 2011/12[113]	Section 5.2.10
One off cost of CT scan	£109	Estimated 95% CI; £93, £127	NHS Reference Costs 2011/12[113]	
2000/01 estimate of palliative care cost, 399 days	£4,789	Estimated 95% CI; £4,277, £5,301	Guest *et al.*[114]	
Proportion of single agent carboplatinAUC5 for platinum sensitive disease	75%	Standard deviation, 18.9%	Assumption	
Number of months between outpatient visits	3	Estimated 95% CI; 1.53, 4.47	Clinical opinion	
Adverse event cost				
SA01F Aplastic Anaemia without CC	£1,076.92	Estimated 95% CI; £661, £1,318	NHS Reference Costs 2011/12[113]	Section 5.2.10
SA13A Single Plasma Exchange, Leucophoresis or Red Cell Exchange	£472.77	Estimated 95% CI; £300, £586	NHS Reference Costs 2011/12[113]	
SA14Z Plasma Exchanges 2 to 9	£2,479.17	Estimated 95% CI; £1,184, £3,315	NHS Reference Costs 2011/12[113]	
SA15Z Plasma Exchanges 10 to 19	£5,520.39	Estimated 95% CI; £2,007, £5,959	NHS Reference Costs 2011/12[113]	
SA16Z Plasma Exchanges 20 or more	£13,187.335	Estimated 95% CI; £4,147, £12,524	NHS Reference Costs 2011/12[113]	
Utilities				
Stable disease	0.718	95% CI; 0.70, 0.74	TA222[19]	Section 5.2.9
Progressed disease	0.649	95% CI; 0.61, 0.69	TA222[19]	
Other				
Time horizon	15 years	N/A	Assumption	Section 5.2.4

Discount rate (costs)	3.5%	N/A	Assumption	
Discount rate (benefits)	3.5%	N/A	Assumption	
Abbreviations used in table: AUC, area under the curve; CI, confidence interval; CrI, credible interval; HR, hazard ratio; KM, Kaplan-Meier; NMA, network meta-analysis; OR, odds ratio; OS, overall survival; PFS, progression free survival; PLDH, pegylated liposomal doxorubicin hydrochloride; PS, platinum sensitive.				

Table 109. Assumptions made within the Technology Assessment Group's economic analysis

Assumption	Rationale	Relevant section	Related sensitivity analyses
The time horizon was assumed to be fifteen years in the base case	Fifteen years was considered to be of sufficient duration to capture the differences in costs and QALYs for the majority of women with recurrent ovarian cancer over their lifetime	Section 5.2.4	Time horizon varied in one-way sensitivity analysis
Carboplatin, rather than cisplatin, was assumed to constitute the platinum therapy of choice in UK clinical practice	The majority of the clinical data obtained for platinum was carboplatin (Section 5.2.7); in addition, carboplatin and cisplatin are considered in practice to have equivalent efficacy (Section 5.2.7 [(115)]) but carboplatin is associated with less toxicity and therefore may be considered the first choice of platinum therapy in clinical practice	Section 5.2.5 and 5.2.7	N/A
The efficacy of PLDH was assumed to be the same at a dose of 40 mg/m^2 as at a dose of 50 mg/m^2 as seen in clinical trials	The licensed indication for PLDH monotherapy is presented as 50 mg/m^2 and clinical data used within the model for PLDH monotherapy was at this dose; however, clinical advice suggested that a dose of 40 mg/m^2 was more likely in clinical practice for reasons of tolerability, and this was not anticipated to affect efficacy	Section 5.2.5 and 5.2.7	A scenario analysis was carried out in which the cost of PLDH was associated with a 50 mg/m^2 dose rather than a 40 mg/m^2 dose
For platinum resistant/refractory patients, it was assumed that the efficacy estimates for three weekly paclitaxel were representative of efficacy from weekly paclitaxel	Clinical advice indicated that for platinum resistant/refractory patients, paclitaxel was more likely to be administered via a weekly regimen rather than a three-weekly regimen. No clinical data was found for weekly paclitaxel that could be included in the PFS and OS networks. This lack of data therefore necessitated an assumption of equivalent efficacy. The TAG understands from clinical experts that this assumption is likely to result in an underestimate of the efficacy of weekly paclitaxel	Section 5.2.5 and 5.2.7	OS and PFS was varied in one-way sensitivity analysis
For sensitivity analysis, etoposide was assumed to be administered as a flat dose of 50-75mg days 1-21 out of 28 days, with oral etoposide for a further 7 weeks	Dose based upon clinical advice and used for costing in sensitivity analysis only. Etoposide does not have a licensed indication for ovarian cancer. For that reason, the SmPC did not provide sufficient information around dosing in recurrent ovarian cancer	Section 5.2.11 and 5.2.12	This assumption is related to a specific sensitivity analysis
No vial sharing	It was assumed in the base case that chemotherapy vials were not shared in clinical practice	Section 5.2.10	A scenario analysis was carried out whereby this assumption was relaxed, and

			vial sharing was possible
It was assumed that every chemotherapy would require 20 minutes pharmacist preparation	Based upon clinical advice reported received for bevacizumab in recurrent ovarian cancer (TA285)	Section 5.2.10	Varied in one-way sensitivity analysis, and probabilistic sensitivity analysis
In the stable period, it was assumed that a patient would require a single outpatient visit every three months	Based upon clinical advice	Section 5.2.10	Varied in one-way sensitivity analysis, and probabilistic sensitivity analysis
It was assumed that 100% platinum sensitive patients entering the model would receive one further line of therapy upon progression with their disease	This was a simplifying assumption designed to reflect the fact that although not all women will go on to receive another line of chemotherapy, some women will receive more than one line of chemotherapy	Section 5.2.10	The cost within the progressed disease health state was varied in one-way and probabilistic sensitivity analysis
It was assumed that for those women going on to receive a further line of therapy, 75% would receive single agent carboplatin and 25% would receive PLDH monotherapy	This was a simplifying assumption based upon the proportions of patients receiving platinum based and non-platinum based therapy upon progression in Kaye *et al.*[116]	Section 5.2.10	This probability was varied in one-way and probabilistic sensitivity analysis
Assumption of proportional treatment hazards	The TAG did not have access to either a single clinical trial, or patient level data for the full range of interventions and comparators of interest for this MTA. For that reason, summary HRs were used to estimate the relative effects between treatments considered within the economic analysis and this necessitated the assumption of proportional hazards	Section 5.2.7	The appropriateness of the assumption of proportional hazards was investigated using log-cumulative hazard plots and is discussed in Section 5.2.15
The likelihood of an adverse reaction was independent of the platinum free interval	To increase the available data, the TAG analysed adverse events without distinction between platinum sensitive and platinum resistant disease	Section 5.2.8	The probability of adverse events was varied in sensitivity analysis
Adverse events occurred in the first month of the model	A simplifying assumption reflecting the likelihood that adverse events would be experienced upon commencement of chemotherapy	Section 5.2.8	N/A
Abbreviations used in table: ERG, evidence review group; HR, hazard ratio; m, metre; mg, milligram; N/A, not applicable; OS, overall survival; PFS, progression free survival; PLDH, pegylated liposomal doxorubicin hydrochloride; QALY, quality-adjusted life year; SmPC, summary of product characteristics; TAG, Technology Assessment Group; UK, United Kingdom; vs, versus.			

5.2.7 Treatment effectiveness

Throughout the fifteen-year time horizon of the TAG's economic model, monthly estimates of PFS and OS are used to capture the effectiveness of treatments for recurrent ovarian cancer. PFS represents the length of time spent within the stable disease health state, and OS represents the length of time spent alive within the model in total. The length of time spent alive in the progressed disease health state is calculated as OS minus PFS.

For each treatment, estimates of PFS and OS have been derived and applied in the model as follows (each step is described in more detail in the sections that follow):

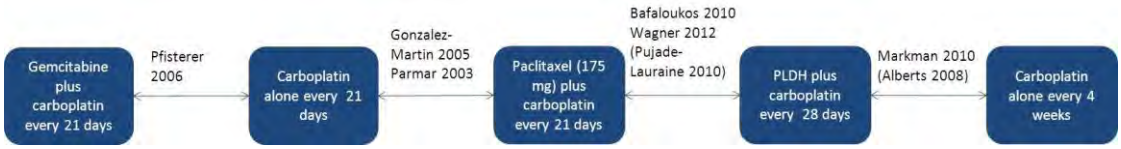
- networks of treatments, by subgroup, for which PFS and OS data were available were established via the clinical systematic review (Section 4.2);
- for each network, a baseline treatment has been selected and monthly estimates of PFS and OS obtained from Kaplan-Meier data. Where required, parametric survival distributions have been fitted to Kaplan-Meier data, to allow extrapolation beyond the trial duration;
- in each network, relative estimates of PFS and OS for each therapy have been synthesised in NMA, using hazard ratios (HR) as the measure of relative effect vs the baseline treatment (Section 4.2);
- HRs obtained from the NMAs are applied to baseline estimates of PFS and OS. Thus providing, for every therapy in each network, monthly estimates of PFS, OS, and therefore the proportion of patients within each health state.

5.2.7.1 Establishing networks of treatments

No single trial comparing all relevant treatments, for either the platinum sensitive or platinum resistant/refractory subgroup, was identified from the clinical literature review. It was therefore necessary to assess which trials could be linked via a network, in order to establish the relative efficacy of treatments using NMA (Section 4.2).

For the platinum sensitive subgroup, two independent networks have been constructed (Figures 26 to 27). Collectively, these two networks contain information on every intervention and comparator outlined within the NICE scope for platinum sensitive disease;[38] however, the absence of a common comparator between these two networks necessitated the separate analysis of these networks. For the platinum resistant/refractory subgroup, a single network has been identified (Figure 28); however, this network contains no information for one of the interventions (paclitaxel plus platinum) and three of the comparators (etoposide monotherapy, etoposide plus platinum, best supportive care) specified in the NICE scope.[38]

Figure 26. Network diagram for the platinum sensitive subgroup (network 1)

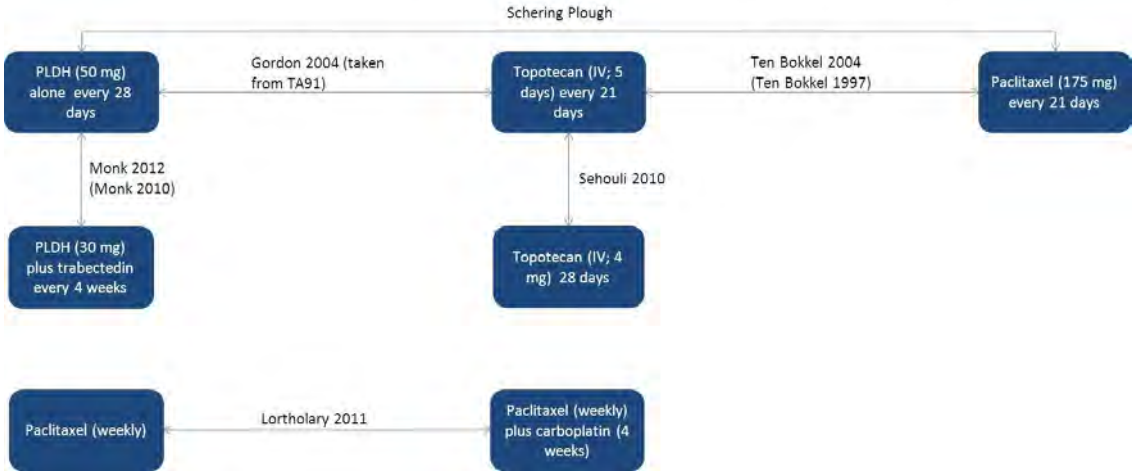


Abbreviation used in figure: PLDH, pegylated liposomal doxorubicin hydrochloride.

Figure 27. Network diagram for the platinum sensitive subgroup (network 2)

Abbreviations used in figure: IV, intravenous; PLDH, pegylated liposomal doxorubicin hydrochloride.

Figure 28. Network diagram for the platinum resistant/refractory subgroup



Abbreviations used in figure: IV, intravenous; PLDH, pegylated liposomal doxorubicin hydrochloride.

5.2.7.2 Establishing baseline PFS and OS for each network

For each network (PS, network 1, PS, network 2, and platinum resistant/refractory), the proportions of patients with PFS and OS were estimated monthly, over a lifetime time horizon (fifteen years in the base-case), for the baseline treatment.

To estimate baseline PFS and OS, the TAG used submitted Kaplan-Meier data or published Kaplan-Meier plots. Published Kaplan-Meier plots were digitised using an online digitising tool, webplotdigitzer[(117)] and the underlying Kaplan-Meier data estimated using methods described in Hoyle *et al.*[(110)] Hoyle *et al*. present an algorithm, informed by the Kaplan-Meier plot and the numbers of patients at risk at given time points, which can be used to estimate the underlying Kaplan-Meier data.

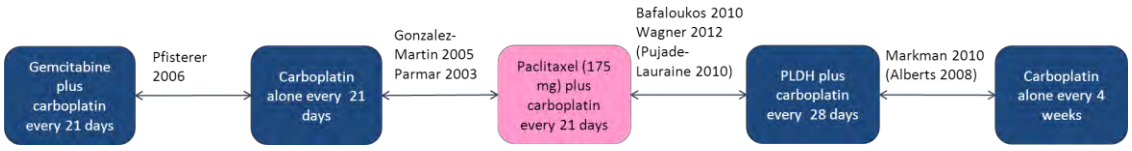
Where required (e.g., where at the end of follow-up some patients remained at risk), parametric survival curves may then be fitted to the estimated Kaplan-Meier data using maximum likelihood estimation (MLE).[110]

For each baseline treatment, requiring extrapolation of estimated Kaplan-Meier data, Weibull, exponential, log-normal and log-logistic survival curves were fitted using methods of MLE described in Hoyle *et al.*[110] The fit of each survival distribution to the (estimated or actual) Kaplan-Meier data was assessed visually and using the Akaike Information Criterion (AIC); the distribution chosen to inform the base case analysis is varied in sensitivity analysis (Section 5.2.13). Details of the distributions selected to inform baseline PFS and OS in each network are presented below.

Platinum sensitive network 1 (baseline treatment: paclitaxel plus carboplatin)

For PS, network 1 paclitaxel plus carboplatin has been selected as the baseline treatment as a result of the quality of information available for this intervention (Kaplan-Meier plots and numbers of patients at risk data available). Furthermore, paclitaxel plus carboplatin is connected to more than one of the therapies considered within PS, network 1 (Figure 29; pink square indicates baseline treatment). For paclitaxel plus platinum, three sources of published survival data are available for PFS (CALYPSO from Pujade-Lauraine *et al.*[31], Gonzalez-Martin *et al.*,[47], ICON4[60]) and OS (CALYPSO from Wagner *et al.*[55], Gonzalez-Martin *et al.*,[47], ICON4[60]). However, no complete PFS or OS data (i.e., no patients remaining at risk at the end of trial follow-up) exist for patients treated with paclitaxel plus carboplatin; therefore, parametric extrapolation has been used.

Figure 29. Network diagram for the platinum sensitive subgroup (network 1); pink square indicates base-line treatment



Abbreviation used in figure: PLDH, pegylated liposomal doxorubicin hydrochloride.

For PFS, data (Kaplan-Meier plots and numbers of patients at risk) presented for CALYPSO from Pujade *et al.*[31] are used to inform PFS for paclitaxel plus carboplatin in the base case analysis. Pujade *et al.*[31] was chosen to inform the base case analysis because of the quality of data presented, study date and purity of comparison made. That is, Pujade *et al*. provides the number of patients at risk at different time points, required in order to use the methods described in Hoyle *et al.*;[110] this information is not presented in Gonzalez-Martin *et al.*[47] Furthermore, although Parmar *et al.*[60] present PFS data for ICON4 with sufficient information to allow estimation of Kaplan-Meier data (as described by Hoyle *et al.*[110]), the year of analysis for Pujade *et al*. is more recent than that of Parmar *et al*. (2010 vs 2003, respectively) and therefore more likely to reflect current clinical practice. In

addition, a proportion of patients considered in ICON4 received paclitaxel in combination with cisplatin, rather than carboplatin. However, data from ICON4[60] are used in sensitivity analysis (Section 5.2.13).

Of the parametric survival distributions considered, to extrapolate Kaplan-Meier PFS data estimated from Pujade *et al.*,[31] (CALYPSO), the log-logistic distribution could be considered to be the best fit based upon the associated AIC value (Table 110). However, the TAG notes that model fit for each distribution is similar, and that whilst the log logistic distribution results in the lowest AIC, the range of AIC values is not large. Moreover, the TAG notes that in a technical support document recently published by NICE's decision support unit (DSU) it is stated that, the application of an HR to the entire modelled period "can be used within proportional hazards models such as the exponential, Gompertz or Weibull but log-logistic and log normal models are accelerated failure time models and do not produce a single hazard ratio (HR) and thus the proportional hazards assumption does not hold with these models".[118] In acknowledgement of this, and given the similarity of the AIC values, a Weibull distribution is used to inform the base-case analysis. However, to test the sensitivity of the cost-effective results to the baseline curve selected, log-logistic, log-normal and exponential distributions are used in sensitivity analyses (Section 5.2.13).

Table 110. Summary of the AIC values for survival curves fitted to PFS Kaplan-Meier data estimated from data for paclitaxel plus carboplatin presented in CALYPSO reported by Pujade *et al.*[31]

Selected distribution	AIC
Weibull	2404.564
Exponential	2618.638
Log normal	2388.568
Log logistic	2351.657
Abbreviations used in table: AIC, Akaike Information Criterion; PFS, progression free survival	

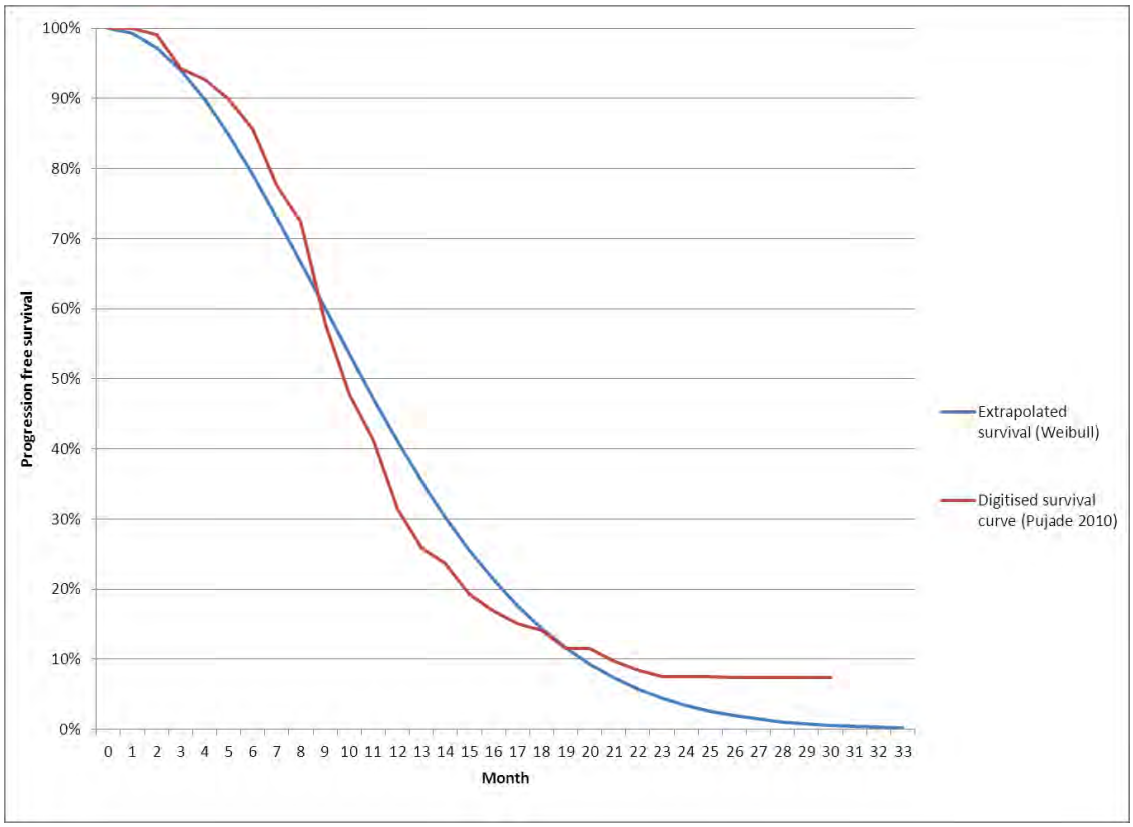
To estimate the monthly probability of PFS for patients receiving treatment with paclitaxel plus carboplatin, the TAG used the following formula (derived from that outlined in the DSU technical support document[118]):

$$survival_t = \exp\left(-\left(\frac{1}{\exp(intercept)^{\frac{1}{\exp(scale)}}}\right).t^{\left(\frac{1}{\exp(scale)}\right)}\right)$$

Where, t is time in months and the intercept and scale parameters have been estimated using MLE methods described in Hoyle *et al.*[110] (intercept = 2.546, scale = -0.656).

Figure 30 presents the survival curve, for paclitaxel plus carboplatin, obtained from digitisation of the Kaplan-Meier plot presented in CALYPSO by Pujade *et al.*[31] vs the Weibull extrapolation.

Figure 30. Progression free survival for paclitaxel plus carboplatin as estimated from data presented in CALYPSO by Pujade *et al.*,[31] versus the extrapolated Weibull survival curve obtained using methods from Hoyle *et al.*[110]



For OS, a similar methodology to that used for PFS was used to derive OS estimates for the baseline treatment; paclitaxel plus carboplatin. OS data (Kaplan-Meier plot and numbers of patients at risk) presented in CALYPSO by Wagner *et al.*[55] are used to inform the base case analysis. Of the three studies presenting OS data for paclitaxel plus carboplatin, Wagner *et al.*[55] was chosen to inform the base case OS distribution because of quality and maturity of data reported, the date of analysis and the purity of the comparison made. That is, the numbers of patients at risk, required for the methods described by Hoyle *et al.*,[110] whilst presented in Wagner *et al.*,[55] are not presented in Gonzalez-Martin *et al.*[47] Furthermore, data presented in Gonzalez-Martin *et al.*[47] were immature compared with data presented in Wagner *et al.*;[55] 70% vs 20% of patients remained alive at the end of follow-up, respectively. As before, data from ICON4 reported by Parmar *et al.*[60] are used in sensitivity analysis (Section 5.2.13).

Based upon the AIC values (Table 111), of the distributions fitted to the Kaplan-Meier data estimated from CALYPSO reported by Wagner *et al.*,[55] the log-logistic distribution could be considered to provide the best fit. However, akin to PFS, the TAG notes that the fit of each considered OS

distribution was similar, and that use of the log-logistic distribution may not be appropriate for the application of HRs. For these reasons, a Weibull distribution is used to inform the base case analysis and the impact of using log-logistic, log-normal and exponential distributions are tested in sensitivity analyses (Section 5.2.13).

Table 111. Summary of the AIC values for survival curves fitted to OS Kaplan-Meier data estimated from data for paclitaxel plus carboplatin presented in CALYPSO reported by Wagner *et al.*[55]

Selected distribution	AIC
Weibull	2473.965
Exponential	2581.839
Log normal	2475.084
Log logistic	2463.795
Abbreviations used in table: AIC, Akaike Information Criterion; OS, overall survival.	

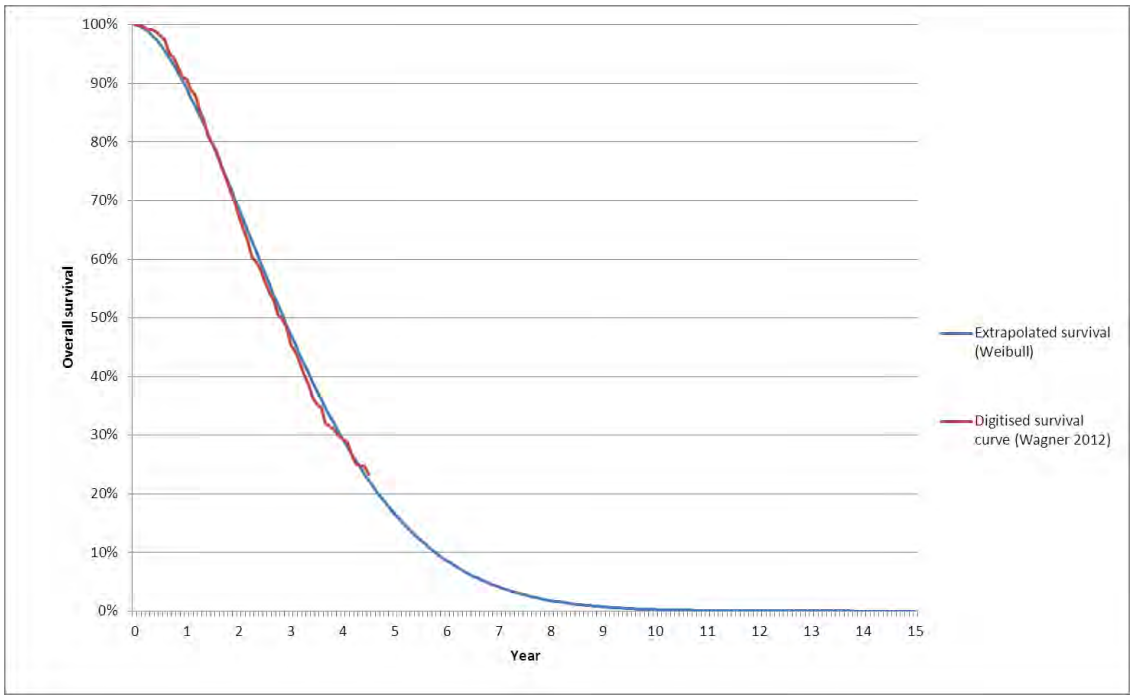
As for PFS, to estimate the monthly probability of OS, for patients receiving treatment with carboplatin plus paclitaxel, the TAG used the following formula:

$$survival_t = \exp\left(-\left(\frac{1}{\exp(intercept)^{\frac{1}{\exp(scale)}}}\right) \cdot t^{\left(\frac{1}{\exp(scale)}\right)}\right)$$

Where, t is time in months, and the intercept and scale parameters have been estimated using MLE methods described in Hoyle *et al.*[110] (intercept = 3.750, scale = -0.534).

Figure 31 presents the survival curve, for paclitaxel plus carboplatin, obtained from digitisation of the KM plot for CALYPSO presented in Wagner *et al.*[55] vs the Weibull extrapolation.

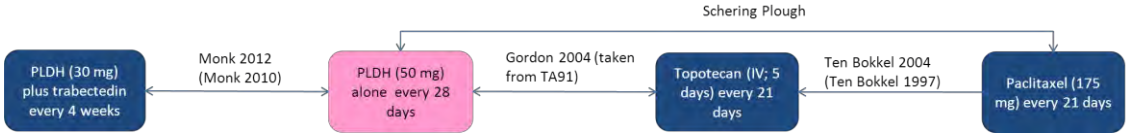
Figure 31. Overall survival for paclitaxel plus carboplatin as estimated from data presented for CALYPSO in Wagner *et al.*,[55] versus the extrapolated Weibull survival curve using methods from Hoyle *et al.*[110]



Platinum sensitive network 2 (baseline treatment: PLDH)

For PS network 2, PLDH has been selected as the baseline treatment as a result of the quality of data available for this intervention (Figure 32; pink square indicates baseline treatment). Furthermore, the TAG notes that relative efficacy (relative to other treatments of interest) data are available to a greater degree for PLDH than for other treatments included in the network. For PLDH, three sources of published survival data are available for PFS (OVA-301 from Monk *et al.*[30], Gordon *et al.*[48] and trial 30-57, Schering-Plough submitted data within the Assessment Report for TA91[13]) and OS (OVA-301 from Monk *et al.*[63], Gordon *et al.*[53] and trial 30-57, Schering-Plough submitted data within the Assessment Report for TA91[13]). In addition, the MS from PharmaMar and CSR for OVA-301, provide PFS and OS Kaplan-Meier data.

Figure 32. Network diagram for the platinum sensitive subgroup (network 2); pink square indicates baseline treatment



Abbreviation used in figure: PLDH, pegylated liposomal doxorubicin hydrochloride.

For PFS, Kaplan-Meier data provided in the MS from PharmaMar are used, in the base case analysis, to provide monthly estimates of PFS for patients treated with PLDH. These data represent the most

up-to-date information on PFS for patients treated with PLDH. In addition, rather than requiring digitisation, these data had the advantage of being presented within an Excel worksheet. Furthermore, the TAG notes that Kaplan-Meier PFS data for PLDH contained within the PharmaMar submission were complete; i.e., 0% of patients remained at risk at the end of follow-up (although the TAG notes that this data was subject to a large degree of censoring, Section 5.1.3). Consequently, no extrapolation of these data was necessary.

However, for the purposes of sensitivity analysis, and to provide a smoothed survival curve, the TAG fitted a number of parametric survival distributions to the manufacturer's Kaplan-Meier data. Based upon the AIC values associated with these distributions (Table 112), the TAG considers the Weibull distribution to provide the best fit of the Kaplan-Meier data.

Table 112. Summary of the AIC values for survival curves fitted to PFS Kaplan-Meier data for PLDH presented in the PharmaMar MS (sensitivity analysis only)

Selected distribution	AIC
Weibull	734.896
Exponential	751.511
Log normal	741.603
Log logistic	746.192
Abbreviations used in table: AIC, Akaike Information Criterion; MS, manufacturer's submission; PFS, progression free survival; PLDH, pegylated liposomal doxorubicin hydrochloride.	

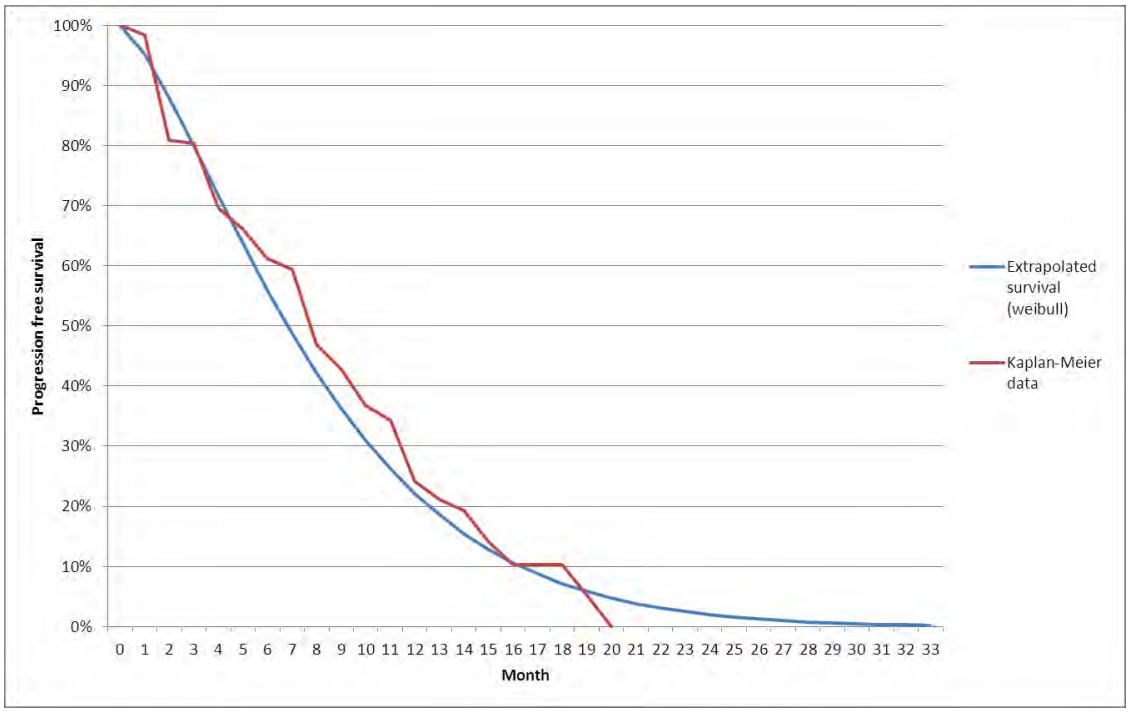
For the sensitivity analysis, the TAG estimated monthly PFS using the following formula:

$$survival_t = \exp\left(-\left(\frac{1}{\exp(intercept)^{\frac{1}{\exp(scale)}}}\right).t^{\left(\frac{1}{\exp(scale)}\right)}\right)$$

Where t is time in months and the intercept (2.186) and scale (-0.320) parameters have been estimated using MLE methods described in Hoyle *et al.*[110].

Figure 33 presents the manufacturer's Kaplan-Meier data, for PLDH, vs the extrapolated Weibull survival curve.

Figure 33. Progression free survival for PLDH as estimated from the PharmaMar MS Kaplan-Meier data, versus the extrapolated Weibull survival curve using methods from Hoyle *et al.*[110] (sensitivity analysis only)



For OS, Kaplan-Meier data presented in the model submitted by PharmaMar as part of this MTA, are used to inform the base case OS distribution for PLDH. These data represent the most recent information, and did not require estimation as a result of being provided within an Excel worksheet.

Of the parametric distributions considered to extrapolate Kaplan-Meier OS data, the TAG considers the Weibull distribution to be the best fit based upon the AIC values (Table 113). However, the TAG notes that model fit was similar for each considered OS distribution, and that whilst the Weibull distribution resulted in the lowest AIC, the range of AIC values was not large. For this reason, the baseline distribution is varied in sensitivity analyses to test the sensitivity of the cost-effective results to the baseline curve selected (Section 5.2.13).

Table 113. Summary of the AIC values for survival curves fitted to OS Kaplan-Meier data in the PharmaMar MS for PLDH

Selected distribution	AIC
Weibull	1116.346
Exponential	1134.797
Log normal	1147.63
Log logistic	1139.511
Abbreviations used in table: AIC, Akaike Information Criterion; MS, manufacturer's submission; OS, overall survival; PLDH, pegylated liposomal doxorubicin hydrochloride.	

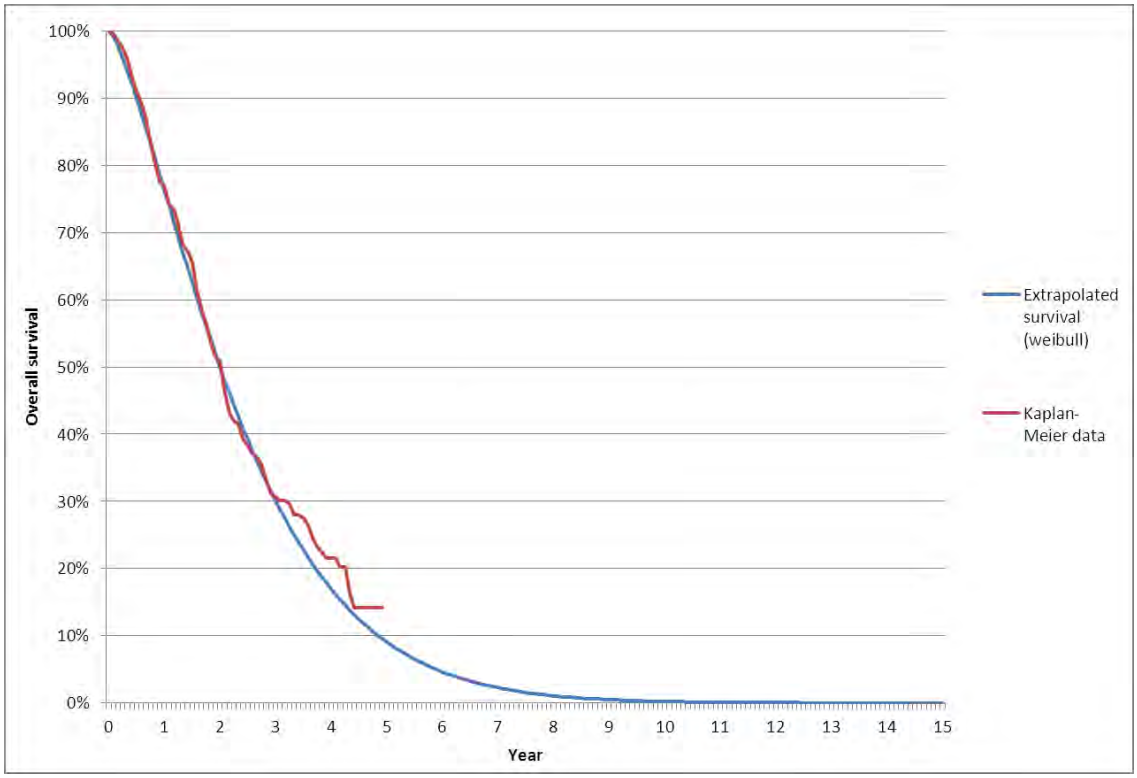
To estimate monthly OS for patients treated with PLDH, the TAG used the following formula:

$$survival_t = \exp\left(-\left(\frac{1}{\exp(intercept)^{\frac{1}{\exp(scale)}}}\right) \cdot t^{\left(\frac{1}{\exp(scale)}\right)}\right)$$

Where t is time in months and the intercept (3.449) and scale (-0.304) parameters have been estimated using MLE methods described in Hoyle *et al.*[110].

Figure 34 presents the manufacturer's Kaplan-Meier data, for PLDH, vs the extrapolated Weibull survival curve.

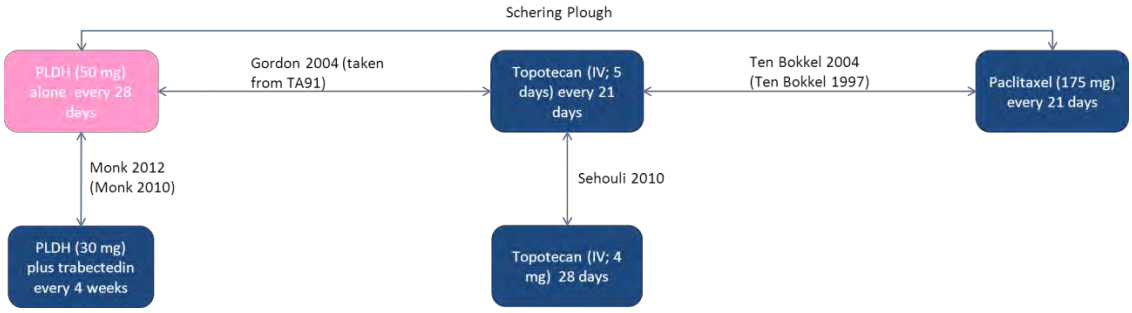
Figure 34. Overall survival for PLDH as estimated from the PharmaMar MS Kaplan-Meier data, versus the extrapolated Weibull survival curve using methods from Hoyle *et al.*[110]



Platinum resistant/refractory (baseline treatment: PLDH)

For the platinum resistant/refractory network, PLDH has been selected as the baseline treatment (Figure 35; pink square indicates baseline treatment). Three sources of published survival data are available for PFS (Gordon *et al.*[48], data submitted by Schering-Plough presented within the Assessment Report for TA91 for trial 30-57[13], and OVA-301 as reported in Monk *et al.*[30]) and OS (data for trial 30-57 submitted by Schering-Plough presented within the Assessment Report for TA91[13], Gordon *et al.*[53], OVA-301 from Monk *et al.*[63]). In addition, the Clinical Study Report (CSR) for OVA-301 provided by PharmaMar, contains PFS and OS Kaplan-Meier data. However, no complete PFS or OS data (i.e., no patients remaining at risk at the end of trial follow-up) exist for patients treated with PLDH; therefore, parametric extrapolation has been used.

Figure 35. Network diagram for the platinum resistant/refractory subgroup; pink square indicates base-line treatment



Abbreviation used in figure: PLDH, pegylated liposomal doxorubicin hydrochloride.

For PFS, data from OVA-301 in Monk *et al.*[30] are used to inform the distribution of PFS, used in the base case for patients treated with PLDH. This is because neither data presented within Gordon *et al.*[48], nor data contained within trial 30-57 from TA91[13] were sufficient, to facilitate use of the methods described in Hoyle *et al.*[110]; i.e., no numbers of patients at risk were presented on Kaplan-Meier plots. The TAG notes that the comparison within OVA-301 from Monk *et al.*[30] is not relevant for the decision problem for this MTA (i.e., trabectedin plus PLDH is not an intervention or comparator of interest for the platinum resistant/refractory subgroup); however, the TAG considers the information contained within Monk *et al.*[30] to be informative for the network, and notes that the trial represents the most recent data identified for PLDH in the platinum resistant/refractory subgroup.

Therefore, Kaplan-Meier PFS data were estimated (from digitisation of the Kaplan-Meier plot and the reported numbers of patients at risk) and a number of parametric survival distributions fitted. Based on the AIC of the survival distributions considered (Table 114), the log normal distribution could be considered to be the best fit of these data. However, as before, the TAG considers that given the similar AIC values, and acknowledging DSU guidance on the application of HRs, the Weibull distribution represents the most appropriate approximation of PFS.[118] Therefore, the Weibull distribution is used to inform the base-case analysis. However, log-normal, log-logistic and exponential distributions are used in sensitivity analyses (Section 5.2.13).

Table 114. Summary of the AIC values for survival curves fitted to PFS Kaplan-Meier data from OVA-301 in Monk *et al.*[30] for PLDH

Selected distribution	AIC
Weibull	514.0249
Exponential	528.9606
Log normal	502.1343
Log logistic	504.6734
Abbreviations used in table: AIC, Akaike Information Criterion; PFS, progression free survival; PLDH, pegylated liposomal doxorubicin hydrochloride.	

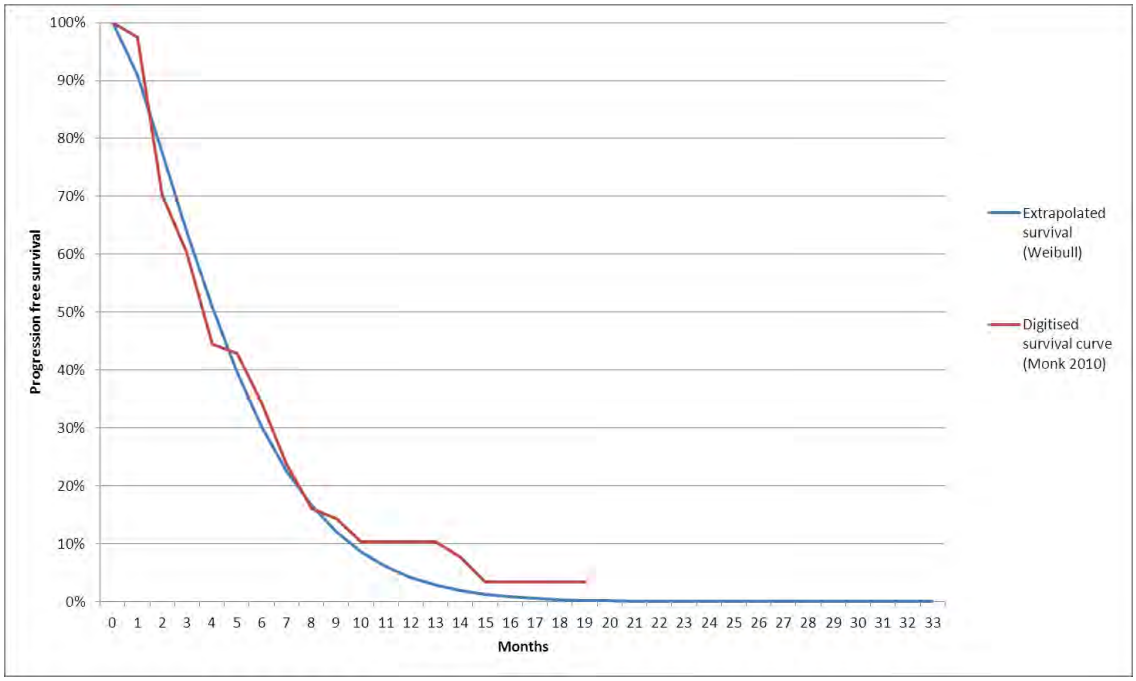
The TAG calculated monthly PFS using the following formula:

$$survival_t = \exp\left(-\left(\frac{1}{\exp(intercept)^{\frac{1}{\exp(scale)}}}\right) \cdot t^{\left(\frac{1}{\exp(scale)}\right)}\right)$$

Where t is time in months, and the intercept (1.665) and scale (-0.345) parameters have been estimated using MLE methods described in Hoyle *et al.*[110]

Figure 36 presents the Kaplan-Meier data, for PLDH, estimated from data presented in Monk *et al.*[30] vs the extrapolated Weibull curve.

Figure 36. Progression free survival for PLDH as estimated from Monk *et al.*[30], versus the extrapolated Weibull survival curve using methods from Hoyle *et al.*[110]



For OS, the Kaplan-Meier OS data available in the CSR for OVA-301 are used to inform the base case OS distribution for PLDH. These data represent the only source of information around numbers of patients at risk at given time points.

The TAG fitted a number of parametric survival distributions to the estimated OS Kaplan-Meier data (estimated from digitisation of Kaplan-Meier plot and numbers of patients at risk). Based on the AIC values of the considered distributions (Table 115), the TAG notes that the log-normal distribution could be considered to be the best fit to the estimated data. However, as before, recognising that AIC values were similar, and that the log logistic and log normal distributions may not represent the most appropriate baseline curve from which to apply HRs,[118] the Weibull distribution has been selected for

use in the base case. However, to test the sensitivity of the cost-effectiveness results to the baseline curve selected, the choice of baseline distribution was varied in sensitivity analysis (Section 5.2.13).

Table 115. Summary of the AIC values for survival curves fitted to OS Kaplan-Meier data estimated from data presented for PLDH in CSR OVA-301

Selected distribution	AIC
Weibull	848.2284
Exponential	850.8514
Log normal	837.5367
Log logistic	841.1105
Abbreviations used in table: AIC, Akaike Information Criterion; CSR, clinical study report; MS, manufacturer's submission; OS, overall survival; PLDH, pegylated liposomal doxorubicin hydrochloride.	

To estimate monthly OS for patients treated with PLDH, the TAG used the following formula:

$$survival_t = \exp\left(-\left(\frac{1}{\exp(intercept)^{\frac{1}{\exp(scale)}}}\right) \cdot t^{\left(\frac{1}{\exp(scale)}\right)}\right)$$

Where t is time in months, and the intercept ([redacted]) and scale ([redacted]) parameters have been estimated using MLE methods described in Hoyle *et al.*[110].

Figure 37 presents the Kaplan-Meier survival curve, for PLDH, from the CSR for OVA-301 vs the extrapolated Weibull survival curve.

Figure 37. [redacted]

5.2.7.3 Network meta-analysis of PFS and OS

For each network constructed, HRs of the relative effect of treatment (vs the baseline treatment) on PFS and OS have been obtained from NMA (Section 4.2). These are summarised in Table 116 below.

Table 116. Summary of results from Technology Assessment Group network meta-analyses

	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.				

Adjusted HRs (calculated from data adjusted for baseline characteristics) are available for some of the treatments considered (for example, trabectedin plus PLDH, PLDH, PLDH plus carboplatin, and paclitaxel plus carboplatin); however, unadjusted HRs were used in all TAG NMAs. This is because data used to inform the adjusted HRs, identified in the clinical systematic review, differed by trial; moreover, some trials only reported unadjusted HRs. Therefore, the TAG considered synthesis of unadjusted HRs to be the most comparable measure of relative effect across trials. Moreover, the TAG considers that the use of a consistent dataset within the NMA to be the most appropriate methodology.

5.2.7.4 Estimating PFS and OS for the remaining treatments in the network

For each network, unadjusted hazard ratios, of treatment effect relative to the baseline treatment, were obtained from the NMAs described in Section 4.2. Within the TAG economic model, each HR is applied to the monthly PFS and OS estimates for the baseline treatment, thus providing monthly estimates of PFS and OS for all treatments in the network. To do this, the monthly probabilities of PFS and OS for the baseline treatment are converted into survival rates using the following formula:

$survival\ rate_t = -ln(1 - p_t)$, where p_t is the proportion of patients surviving at month t

The HR obtained from the NMA is then applied to the survival rate and the resultant rate converted back into a probability using the following formula:

$survival\ proportion_t = 1 - \exp(-HR \cdot survival\ rate_t)$, where t is the time in months and HR is the hazard ratio expressed as the relative hazard of survival (rather than the relative hazard of death).

For each network, the survival curves (PFS and OS) estimated using this method are presented in Appendix 9. A summary of the estimated mean PFS and mean OS from the TAG analysis are presented in Table 118 for each therapy.

Table 117. Summary of mean progression free survival and mean overall survival estimated from the Technology Assessment Group analyses, by network

Platinum sensitive network 1		
Treatment	**Mean progression free survival (months)**	**Mean overall survival (months)**
Platinum	10.3	33.9
Gemcitabine plus carboplatin	11.9	34.5
Paclitaxel plus platinum	11.8	38.4
PLDH plus platinum	12.8	38.0
Platinum sensitive network 2		
Treatment	**Mean progression free survival (months)**	**Mean overall survival (months)**
Paclitaxel	6.9	26.3
PLDH	8.9	29.3
Topotecan	7.8	24.6
Trabectedin plus PLDH	10.3	32.2
Platinum resistant/refractory network		
Treatment	**Mean progression free survival (months)**	**Mean overall survival (months)**
Paclitaxel	4.6	18.0
PLDH	5.3	18.6
Topotecan	5.3	18.9
Abbreviation used in table: PLDH, pegylated liposomal doxorubicin hydrochloride		

5.2.7.5 Issues considered by the TAG

The TAG notes that the effectiveness data used in the model was subject to a number of limitations. Therefore, the likely impact of these limitations has been explored in a variety of sensitivity analyses (see Section 5.2.11); a summary of the keys issues and conclusions is provided below.

Appropriateness of clinical data used for the decision problem

Table 118 outlines the treatment regimens used in the clinical trials upon which the NMAs are based vs the treatment regimens assumed to be used in the economic model. The following differences between the treatment regimens used to inform the effect of treatment (with respect to PFS and OS) within the model, and the modelled regimens have been identified:

- no regimens used to inform estimates of treatment effectiveness were limited to six cycles, whereas the number of cycles of therapy modelled is limited to six;

- the efficacy of platinum monotherapy and platinum in combination with paclitaxel has been estimated from, amongst other trials, a trial which included treatment with cisplatin, whereas only treatment with carboplatin (with or without paclitaxel) is modelled;
- clinical effectiveness data from paclitaxel administered at three weekly intervals were used to inform estimates of PFS and OS in the platinum resistant/refractory population, whilst a weekly paclitaxel regimen is modelled;
- estimates of the treatment effectiveness of PLDH monotherapy was based upon a dose of 50 mg/m^2, whereas PLDH monotherapy at 40 mg/m^2 is modelled.

These differences are expected to have minimal impact upon the model results; however, for completeness, the potential impact of the differences is discussed in more detail below.

For all clinical data used to inform PFS and OS in the economic model, estimates are based on treatment regimens in which patients could receive more than six cycles of therapy. However, in the economic model, cycles are limited to a maximum of six to reflect UK clinical practice. The TAG considers that this difference is unlikely to materially impact the cost-effectiveness results. This is because it is generally considered that treatment beyond six cycles is unlikely to impact upon efficacy.[18]

PFS and OS data from Parmar *et al.*[60] have been used to inform the effectiveness of treatment with platinum and platinum in combination with paclitaxel through the TAG NMA. These data include information from patients treated with either carboplatin or cisplatin; although, carboplatin was the agent used most commonly (71% of monotherapy patients, and 80% of combination therapy patients). The TAG notes that in 2010 a Cochrane review was published in which a systematic review and meta-analysis comparing carboplatin and cisplatin in advanced ovarian cancer were carried out. The review estimated that the relative difference in survival, expressed as an odds ratio, for patients treated with these two agents was 1.02 (0.93, 1.12, favours cisplatin).[115] The TAG considers that this result implies that the two agents may be considered similar. Moreover, clinical expert advice received by the TAG suggested that cisplatin and carboplatin have similar efficacy; with carboplatin preferred as a result of greater tolerability. For these reasons, the TAG considers that the assumption of equivalent efficacy between cisplatin and carboplatin is unlikely to impact upon the cost-effectiveness results.

For the platinum resistant/refractory population, clinical advice suggested that paclitaxel monotherapy would be administered weekly rather than three weekly. This is because weekly administration is perceived to be more efficacious than administration every three weeks However, for the platinum resistant/refractory population, no PFS or OS data are available for paclitaxel administered weekly. Therefore, whilst a weekly paclitaxel regimen is modelled, 175 mg/m^2 paclitaxel administered every three weeks has been used to inform PFS and OS. However, evidence from Rosenberg *et al.* suggests that efficacy may not be affected by the use of weekly rather than three weekly administrations.[59] Rosenberg *et al.* presented evidence on the safety and efficacy, in patients with platinum resistant or

platinum refractory disease, of paclitaxel administered at a dose of 67 mg/m^2 per week vs paclitaxel administered at a dose of 200 mg/m^2 every 3 weeks. [59] The study concluded that paclitaxel administered weekly was better tolerated yet comparably efficacious to paclitaxel administered every 3 weeks. Therefore, the TAG considers it unlikely that the efficacy of paclitaxel will be understated to an extent likely to materially affect the cost-effectiveness results.

Finally, estimates of the clinical effectiveness of PLDH monotherapy were based upon a dose of 50 mg/m^2, whereas PLDH monotherapy administered at a dose of 40 mg/m^2 is modelled. This is because, as a result of tolerability issues, clinical advice highlighted that a 50 mg/m^2 dose would not typically be used in clinical practice. Clinical opinion considered that efficacy would not be affected by this dose reduction; therefore the TAG considers that the assumption of equivalent efficacy between 50 mg/m^2 and 40 mg/m^2 PLDH is unlikely to impact upon model results. However for completeness, the TAG investigated the impact of modelling 50 mg/m^2 of PLDH in sensitivity analysis (Section 5.2.11).

Table 118. Comparison of the chemotherapy regimens modelled with the chemotherapy regimens from which effectiveness data was extracted

Chemotherapy	Regimen modelled, and typically used in clinical practice	Regimens from which data is used to inform the effectiveness estimates
Paclitaxel	For platinum resistant/refractory disease: paclitaxel 80mg/m^2 weekly for 18 weeks or until progression For platinum sensitive disease: paclitaxel 175 mg/m^2 on day 1 of every 21 day cycle (maximum six cycles)	For both platinum sensitive, and platinum resistant/refractory: paclitaxel 175 mg/m^2 day 1 of every 21 day cycle. For the Schering Plough submission for TA91, minimum number of cycles was 6. The number of cycles was not limited, although median number of cycles was five (ten Bokkel *et al.*[21]).
Paclitaxel plus platinum	For platinum resistant/refractory disease: paclitaxel 80mg/m^2 plus carboplatin AUC three, weekly for 18 weeks or until progression* For platinum sensitive disease: paclitaxel 175 mg/m^2 and carboplatin AUC five, on day 1 of every 21 day cycle (maximum six cycles)	No clinical data were found for the platinum resistant/refractory population and this intervention was modelled only in sensitivity analysis. For the platinum sensitive population, the regimens on which the clinical data were based was a combination of: • paclitaxel 175mg/m^2 plus carboplatin AUC five on day 1 of every 21 day cycle for a *minimum* of six cycles (Gonzalez Martin *et al.* [47] and CALYPSO.) • paclitaxel 175mg/m^2 plus carboplatin AUC minimum five on day 1 of every 21 day cycle for a *minimum* of six cycles *or* paclitaxel 175mg/m^2 plus cisplatin 50mg/m^2 on day 1 of every 21 day cycle for a *minimum* of six cycles (Parmar *et al.*[60])
PLDH	40 mg/m^2 on day 1 of every 28 day cycle (maximum six cycles)	The regimen on which the clinical data were based was: • 50 mg/m^2 on day 1 of every 28 day cycle until progression (Monk *et al.*[30], Gordon *et al.* [48] and the trial submitted by Schering-Plough for TA91, for at least six cycles.
PLDH plus platinum	PLDH 30 mg/m^2; carboplatin target AUC of five, on day 1 of every 28 day cycle (maximum six cycles)	The regimens on which the clinical data were based were: • PLDH 30 mg/m^2; carboplatin target AUC of five, on day 1 of every 28 day

		cycle, until progression (Alberts *et al.* [28]) • PLDH 30 mg/m^2; carboplatin target AUC of five, day 1 every 28 day cycle, minimum six cycles (Pujade *et al.*[31])
Gemcitabine plus carboplatin	Gemcitabine 1,000 mg/m^2 on days 1 and 8 of every 21 day cycle, carboplatin target AUC of four on day 1 of every 21 day cycle (maximum six cycles)	Gemcitabine 1,000 mg/m^2 on days 1 and 8 of every 21 day cycle, carboplatin target AUC of four on day 1 of every 21 day cycle; maximum of ten cycles (median six cycles) (Pfisterer *et al.*[49])
Trabectedin plus PLDH	Trabectedin 1.1 mg/m^2; PLDH 30 mg/m^2, on day 1 of every 21 day cycle (maximum six cycles)	Trabectedin 1.1 mg/m^2; PLDH 30 mg/m^2, on day 1 of every 21 day cycle, until progression (Monk *et al.*[30])
Topotecan	1.5 mg/m^2, on days 1-5 of every 21 day cycle (maximum six cycles)	The regimen on which the clinical data were based was 1.5 mg/m^2, day 1-5 every 21 day cycle until progression (Gordon *et al.*[48], Ten Bokkel *et al.*[21])
Platinum monotherapy	Carboplatin target AUC of five, on day 1 of every 21 day cycle (maximum six cycles)	The regimens on which the clinical data were based were: • carboplatin AUC five on day 1 of every 21 day cycle for a *minimum* of six cycles (Gonzalez Martin *et al.* [47] and Pfisterer *et al.*[49] • carboplatin AUC five or six, or cisplatin 75 mg/m^2 on day 1 of every 21 day cycle for a *minimum* of six cycles (Parmar *et al.*[60])
*Etoposide**	*50mg flat dose on days 1-21 of every 28 day cycle (maximum six cycles)*	*No clinical data were identified and costs were included in sensitivity analysis only*
*Etoposide plus cisplatin**	*Etoposide 50mg flat dose on days 1-21 every 28 day cycle plus cisplatin IV 50 mg days 1, 8, and 15 every 28 days (maximum six cycles)*	*No clinical data were identified and costs were included in sensitivity analysis only*
*Best supportive care**	*Costs associated with supportive care*	*No clinical data were identified and costs were included in sensitivity analysis only*
* Sensitivity analysis only Abbreviations used in table: AUC, area under the curve; m, metres; mg, milligram; PLDH, pegylated liposomal doxorubicin hydrochloride.		

Appropriateness of hazard ratios obtained from the literature

The TAG considers that the HR is the most appropriate measure of relative treatment effect for survival (PFS and OS). This is because the HR is specifically designed to account for time to event data and allows for censoring frequently present in time to event data. Ideally, an IPD NMA would have been carried out to estimate HRs for all treatments, by subgroup; IPD NMA has the potential to account for differences in baseline characteristics within and between trials through the incorporation of covariates. However, the TAG did not have access to IPD that was sufficiently granular to facilitate such an analysis. Therefore, synthesis of published HRs within standard NMAs were carried out. Many (although not all) of the studies identified for inclusion within the networks provided HRs and, where HRs were not available and sufficient information was provided, they were calculated using methods outlined in Tierney.[(76)]

Additionally, although some of the clinical trials identified for inclusion in the NMA reported HRs adjusted for particular baseline characteristics, the TAG used unadjusted HRs within the NMAs and therefore economic analyses. The TAG recognises that imbalances in baseline characteristics between treatment arms may introduce bias into the HR; however, of those trials reporting adjusted HRs, each had adjusted for different factors. Moreover, for some comparisons only unadjusted HRs were reported. Therefore, the TAG considers the use of unadjusted HRs to be the most equitable way to compare therapies. Moreover, the TAG considers that the use of consistent data is appropriate for meta-analysis.

The TAG notes that within the DSU technical support document it is acknowledged that there are practical difficulties in modelling survival based upon summary data such as HRs rather than patient level data, and notes that it is anticipated that this issue will be considered in a future technical support document.[(118)] Specifically, two key concerns are raised within this document about the use of summary HRs:

- the assumption of proportional hazards (discussed below): *"where one HR is applied to the entire modelled period, the proportional hazards assumption must be made – that is, the treatment effect is proportional over time and the survival curves fitted to each treatment group have a similar shape."*
- that HRs should be obtained from the same parametric model as used to estimate base line survival: *"care should be taken to ensure that only the HR obtained from the chosen parametric model is applied to the control group survival curve derived from the parametric model fitted with the treatment group as a covariate – it is theoretically incorrect to apply a HR derived from a different parametric model, or one derived from a Cox proportional hazards model"*

For the analyses carried out for this MTA, IPD were not available for all treatments considered; therefore, it was not possible to estimate HRs for each treatment using the same parametric model as

fitted for the baseline treatment. Consequently, HRs were obtained from published or submitted literature. The TAG recognises that the use of published HRs is a weakness of the analysis and notes that it is unclear what impact this would have upon model results. However, to provide an indication of how sensitive model results were to the effect of treatment on PFS and OS, the survival curves estimated from application of the HR were tested in sensitivity analysis (Section 5.2.11).

Appropriateness of the proportional hazards assumption

The TAG did not have access to either a single clinical trial, or IPD for the full range of interventions and comparators of interest for this MTA. For that reason, as discussed, the TAG used summary HRs, synthesised from published or submitted literature, to estimate the relative effects of treatments considered within the economic analysis. Consequently, it is implicitly assumed that the relative treatment effects captured by the HRs holds true across all time points. In other words, use of HRs in the economic model assumes that the relative hazards between treatments are proportional.

The TAG explored whether the assumption of proportional hazards was appropriate for the data used within the analysis. This was explored, as per the DSU technical support document for survival analysis, with log-cumulative hazard (LCH) plots.[118] The LCH plots were created by digitising (where available) Kaplan-Meier plots for each of the treatments included within the analysis, **ln(time)** was then plotted against **ln(-ln(survival probability)**. For each network, LCH plots based on Kaplan-Meier data used to inform PFS and OS are presented in Appendix 10; LCH plots are presented for the individual and total comparisons made.

Based on the LCH plots, the TAG considers that the assumption of proportional hazards may not be entirely appropriate. In particular, for progression free survival in platinum sensitive patients, where in many cases the relative hazards of progression seem to decrease over time. The impact, on model results, of incorrectly assuming proportional hazards will depend on the nature of the true hazard function. In cases where the relative hazard (treatment A vs treatment B) decreases over time (for both PFS and OS), the model is likely to overestimate the relative benefit of treatment A vs treatment B. Conversely, when relative hazards increase over time (for PFS and OS), the model is likely to underestimate the benefit of treatment A over treatment B. In cases where the relative hazards are non-monotonic (i.e., increase and then decrease or vice versa) or differ between PFS and OS, it is more challenging to determine the possible direction of bias. With this in mind, when reporting the cost-effectiveness results the TAG has endeavoured to indicate the potential direction of bias resulting from inappropriate assumption of proportional hazards (Section 5.2.12).

Crossover bias

Crossover bias occurs when a patient switches from a control therapy to the treatment being evaluated during a clinical trial. Here, the switch of therapy results in a possibility that any clinical benefit

associated with the experimental treatment will be underestimated.[119] In the clinical trials evaluated for this review, several allowed women to undergo further therapy following progression. This means that it is possible that crossover bias will have influenced OS results used within the analysis; indeed, confounding of OS data is a well-recognised complexity in clinical trials evaluating treatments for cancer.

A number of approaches have been suggested that attempt to quantify the degree of confounding; these are discussed in detail in Morden *et al*.[119] Within this paper it is suggested that the iterative parameter estimation algorithm put forward by Branson and Whitehead, may be considered when analysing the degree of bias.[120]

The TAG was unable to investigate the degree of crossover bias within the estimates of OS for this MTA. This is because not all trials described the further treatments received by the women within the trial, and furthermore, application of the Branson and Whitehead method requires IPD in order to assess the degree of bias. As such, the degree to which crossover bias has influenced results is unclear. The TAG considers that underestimation of survival benefit may have affected all comparisons, although the degree to which comparisons are affected is unknown. It is however possible that the degree of bias may be balanced.

However, for completeness, and to address this uncertainty, the TAG carried out sensitivity analyses on the OS curves included in the economic analysis (Section 5.2.11).

5.2.8 Adverse event incidence

Following appraisal of the studies identified as part of the clinical effectiveness review and after discussion with clinical experts, a shortlist was drawn up of adverse events considered to have a noteworthy impact on cost or patient quality of life. These were: allergic reaction, alopecia, anaemia, fatigue, febrile neutropenia, nausea and vomiting, and neuropathy (Section 4.2.2.5). For the purposes of the economic model, only adverse events of Grade 3 and Grade 4 were considered; this was consistent with the approach taken in TA91 and reflected the likelihood that Grade 1 or 2 adverse events are likely to impact little on cost or QoL.

In the base case, only the subset of adverse events associated with a notable cost were included in the analysis; quality of life decrements are included in sensitivity analysis only. This is because the reliability of the estimates identified for quality of life decrements is uncertain. In addition, the impact of adverse events on patient quality of life associated with trabectedin plus PLDH and PLDH monotherapy are implicitly included within the health state utility estimates from TA222; therefore the addition of disutility values may result in double counting of the impact of adverse events for these therapies (Section 5.2.9).

Of the adverse events considered for inclusion in the model, four were deemed to result in a cost to the NHS (Section 5.2.10). These are allergic reaction, anaemia, febrile neutropenia, and nausea and vomiting. However, where data were available, the impact of adverse events on patient quality of life is considered in sensitivity analysis (Section 5.2.11).

The relative likelihood of an adverse event associated with each therapy was estimated from a series of NMAs carried out by the TAG (Section 4.2.2.5). The outcome measure selected to assess the relative likelihood was the odds ratio (OR). As a result of data paucity, adverse events were not analysed by population; instead, adverse event data from any population (platinum sensitive or platinum resistant/refractory) were included in analysis. The TAG considered this approach to be appropriate in order to utilise all available data. However, the TAG notes that this approach necessitates the assumption that the likelihood of an adverse reaction is independent of the PFI.

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. Therefore, within the model, the following steps are taken:

- for the baseline treatment in each network (PS network 1, PS network 2, and PRR) the probability of each adverse event has been estimated;
- where available, ORs for treatments within the same network are used to inform the probability of each adverse event;
    - ORs that are statistically significant (at the 5% level) are converted into a probability using the following formula:

      $odds_B = \frac{odds_B}{odds_A} \cdot \frac{p_A}{(1-p_A)}$, and $p_B = \frac{odds_B}{1+odds_B}$, where p_A is the probability of an adverse event for the baseline treatment, and where p_B is the probability of an adverse event for all other treatments;
    - ORs that are not statistically significant (at the 5% level) are assumed to be equal to 1 (i.e., the baseline probability is used).
- where no OR was calculable, and therefore the relative effect is unknown, or where resultant probabilities were considered by clinical experts to represent unlikely values, expert opinion was sought in order to inform the rate of adverse event.

The adverse event rates used in the base case model are presented, by network (PS network 1, PS network 2, and PRR), in Tables 119 to 121.

Table 119. Grade 3/4 adverse event rates used in the base case model (platinum sensitive network 1)

Chemotherapy	OR (95% CrI)	Adverse event probability	Comments
Allergic reaction			
Paclitaxel plus platinum	Baseline treatment	3.94%	Source of baseline probability: a weighted average of Bafaloukos[29] (1 event, 89 patients) and Gonzalez-Martin[47] (4 events, 38 patients)
PLDH plus platinum	0.130 (0.001, 0.705)	0.53%	–
Gemcitabine plus carboplatin	0.757 (0.030, 3.798)	3.94%	Non-statistically significant difference, therefore OR assumed to equal 1; probability was set to equal the baseline treatment
Platinum	0.755 (0.057, 3.043)	3.94%	Non-statistically significant difference, therefore OR assumed to equal 1; probability was set to equal the baseline treatment
Anaemia			
Paclitaxel plus platinum	Baseline treatment	5.10%	Source of baseline probability: a weighted average of Bafaloukos[29] (3 events, 89 patients), Gonzalez-Martin[47] (2 events, 38 patients), and Pujade-Lauraine[31] (27 events, 501 patients)
PLDH plus platinum	1.926 (1.164, 3.039)	9.38%	–
Gemcitabine plus carboplatin	5.848 (1.158, 18.040)	23.91%	–
Platinum	1.255 (0.305, 3.479)	5.10%	Non-statistically significant difference, therefore OR assumed to equal 1; probability was set to equal the baseline treatment
Febrile neutropenia			
Paclitaxel plus platinum	Baseline treatment	4.19%	Source of baseline probability: Pujade-Lauraine[31] (21 events, 501 patients)
PLDH plus platinum	0.614 (0.299, 1.263)	4.19%	Non-statistically significant pair-wise difference, therefore OR assumed to equal 1; probability was set to equal the baseline treatment
Gemcitabine plus carboplatin	N/A	4.19%	No OR calculable, therefore set equal to baseline treatment (4.19%) based upon clinical advice
Platinum	N/A	0%	No OR calculable, therefore set equal to 0% based upon clinical advice
Nausea and vomiting			
Paclitaxel plus platinum	*Baseline treatment*	1.57%	Source of baseline probability: weighted average of Bafaloukos[29] (1 event, 89 patients) and Gonzalez-Martin[47] (1 event, 38 patients). Clinical expert opinion implied that this rate appeared low; therefore, this was varied in a scenario analysis (Section 5.2.11)
PLDH plus platinum	2.055 (1.598, 2.608)	3.17%	Given the uncertainty associated with this network, ORs estimated from analysis of all grades were used. OR for grade 3/4 provided extreme values; therefore, ORs estimated from analysis of all grades were used. Probabilities based upon clinical expert opinion were used in scenario analysis (Section 5.2.11)
Gemcitabine plus carboplatin	*N/A*	3.17%	No data; therefore, set equal to PLDH plus platinum in the base case based upon clinical advice
Platinum	*1.305 (0.981,*	1.57%	Given the uncertainty associated with this network,

	1.706)		ORs estimated from analysis of all grades were used. This analysis provided a non-statistically significant difference between platinum and the baseline therapy; therefore, OR assumed to equal 1; probability was set to the same as the baseline treatment. Probabilities based upon clinical expert opinion were used in scenario analysis (Section 5.2.11)
Abbreviations used in table: CrI, credible interval; N/A, not applicable; OR, odds ratio; PLDH, pegylated liposomal doxorubicin hydrochloride.			

Table 120. Grade 3/4 adverse event rates used in the model (platinum sensitive network 2)

Chemotherapy	OR (95% CrI)	Adverse event rate	Comments
Allergic reaction			
Paclitaxel	N/A	20%	Set equal to 20% based upon clinical advice
PLDH	N/A	5%	Set equal to 5% based upon clinical advice
Trabectedin plus PLDH	N/A	5%	Set equal to 5% based upon clinical advice
Topotecan	N/A	0%	Set equal to 0% based upon clinical advice
Anaemia			
Paclitaxel	0.742 (0.209, 1.848)	4.73%	Non-statistically significant difference, therefore OR assumed to equal 1; probability was set to equal the baseline treatment
PLDH	Baseline	4.73%	Source of baseline probability: weighted average of Schering-Plough submission from TA91[13] (3 events, 108 patients), Gordon[48](13 events, 239 patients), and Monk[30](16 events, 330 patients)
Trabectedin plus PLDH	2.940 (1.559, 5.202)	12.74%	–
Topotecan	7.374 (3.775, 13.590)	26.80%	–
Febrile neutropenia			
Paclitaxel	N/A	5%	Set equal to 5% based upon clinical advice
PLDH	Baseline	2.12%	Source of baseline probability: Monk[30] (7 events, 330 patients)
Trabectedin plus PLDH	3.256 (1.378, 7.692)	6.59%	–
Topotecan	N/A	5%	Set equal to 5% based upon clinical advice
Nausea and vomiting			
Paclitaxel	0.279 (0.120, 0.535)	2.93%	–
PLDH	Baseline	9.75%	Source of baseline probability: a weighted average of Monk[30] (15 events, 330 patients), Schering-Plough submission from TA91[13] (19 events, 108 patients), and Gordon[48](32 events, 239 patients)
Trabectedin plus PLDH	5.291 (2.866, 9.342)	36.37%	–
Topotecan	1.460 (0.886, 2.294)	9.75%	Non-statistically significant difference, therefore OR assumed to equal 1; probability was set to equal the baseline treatment
Abbreviations used in table: CrI, credible interval; N/A, not applicable; OR, odds ratio; PLDH, pegylated liposomal doxorubicin hydrochloride.			

Table 121. Grade 3/4 adverse event rates used in the model (platinum resistant / refractory network)

Chemotherapy	OR (95% CrI)	Adverse event rate	Comments
Allergic reaction			
Paclitaxel	N/A	20%	Set equal to 20% based upon clinical advice
PLDH	N/A	5%	Set equal to 5% based upon clinical advice
Trabectedin plus PLDH	N/A	5%	Set equal to 5% based upon clinical advice
Topotecan	N/A	0%	Set equal to 0% based upon clinical advice
Etoposide*	N/A	0%	Set equal to 0% based upon clinical advice
Etoposide plus carboplatin*	N/A	10%	Set equal to10% based upon clinical advice
Anaemia			
Paclitaxel	0.742 (0.209, 1.848)	4.73%	Non-statistically significant difference, therefore OR assumed to equal 1; probability was set to equal the baseline treatment
PLDH	Baseline	4.73%	Source of baseline probability: weighted average of Schering-Plough submission from TA91[13] (3 events, 108 patients), Gordon[48] (13 events, 239 patients), and Monk[30] (16 events, 330 patients)
Trabectedin plus PLDH	2.940 (1.559, 5.202)	12.74%	–
Topotecan	7.374 (3.775, 13.590)	26.80%	–
Etoposide*	N/A	4.73%	Set equal to paclitaxel (4.73%) based upon clinical advice
Etoposide plus carboplatin*	N/A	4.73%	Set equal to paclitaxel (4.73%) based upon clinical advice
Febrile neutropenia			
Paclitaxel	N/A	5%	Set equal to 5% based upon clinical advice
PLDH	Baseline	2.12%	Source of baseline probability: Monk[30](7 events, 330 patients)
Trabectedin plus PLDH	3.256 (1.378, 7.692)	6.59%	–
Topotecan	N/A	5%	Set equal to 5% based upon clinical advice
Etoposide*	N/A	0%	No data
Etoposide plus carboplatin*	N/A	0%	No data

Nausea and vomiting			
Paclitaxel	0.279 (0.120, 0.535)	2.93%	–
PLDH	Baseline	9.75%	Weighted average of Monk[30] (15 events, 330 patients), Schering-Plough submission from TA91[13] (19 events, 108 patients), and Gordon[48] (32 events, 239 patients)
Trabectedin plus PLDH	5.291 (2.866, 9.342)	36.37%	–
Topotecan	1.460 (0.886, 2.294)	9.75%	Non-statistically significant difference, therefore OR assumed to equal 1; probability was set to equal the baseline treatment
Etoposide*	N/A	9.75%	Set equal to PLDH (9.75%) based upon clinical advice
Etoposide plus carboplatin*	N/A	9.75%	Set equal to PLDH (9.75%) based upon clinical advice
* Sensitivity analysis only Abbreviations used in table: CrI, credible interval; N/A, not applicable; OR, odds ratio; PLDH, pegylated liposomal doxorubicin hydrochloride.			

5.2.9 Health-related quality of life (HRQoL) data

5.2.9.1 Technology Assessment Group systematic review of HRQoL data

A systematic review was carried out in December 2012 to identify relevant published HRQoL evidence to support the development of this MTA. The following databases were searched:

- MEDLINE (Ovid);
- EMBASE (Ovid);
- HTA database (HTA);
- NHS Economic Evaluations Database (NHS EED).

The search strategy for all databases combined terms to capture the target condition (ovarian cancer); and terms to capture quality of life. As this MTA is in part an update of TA91 in which a systematic review was carried out (search date of April 2004) to identify HRQoL studies, searches were limited from 2004. Full details of the search terms are presented in Appendix 5.

In addition to searches of the above databases, the following sources of potentially relevant publications were explored:

- experts in the field were contacted with a request for details of relevant published and unpublished studies of which they may have knowledge;
- the NICE Technology Appraisal website was searched for any recently published Technology Appraisals in ovarian cancer that had not already been identified via the database searches or that may include additional HRQoL data;
- reference lists of key identified studies were reviewed for any potentially relevant studies.

No restrictions on language or setting were applied to any of the searches. Two health economists reviewed a sample of citations identified from the search and, upon confirming that the same inclusions and exclusions were applied for those papers, one health economist reviewed the remaining papers. Inclusion and exclusion criteria are presented in Table 122.

Table 122. Inclusion and exclusion criteria for the HRQoL systematic review

Inclusion criteria	Exclusion criteria
Q1: possible generic, preference based measure of HRQoL (e.g. EQ-5D, SF-6D, HUI) or standard gamble/time trade-off studies any setting (to be as inclusive as possible Q2: possible generic, non-preference based measure of HRQoL (e.g. SF-36) Q3: possible condition specific measure of HRQoL	Abstracts with insufficient methodological details, systematic reviews
Abbreviations used in table: HRQoL, health-related quality of life; HUI, health utilities index.	

The systematic review was updated in May 2013 whilst the report was under peer review. The search strategy remained the same as outlined above; however, results were limited from 5th December 2012 to 23rd May 2013 in order to identify only additional relevant studies.

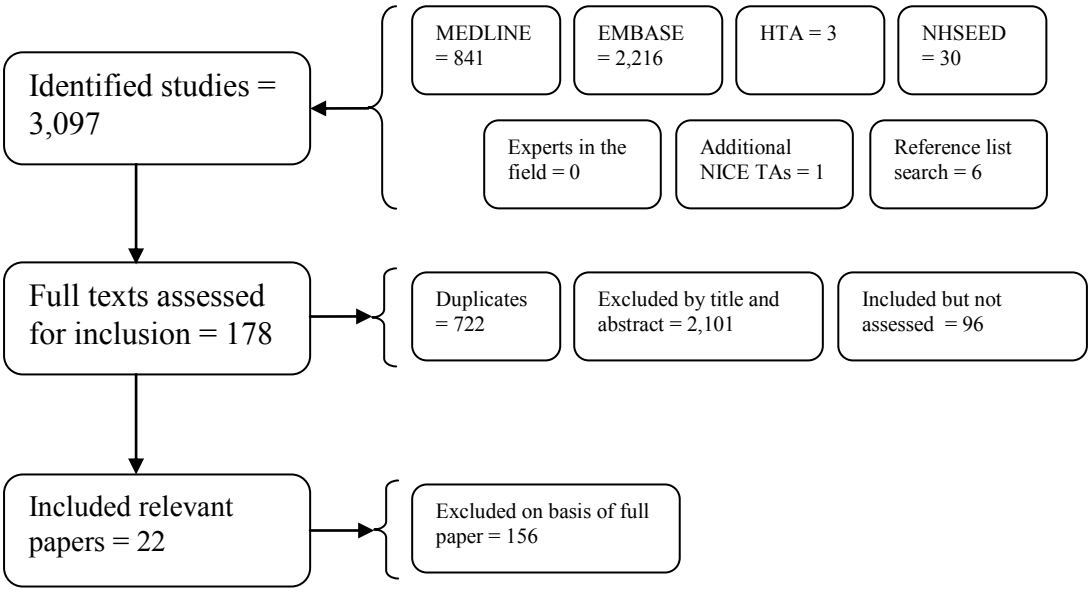
A total of 3,090 studies were identified from the December 2012 search of MEDLINE, EMBASE, HTA and NHS EED (Figure 38). Two health economists reviewed the first 100 citations identified from the search and, upon confirming consistency in the inclusions and exclusions made; one health economist reviewed the remaining 2,990 papers. Of these, 722 were identified as duplicates and 2,101 studies were excluded on the basis of title and abstract. A total of 267 papers were therefore identified as potentially relevant. Of these papers, 96 were identified, from the abstract, as either condition specific measures of HRQoL or generic non-preference based measures of HRQoL. Furthermore, 171 papers were identified as possible generic, preference-based measures of HRQoL (Q1, Table 122). If it was unclear which type of HRQoL measure was included in the study, the reviewer was inclusive and labelled the study as a potential generic, preference-based measure of HRQoL.

The 96 studies identified as either condition specific measures of HRQoL or generic non-preference based measures of HRQoL during the December search were provisionally included; that is, these studies were not ordered in full in the first instance. Instead, studies identified as reporting possible generic, preference-based measures of HRQoL were reviewed in full (171 papers). This is because a generic, preference-based measure of HRQoL, in particular the EQ-5D, is preferable for use within an economic evaluation.[109] It was therefore considered appropriate to assess the suitability of condition specific or generic non-preference based measures of HRQoL, if and only if, no suitable generic, preference-based measures of HRQoL were identified.

In addition to the studies identified through the database search, the ERG report for TA222,[90] was identified through review of the NICE technology appraisal website. The ERG report for TA222 was not detected in the database search; the TAG notes that this was because the date of the report was erroneously indexed within the search engine as the year 2000 rather than 2011, and was therefore excluded when date filters were applied to the search results. Additionally, through review of the reference lists of included studies, six studies were identified as possible preference-based measures of HRQoL. All six studies were published prior to 2004 and therefore were not detected in the database search; however, because these studies were referenced as the source of HRQoL data included within identified studies, they were included for completeness.

The studies identified from the database search and additional sources were reviewed in full. Of the 178 identified studies, a total of 22 studies included generic, preference-based HRQoL data. See Appendix 6 for an overview of reasons for exclusion of papers that were reviewed in full.

Figure 38. Identified HRQoL studies, December 2012 search



A further 239 papers were identified from the updated search in May 2013. Of these, a total of seven papers were identified as potentially relevant and ordered for full review. Of the seven ordered papers, four were excluded on the basis of the full paper and three papers were identified as including generic, preference-based HRQoL data. For a detailed description of the reasons for exclusion, see Appendix 6. In addition to the included three papers, TA284 and TA285 were identified from an updated review of the NICE technology appraisal website.

Of the 187 papers included in the December 2012 and May 2013 searches, a total of 27 papers reported generic, preference-based HRQoL data. Information on the populations, health states,

instruments and utility values reported in these studies are presented in Appendix 7; a summary of the HRQoL instrument used in each included study is presented in Table 123.

Table 123. Summary of the HRQoL instrument used within each included study

Author; year	Instrument
Identified from the literature search and previous NICE technology appraisals	
Hess *et al*.; 2013[121]	Valuation of the FACT questionnaire using methods described in Cheung *et al.*[122] and Dobrez *et al.*[123]
NICE 2013; TA285 (ERG report)[124]	*N/A – utilities sourced from TA222*[90]
NICE 2013; TA284 (manufacturer submission) [11]	EQ-5D
Bradford *et al.* 2013[125]	Time trade-off
Montalar *et al*.; 2012[97]	*N/A – utilities sourced from OVA-301 as reported in Krasner et al.*[65]
Havrilesky et al; 2012[101]	Valuation of the FACT questionnaire using time trade-off
Havrilesky et al; 2012[126]	*N/A – utilities stated as sourced from Leung et al.*[127]
Krasner et al; 2012[65]	EQ-5D
Pickard et al; 2012[128]	EQ-5D
Grann et al; 2011[129]	*N/A – utilities stated as sourced from Grann 2010*[130]
Lesnock et al; 2011[103]	*N/A – utilities stated as sourced from Greving et al.*[131]
NICE 2011; TA222 (ERG report) [90]	EQ-5D
Gordon et al; 2010[132]	SF-6D
Grann *et al*.; 2010[130]	Time trade-off
Hess; 2010[133]	Standard gamble
Greving et al; 2009[131]	*N/A – utilities stated as sourced from Grann 1998*[134] *and Grann 1999*[135]
Havrilesky et al; 2009[136]	Time trade-off
Havrilesky et al; 2007[105]	*N/A – utilities stated as sourced from Sun 2002*[137]
Stein et al; 2007[138]	Standard gamble
Main et al; 2006[99]	*N/A – utilities stated as sourced from Tengs 2000*[88] *and Brown 1998*[89]
Calhoun et al; 2004[139]	Time trade-off
Identified from review of reference lists of the above identified studies	
Sun; 2002[137]	Time trade-off
Tengs; 2000[88]	*N/A – utilities stated as sourced from Grann 1998*[134]
Grann; 1999[135]	Time trade-off
Leung; 1999[127]	Time trade-off
Brown; 1998[89]	Standard gamble
Grann; 1998[134]	Time trade-off
Abbreviations used in table: FACT, Functional Assessment of Cancer Therapy; N/A, not applicable; NICE, National Institute for Health and Care Excellence.	

Of the included studies, four reported using EQ-5D questionnaires to collect QoL data; Krasner *et al.*[65], Pickard *et al.*[128], TA222[90], and TA284[11]. However, no EQ-5D scores for people with ovarian cancer were presented within the study by Pickard *et al;.*[128] therefore, this study could not be used to inform the economic model. In both Krasner *et al.*[65] and TA222[90] EQ-5D data collected as part of OVA-301 were reported. OVA-301 was a phase III clinical trial which recruited women with recurrent ovarian cancer after failure of first-line, platinum-based chemotherapy. Women were randomised to either PLDH or PLDH with trabectedin. For each treatment group, Krasner *et al.*[65]

reported baseline EQ-5D scores and the change in EQ-5D from baseline to end of follow-up. By contrast, TA222 reported EQ-5D data by health state (progression free disease and progressed disease) regardless of treatment received (Table 124).

Table 124. EQ-5D data from OVA-301 identified from the HRQoL systematic review

Study	Health State	Mean estimate of EQ-5D valuation	Measure of variance	n
Krasner *et al.*[65]	PLDH (baseline)	0.78	0.163 (sd)	318
	PLDH (change from baseline)	-0.05	0.191 (sd)	211
	Trabectedin plus PLDH (baseline)	0.78	0.171 (sd)	323
	Trabectedin plus PLDH (change from baseline)	-0.05	0.201 (sd)	233
TA222[90]	PFS	0.718	0.01 (se)	NR
	PD	0.649	0.019 (se)	NR
Abbreviations used in table: HRQoL, health-related quality of life; n, sample size; NR, not reported; PD, progressed disease; PFS, progression free survival; PLDH, pegylated liposomal doxorubicin hydrochloride; sd, standard deviation; se, standard error.				

TA284 reported EQ-5D data from ICON 7, a randomised, two arm, multi-centre, phase III trial considering the addition of bevacizumab to first-line treatment with carboplatin and paclitaxel (vs carboplatin and paclitaxel) in patients with epithelial ovarian cancer.[11] EQ-5D data were presented for stable disease and for progressed disease, with utilities associated with stable disease dependent upon time (Table 125).

Table 125. EQ-5D data used within the manufacturer submission for TA284 (reproduced from MS page 152)

Health state	Mean EQ-5D	Standard error	n
Stable disease weeks 0-2	0.6571	0.0133	335
Stable disease weeks 3-5	0.7153	0.0118	378
Stable disease weeks 6-8	0.7443	0.0110	375
Stable disease weeks 9-11	0.7683	0.0100	361
Stable disease weeks 12-14	0.7643	0.0112	363
Stable disease weeks 15-20	0.7444	0.0121	353
Stable disease weeks 21-26	0.7638	0.0131	303
Stable disease weeks 27-32	0.7718	0.0129	295
Stable disease weeks 33-38	0.7638	0.0136	282
Stable disease weeks 39-44	0.7785	0.0155	220
Stable disease weeks 45-50	0.7533	0.0165	202
Stable disease weeks 51-53	0.7760	0.0170	178
Stable disease weeks 54+	0.8129	0.0113	338
Progressed disease	0.7248	-	-
Abbreviations used in table: PFS, progression free survival; n, sample size.			

One study reported SF-6D data (Gordon *et al.*[132]). In this study, utility scores from 85 Australian women were reported by stage of disease (stage I/II; stage III; stage IV). For each disease stage a mix of drug therapies, platinum status, and line of therapy were possible. No data by progression status was presented.

Ten studies valued health states using the time trade-off method:

- Hess *et al.*[121] used algorithms developed by Dobrez *et al.*[123] and Cheung *et al.*[122] to value responses to the Functional Assessment of Cancer Therapy (FACT) questionnaire from 746 people with ovarian cancer, where Dobrez *et al.*[123] used time trade-off to value FACT questionnaire health states, and Cheung *et al.*[122] developed a mapping algorithm between FACT and EQ-5D.
- Bradford *et al.*[125] used time trade-off to value sexual dysfunction and other hypothetical treatment-related side effects.
- Havrilesky *et al.*[101] used estimates developed by Dobrez *et al.*[123] using time trade-off to value FACT questionnaire health states.
- Grann *et al.*[130] estimated a single mean preference rating for ovarian cancer of between 0.83 and 0.84 based upon the responses from Canadian women with (n=83) or without (n=160) a personal or family history of breast or ovarian cancer.
- Havrilesky *et al.*[136] valued 25 different health states based upon the responses of 37 female members of the public, and 13 women with a prior diagnosis of ovarian cancer. Health states valued included cancer states and adverse event states.
- Calhoun *et al.* [139] valued six health states that reflected various levels of toxicity in women with ovarian cancer based upon the responses of 39 ovarian cancer patients, 15 women at increased risk, 39 women in the general population and 11 gynaecologic oncologists.

- Sun *et al.* [137] valued adverse event health states based upon the responses from 34 women with ovarian cancer.
- Grann *et al.*[135] estimated a mean preference rating for ovarian cancer, and metastatic cancer based upon the responses of 21 breast cancer patients, 28 women with a personal history of multiple breast biopsies or a family history of breast cancer, and 135 women without these conditions.
- Leung *et al.*[127] valued nine health states for breast cancer; toxicity from treatment, response to treatment, no response to treatment for each of treatment with paclitaxel, docetaxel and vinorelbine in breast cancer patients. Values were estimated based upon the responses of 25 healthy volunteers and 25 women with breast cancer.
- Grann *et al.*[134] estimated a mean preference rating for ovarian cancer, and metastatic cancer based upon the responses of 54 participants. The mean ovarian cancer utility was estimated to be 0.82, with metastatic disease estimated at 0.63.

In addition, three studies valued health states using the standard gamble technique. Hess *et al.* [133] valued six health states (with varying degrees of efficacy and adverse events) based upon the responses of 51 women with ovarian cancer and 34 oncologists in the US. Stein *et al.*[138] valued six clusters of patient characteristics (with varying proportions of performance status, disease stage and response after treatment) based upon the responses of 39 Value of Health Panel members. Brown *et al.* [89] valued breast cancer health states based upon the responses from 29 US oncology nurses and 25-30 nurses from each of Germany, Italy, the Netherlands, Spain and the UK.

The remaining nine included studies were not the primary source of utility data. For example, four studies (Greving *et al.,*[131] Main *et al.,* [99] Tengs and Wallace,[88] and Lesnock et al[103]) referenced (either directly or indirectly) Grann *et al.*[134]; although it is unclear how Greving *et al.*[131] used the data in Grann *et al.*[134] to estimate the utility values stated within the study.

5.2.9.2 Quality of life data included in the manufacturer's submissions

One manufacturer (PharmaMar) submitted cost-effectiveness evidence, including estimates of HRQoL used in the economic model. The estimates used by the manufacturer were not obtained from a systematic review; instead, as described in Section 5.1.3, the manufacturer used EQ-5D data obtained from the OVA-301 clinical trial. 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 therefore identical to the EQ-5D data identified by the TAG from the systematic review of the literature.

5.2.9.3 Quality of life data selected for the TAG economic analysis

In order to assess quality adjusted life years in the *de novo* economic analysis, it was necessary to identify health state utility values for the stable (progression free) and progressive disease health states (Section 5.2.4). In addition, given the importance of adverse treatment effects on quality of life, it was desirable to identify disutilities associated with adverse treatment effects.

The health state utility values selected for use within the TAG economic model are those used within TA222 (Table 126). This is because TA222 represents the only literature source identified which reports EQ-5D utility values in the recurrent ovarian cancer population by the health states required for the economic model. As described within the NICE Guide to the methods of technology appraisal, EQ-5D represents the preferred measure of HRQoL in adults.[109] In addition, the TAG notes that HRQoL data within TA222 were based upon a sample of over 600 patients; the largest sample identified from the included HRQoL studies. EQ-5D data from TA284 were not used in the economic analysis because these data were reflective of first-line ovarian cancer patients.

Table 126. Health state utility values used within the Technology Assessment Group's *de novo* economic evaluation

	Mean estimate	Standard error
Stable disease	0.718	0.01
Progressed disease	0.649	0.02

With respect to disutilities associated with adverse treatment effects, four studies were identified that reported utilities associated with adverse events in ovarian cancer (Hess *et al.* [133], Havrilesky *et al.*[136], Calhoun *et al.* [139], Sun *et al.* [137]). Havrilesky *et al.*[136] and Calhoun *et al.* [139] report mean values of health state valuations carried out by members of the public. By contrast, Sun *et al.* [137] and Hess *et al.*[133] report median values of patient and physician health state valuation. Therefore, as mean vs median values and public vs patient preferences are recommended for use in economic evaluations,[109] utility data from Havrilesky *et al.*[136] and Calhoun *et al.* [139] were selected over utility data from Sun *et al.* [137] and Hess *et al.*[133].

The mean utility values reported for adverse events in Calhoun *et al.* [139] are presented in Table 127. The mean utility values reported for adverse events in Havrilesky *et al.*[136] are presented in Table 128.

Table 127. Utilities for chemotherapy-related health states; general population time trade-off valuations in Calhoun *et al.* [139]

Adverse event	Mean	n	Standard deviation
Mild ototoxicity	0.88	39	NR
Mild nephrotoxicity	0.95	39	NR
Mild neurotoxicity	0.92	39	NR
Severe ototoxicity	0.38	39	NR
Severe nephrotoxicity	0.27	39	NR
Severe neurotoxicity	0.47	39	NR
Abbreviations used in table: n, sample size; NR, not reported.			

Table 128. Utilities for chemotherapy-related health states; volunteer time trade-off valuations with Havrilesky *et al.*[136]

Adverse event	Mean	n	Standard deviation
Alopecia Grade 2	0.84	14	0.29
Peripheral neuropathy Grades 1-2	0.81	15	0.29
Stomatitis Grade 2	0.91	14	0.08
Myalgia/pain Grades 1-2	0.89	15	0.12
Nausea/vomiting Grades 1-2	0.76	15	0.28
Myalgia/pain Grades 3-4	0.46	15	0.39
Neutropenia Grade 4	0.64	16	0.36
Peripheral neuropathy Grades 3-4	0.65	14	0.31
Nausea/vomiting Grades 3-4	0.63	16	0.30
Fatigue Grades 3-4	0.58	13	0.33
Febrile neutropenia	0.56	15	0.34
Abbreviation used in table: n, sample size.			

Havrilesky *et al.*[136] also describe health state valuations via time trade-off for recurrent ovarian cancer with and without Grade 1-2 and Grade 3-4 toxicity. These valuations were based upon both volunteers and women with ovarian cancer. These are presented within Table 129.

Table 129. Utilities for diagnosis-related health states; volunteer and women with ovarian cancer time trade-off valuations within Havrilesky *et al.*[136]

Health state	Mean	n	Standard deviation
Recurrent ovarian cancer – responding to chemotherapy Grades 1-2 toxicity	0.50	15	0.34
Recurrent ovarian cancer – responding to chemotherapy Grades 3-4 toxicity	0.61	14	0.24
Recurrent ovarian cancer – progressive Grades 1-2 toxicity	0.40	16	0.33
Recurrent ovarian cancer – progressive Grades 3-4 toxicity	0.47	15	0.34
End stage ovarian cancer	0.16	15	0.25
Abbreviation used in table: n, sample size.			

There are a number of reliability issues with the incorporation, in the economic model, of disutility values calculated from either Calhoun *et al.* [139] or Havrilesky *et al.*[136].

Firstly, the sample size on which the estimates are based is small; ranging from 13 people to 16 people for Havrilesky *et al.*[136] and up to 39 people for Calhoun *et al.*[139] Secondly, for Havrilesky *et al.*[136], certain mean values (presented in Table 129) are counter intuitive. For example, the utility value for recurrent ovarian cancer with Grade 1-2 adverse events is lower than recurrent ovarian cancer with Grade 3-4 adverse events (whether progressive ovarian cancer or responding to therapy).

Finally, the impact of adverse events on patient quality of life associated with trabectedin plus PLDH and PLDH monotherapy are already implicitly included within health state EQ-5D estimates from TA222. This means that addition of disutility values may result in double counting of the impact of adverse events for these therapies. For these reasons, the impact of applying disutilities as a result of treatment- related adverse events has been excluded from the base case analysis and tested in sensitivity analysis. Therefore, the base case analysis assumes that the impact of adverse events on patient quality of life is accounted for in the mean estimates of utility associated with the model health states; however, costs of Grade 3 and 4 adverse events were applied in the base case (Section 5.2.10).

5.2.10 Costs

The following costs are captured within the TAG's economic model: chemotherapy; administration; health state related; and adverse events. A systematic search for UK-based cost studies to populate these parameters was carried out as part of the systematic review for economic evaluation studies. The search strategy is described in Section 5.1.2. A total of 18 studies were identified as purely costing studies; however, none of these studies were UK-based and were therefore not considered relevant for this MTA (reasons for exclusion described in Appendix 6). Consequently, where appropriate, costs included in the *de novo* analysis have been estimated from standard UK sources; these are described in further detail below.

5.2.10.1 Intervention/comparator chemotherapy costs

A summary of the chemotherapy regimens, and cost per administration applied within the economic model is presented in Table 130.

Table 130. Estimated chemotherapy costs applied within the Technology Assessment Group's base case *de novo* economic evaluation

Chemotherapy	Regimen description	Chemotherapy cost per cycle
Paclitaxel	For platinum resistant/refractory disease: paclitaxel 80 mg/m^2 weekly for 18 weeks or until progression	£306
	For platinum sensitive disease: paclitaxel 175 mg/m^2 day 1 every 21 day cycle (maximum of six cycles)	£638
Paclitaxel plus platinum	For platinum resistant/refractory disease: paclitaxel 80mg/m^2 plus carboplatin AUC three*, weekly for 18 weeks or until progression	£442
	For platinum sensitive disease: paclitaxel 175 mg/m^2 and carboplatin AUC five*, day 1 every 21 day cycle (maximum of six cycles)	£855
PLDH	40 mg/m^2 day 1 every 28 day cycle (maximum of six cycles)	£1,211
PLDH plus platinum	PLDH 30 mg/m^2; carboplatin target AUC of five*, day 1 every 28 day cycle (maximum of six cycles)	£1,137
Gemcitabine plus carboplatin	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 (maximum of six cycles)	£706
Trabectedin plus	Trabectedin 1.1 mg/m^2; PLDH 30 mg/m^2, day 1 every 21	£3,679

PLDH	day cycle (maximum of six cycles)	
Topotecan	1.5 mg/m^2, day 1-5 every 21 day cycle (maximum of six cycles)	£1,305
Platinum monotherapy	Carboplatin target AUC of five*, day 1 every 21 day cycle (maximum of six cycles)	£217
Etoposide (sensitivity analysis only)	50 mg (oral) days 1-21 every 28 days (maximum of six cycles)	£200
Etoposide plus platinum (sensitivity analysis only)	Etoposide 50mg (oral) days 1-21 every 28 day cycle plus cisplatin IV 50 mg/m^2 day 1, 8 and 15 every 28 day cycle (maximum of six cycles)	£340
* Carboplatin dose (mg) = target AUC (mg/ml x min) x [glomerular filtration rate (ml/min) + 25]; where glomerular filtration rate (GFR) is estimated as the creatinine clearance rate using the Cockcroft-Gault formula[(140)] such that GFR = (((140 – age[years]) x weight[kg] x 1.04)/serum creatinine level), assuming that serum creatinine is 67.5 micromol/L (i.e. middle of the normal range for women, 45 to 90 micromol/L) Abbreviations used in table: AUC, area under the curve; m, metre; mg, milligram; PLDH, pegylated liposomal doxorubicin hydrochloride.		

The regimen descriptions presented in Table 130 were obtained through review of each relevant SmPC, with verification and amendment from clinical experts. The costs per cycle outlined in Table 130 are applied within the model to people within the stable disease health state, for up to the stated maximum number of cycles. The single exception to this is for patients treated with trabectedin plus PLDH. For this regimen, although the maximum number of cycles likely to be used in clinical practice is 6 cycles, the manufacturer for trabectedin has submitted a patient access scheme (PAS). The manufacturer's PAS limits the number of cycles for which the NHS would bear the cost to 5 cycles. Therefore, in the base case analysis, for trabectedin plus PLDH, a maximum of 5 cycles were costed. Furthermore, as highlighted by PharmaMar, 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 TAG model. Within the manufacturer's PAS submission, the total cost of PAS administration was estimated as £560.74 (Table 131). The TAG notes that this cost was subject to discounting and, given that treatment would occur in the first year of the model, the TAG included the non-discounted cost (£598.04) within the TAG economic analysis.

Table 131. Estimate of PAS implementation cost (adapted from PharmaMar PAS submission, page 21)

PAS implementation costs	Annual cost	Years	Discounted cost
NHS trust costs of the PAS	£151.74	0.938	£140.07
NHS trust costs of claiming free of charge stock	£204.36	0.938	£188.64
NHS trust implementation and training	£66.50	–	£66.50
NHS trust scheme agreement	£46.80	–	£46.80
PCT costs of the PAS	£128.64	0.938	£118.74
Total	**£598.04**	**–**	**£560.74**
Abbreviations used in table: PAS, patient access scheme; PCT, primary care trust.			

For each regimen, the cost of treatment relies upon one or more patient characteristic, e.g. age, weight, or body surface area (BSA) in m^2. To reflect the variation in such characteristics at a patient level, and the associated impact upon estimated cost, data from 321 ovarian cancer patients described by Sacco *et al.* has been used to estimate dose, and therefore cost, at an individual level.[(111)] The cost reported in Table 130, is an average of the cost associated with each of the 321 patients for which treatment cost has been calculated. Therefore, uncertainty associated with patient characteristics has been accounted for in the base case analysis. Full details of the calculations used to estimate the average cost per administration are presented below.

Patient level characteristics

Patient level characteristics of age and BSA were taken from Sacco *et al*.[(111)] Sacco *et al.* report the results of a multicentre, retrospective study of the BSA of adult cancer patients in the UK. Sacco *et al.* measured the BSA of 3,613 patients receiving chemotherapy for various cancers, including 321 patients with ovarian cancer, for which the age and BSA of each patient is freely available online. [(111)] The average age and BSA of the 321 patients with ovarian cancer as reported in Sacco *et al*. are 61.4 years old and 1.71m^2, respectively.

For the majority of the chemotherapy agents of interest for this MTA, doses are based upon BSA, for which individual patient data were available for analysis from Sacco *et al*.; however, for estimates of carboplatin dose, individual weight data are also required. Therefore, a calculation was necessary to estimate, given their BSA and age, weight for each of the 321 patients assessed by Sacco *et al*. The TAG employed the commonly used Du Bois and Du Bois formula to estimate weight based upon BSA and height; noting that data on individual height were unknown and therefore required estimation:[(141)]

Where if: $BSA(m^2) = 0.20247 * Height(m)^{0.725} * Weight(kg)^{0.425}$, then

$$\text{Weight(kg)} = (\text{BSA}(m^2) / 0.20247 * \text{Height}(m)^{0.725})^{1/0.425}$$

Estimates of individual BSA were taken directly from the ovarian cancer dataset in Sacco *et al.*[111] For each individual patient, height was estimated based upon the age of the patients within Sacco *et al*. using the Health Survey for England (HSE, 2011); in which average height by age and gender is provided.[142] The BSA and height information for each individual patient were then used to estimate weight for each individual patient; the average weight for the patient cohort estimated using this formula is 69.1kg.

The TAG compared this estimate of weight with the estimate of weight determined using the Health Survey for England (HSE, 2011[142]) in which average weight by age and gender is provided. For the patient cohort, the average weight using the HSE data is 72.1kg. The TAG notes that the difference in average weight between the two estimates was 3kg. The TAG considers that the estimates based upon BSA are more likely to reflect the weight associated with women with ovarian cancer; however, a scenario analysis using weight estimated from the HSE was tested in sensitivity analysis (Section 5.2.11).

Unit prices of chemotherapy agents

Unit prices were obtained from the BNF 65 (Table 132).[143] Where available, unit costs were obtained for the non-proprietary formulation. The impact of branded unit costs was explored in sensitivity analysis (Section 5.2.11).

Table 132. Unit costs for chemotherapy agents used within the Technology Assessment Group's economic analysis

Chemotherapy (IV)	Vial size	Mg per mL	Mgs	Price per vial
Paclitaxel (non-proprietary)	5 mL	6	30	£66.85
	16.7 mL	6	100.2	£200.35
	25 mL	6	150	£300.52
	50 mL	6	300	£601.03
Carboplatin (non-proprietary)	5 mL	10	50	£22.04
	15 mL	10	150	£56.92
	45 mL	10	450	£168.85
	60 mL	10	600	£260.00
Cisplatin (non-proprietary)*	10 mL	1	10	£5.85
	50 mL	1	50	£24.50
	100 mL	1	100	£50.22
PLDH (Caelyx®)	10 mL	2	20	£360.23
	25 mL	2	50	£712.49
Gemcitabine (non-proprietary)	200 mg	NA	200	£32.00
	1,000 mg	NA	1,000	£162.00
	1,500 mg	NA	1,500	£213.93
	2,000 mg	NA	2,000	£324.00

Trabectedin (Yondelis®)	0.25 mg	NA	0.25	£363.00
	1 mg	NA	1	£1,366.00
Topotecan (non-proprietary)	1 mL	1	1	£87.88
	4 mL	1	4	£261.55
Chemotherapy (tablets)	**Tablets per pack**	**Mg per tablet**	**Price per pack**	**Price per tablet**
Vepesid® (etoposide)*	20	50	£99.82	£4.99
* Used in sensitivity analysis only Abbreviations used in table: IV, intravenous; mg, milligram; mL, millilitre; PLDH, pegylated liposomal doxorubicin hydrochloride.				

For the purposes of the base case analysis, it was assumed that no vial sharing would occur. Therefore, for each therapy, a series of dosing "rules" were established to indicate, for a given individual dose, which vial(s) would be used. It was assumed that for each individual, the selected vial or combination of vials would be those resulting in the lowest possible total cost. Vial sharing was included as a scenario analysis (Section 5.2.11).

Additional treatment costs: pre-, concomitant, and maintenance treatment

In clinical practice, patients would typically be pre-treated with a variety of anti-sickness therapies (e.g. ondansetron, granisetron) with such treatment typically continuing throughout the course of treatment. For simplicity, given that these costs are applicable for all therapies, they have been excluded from the economic analysis.

For regimens including paclitaxel, in addition to the usual pre-treatment with anti-sickness therapies, pre-treatment with corticosteroids is required to prevent severe hypersensitivity reactions. This requirement is not necessary for other therapies; therefore, it was considered appropriate to include a cost associated with dexamethasone within the analysis (cost per cycle £4.15, based upon the cost of five 1-mL amp at 83p each[(143)]).

Finally, in the sensitivity analysis assessing the difference in cost of therapies used to treat patients with platinum resistant/refractory disease, the two etoposide regimens are associated with the additional cost of maintenance therapy. Specifically, following completion of the etoposide regimen, six to eight weeks of oral etoposide at 50 mg/day would typically be prescribed on an outpatient basis; this cost is included in the analysis with the assumption that packs of oral etoposide could not be shared. In addition, an average duration of seven weeks of therapy is assumed (i.e. mid way between 6 and 8 weeks), equating to 49 tablets or three packs of tablets. The cost for a single pack of oral etoposide tablets is £99.82, resulting in a total cost for the maintenance period of £299.46 (Table 133).[(143)]

Table 133. Cost of oral etoposide as maintenance treatment (sensitivity analysis only)

Chemotherapy (tablets)	Tablets per pack	Mg per tablet	Price per pack	Cost per 7 weeks treatment (no pack sharing)
Vepesid (etoposide)	20	50	£99.82	£299.46
Abbreviation used in table: mg, milligram.				

5.2.10.2 Administration costs

With the exception of oral etoposide, every chemotherapy regimen is assumed to be administered as an infusion within a hospital. To capture the costs associated with this, for each regimen, a cost of administration is applied within the economic model. This cost is assumed to comprise, the cost of preparing the infusion(s) in the pharmacy, and the cost associated with delivering the infusion in the hospital. A summary of the administration costs applied within the economic model is presented in Table 134. The calculation of these costs is described below.

Table 134. Summary of administration costs applied within the Technology Assessment Groups' economic model

Regimen		Pharmacy preparation cost per cycle	First cycle delivery cost	Subsequent cycle delivery costs
Paclitaxel	Paclitaxel 80mg/m^2 weekly for 18 weeks or until progression	£16	£200	£270
	Paclitaxel 175 mg/m^2 day 1 every 21 day cycle	£16	£331	£270
Paclitaxel plus platinum	Paclitaxel 80mg/m^2 plus carboplatin AUC three, weekly for 18 weeks or until progression	£31	£200	£270
	Paclitaxel 175 mg/m^2 and carboplatin AUC five, day 1 every 21 day cycle	£31	£331	£270
PLDH 40 mg/m^2 day 1 every 28 day cycle		£16	£249	£270
PLDH 30 mg/m^2; carboplatin target AUC of five, day 1 every 28 day cycle		£31	£331	£270
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		£47	£520	£541
Trabectedin 1.1 mg/m^2; PLDH 30 mg/m^2, day 1 every 21 day cycle		£31	£331	£270
Topotecan 1.5 mg/m^2, day 1-5 every 21 day cycle		£78	£1,281	£1,351
Carboplatin target AUC5, day 1 every 21 day cycle		£16	£200	£270
Etoposide* 50 mg (oral) days 1-21 every 28 days		£0	£0	£0
Etoposide* 50 mg (oral) days 1-21 and cisplatin 50 mg/m^2 day 1, 8, 15 every 28 day cycle		£47	£872	£811
* Used for sensitivity analysis only Abbreviations used in table: AUC, area under the curve; m, metre; mg, milligram; PLDH, pegylated liposomal doxorubicin hydrochloride.				

For the cost of preparing the infusion(s) it was assumed, based upon clinical expert opinion described in a recently published STA, that preparation of one infusion would in practice take approximately 20 minutes.[15] Therefore, for all single agents, the cost of preparation of each infusion was estimated as the cost per minute associated with a hospital pharmacist, multiplied by 20 minutes. For combination therapies, the cost of preparation of each infusion was estimated as the cost per minute associated with a hospital pharmacist multiplied by 40 minutes (two agents at 20 minutes each). The cost associated with a hospital pharmacist was taken from the Unit Costs of Health and Social Care 2012 (cost per hour, £47; cost per minute, £0.78).[112]

For the cost of delivering the infusion, the following NHS Reference Costs were selected:[113]

- Deliver complex chemotherapy, including prolonged infusional treatment at first attendance (SB14Z), £331;
- Deliver more complex parenteral chemotherapy at first attendance (SB13Z), £249;
- Deliver simple parenteral chemotherapy at first attendance (SB12Z), £200;
- Deliver subsequent elements of a chemotherapy cycle (SB15Z), £270.

The selection of the relevant first attendance code was based upon the maximum infusion time recommended within the associated SmPC. For chemotherapy agents considered to require up to 60 minutes infusion time (weekly paclitaxel, carboplatin monotherapy, topotecan), the cost of SB12Z: *Deliver simple parenteral chemotherapy at first attendance* (£200) is applied; for agents considered to require up to 120 minutes infusion time (PLDH, gemcitabine and carboplatin combination, etoposide and carboplatin combination), the cost of SB13Z: *Deliver more complex parenteral chemotherapy at first attendance* (£249) is applied; and for agents considered to require more than 120 minutes of infusion (cisplatin, paclitaxel monotherapy, paclitaxel combination therapy, PLDH and carboplatin combination, PLDH and trabectedin combination), the cost of SB14Z: *Deliver complex chemotherapy, including prolonged infusional treatment at first attendance* (£331) is applied. For combination therapies, based upon clinical advice it was considered, that infusions would occur sequentially, and therefore the combined duration of infusion was used to infer the relevant HRG code at first attendance. For subsequent cycles, for all therapies, the cost of SB15Z: *Deliver subsequent elements of a chemotherapy cycle* (£270) is applied.

It is noted within the trabectedin SmPC that insertion of a central line is required for administration of trabectedin. The manufacturer for trabectedin, PharmaMar, accounted for this within the submission for this MTA by including a one-off cost associated with insertion of a central line. Following consultation with clinical experts, the TAG notes that in clinical practice, many women eventually require insertion of a central line due to increasing difficulties gaining venous access. For this reason,

the TAG considers that the cost of insertion of a central line would be similar across treatment regimens and have therefore omitted this cost from the economic analysis.

5.2.10.3 Health state costs

Costs attributable to the stable disease period and the progressed disease period are included in the economic analysis. A summary of these costs is presented in Table 135. These costs are applied monthly to the number of patients residing in each health state. The calculation of these costs is discussed in detail below.

Table 135. Monthly health state costs applied within the Technology Assessment Group's model

	Stable disease health state	Progressed disease health state (platinum sensitive patients)	Progressed disease health state (platinum resistant/ refractory patients)
One-off initial cost	N/A	£109	£109
Cost per month (first six months)	£45	£796	£531
Cost per month (subsequent months)	£45	£531	£531
Abbreviation used in table: N/A, not applicable.			

Stable disease health state costs

The cost associated with the stable disease health state comprises the cost of monitoring for patients with stable disease. In the base case analysis it is assumed, based upon discussions with clinical experts, that patients with stable disease require one outpatient visit every three months. The cost of an outpatient visit was estimated; based upon NHS Reference Costs (2011/2012) *outpatient attendance data, service code 503, gynaecologic oncology,* to be £135.[(113)] This equates to £45 per month for a patient within the stable disease health state.

Progressed disease health state costs

For patients with recurrent ovarian cancer whose disease progresses after treatment for recurrent disease, treatment can vary. A proportion of women will receive subsequent lines of chemotherapy and may respond to these agents; many women may complete a further five or more lines of chemotherapy. However, for other patients with recurrent disease, treatment following progression can be considered palliative in intent, and may focus on ameliorating symptoms of disease.[(144)]

To better understand these differences in treatment following progression, the TAG consulted with clinical experts. Following which the TAG considers that, women who subsequently progress following treatment for platinum resistant/refractory disease, prognosis would indicate that subsequent treatment may more typically be palliative in intent. For these women, a cost associated with palliative care is applied for each month spent in the progressed health state. For women who

subsequently progress following treatment for platinum sensitive disease, a cost associated with a further line of chemotherapy is applied. This cost is applied for six months, following progression. After this point, a cost associated with palliative care is applied for each month spent in the progressed health state. The TAG acknowledges that the approach taken is a simplification of the reality of treatment following progression, which can and does vary for every woman; however, the TAG considers that by applying costs in this way, some key aspects of the cost of progressed disease may be captured within the model. These costs were tested in sensitivity analysis (Section 5.2.11).

The cost associated with a further line of therapy (for patients progressing following treatment for platinum sensitive disease) included the cost of chemotherapy, administration, and further monitoring for a six month period. A study by Kaye *et al.*, reporting the use of chemotherapy agents following progression in patients treated for recurrent ovarian cancer, was used inform the cost of chemotherapy.[116] Kaye *et al.*, reported in that, ~80% of platinum sensitive women went on to receive at least one subsequent therapy. Of these, the majority of women received chemotherapy (~75%). For women who received chemotherapy, ~75% received platinum-based chemotherapy and ~25% received non-platinum based therapy.[116]

Therefore, in the economic analysis it was assumed that 100% of women who progressing following treatment for platinum sensitive disease, went on to receive a further line of therapy. This simplifying assumption was designed to reflect the fact that although not all women will go on to receive another line of chemotherapy, some women will receive more than one line of chemotherapy. Following discussion with clinical experts, who advised that PLDH monotherapy and platinum monotherapy would be the most likely treatment options, the cost applied within the economic model was estimated as 75% the cost of carboplatin AUC5 (to reflect the ~75% of women receiving platinum based therapy), and 25% the cost of PLDH (to reflect the ~25% of women receiving non-platinum based therapy) (Table 136).

Table 136. Cost of an additional line of chemotherapy for women entering the model with platinum sensitive disease

	Cost of chemotherapy agent per cycle	Cost of administration / pharmacy infusion per cycle	Total per cycle	Weight
Carboplatin AUC5	£216	£286	£539	75%
PLDH	£1,211	£286	£1,497	25%
Total			**£751**	
Abbreviations used in table: AUC, area under the curve; PLDH, pegylated liposomal doxorubicin hydrochloride.				

Given that, in clinical practice, both carboplatin and PLDH monotherapy would typically be limited to six cycles, the average cost per month over a six month period was estimated to be £751 for

chemotherapy and administration. Including the cost of monitoring, as estimated for patients in the stable disease period (£45 per month), the cost per month applied to platinum sensitive patients for the first six months following progression is £796. The TAG recognises that this estimate is a simplification of the true value and therefore tested this figure in sensitivity analysis (Section 5.2.11).

To establish a published source of palliative care, the TAG carried out a rapid review of the literature in PubMed in February 2013. The TAG used broad disease terms ([ovarian or ovary] and [cancer]) alongside terms for palliative care ([palliative care] or [end of life]), cost (cost), and country (UK OR united kingdom OR britain OR england OR scotland OR wales OR ireland). A total of three studies were identified from this search, of which one study was considered relevant. This study, by Guest *et al.,* has previously been identified by the ERG responsible for considering evidence submitted for TA222.[(114)]

Guest *et al.* investigated the resource use and cost associated with patients with a malignant neoplasm from the time they started strong opioid treatment until death.[(114)] The study estimated the cost associated with a total of 547 patients, of which 21 patients (4% of the sample) were diagnosed with ovarian cancer. The palliative cost associated with ovarian cancer was estimated by Guest *et al.* to be £4,789 (at 2000/2001 prices) for an average time period of 399 days.[(114)] This cost predominantly consisted of hospitalisation costs (71% of costs). Updating the estimate of palliative care for ovarian cancer patients from Guest *et al*. to current prices using the Hospital & Community Health Services index results in a cost of £6,963;[(112)] equating to £531 per month. This cost is applied monthly to all platinum resistant / refractory patients following entry into the progressed disease health state, and all platinum sensitive patients following six months of residence in the progressed disease health state.

The TAG notes that the analysis carried out by Guest *et al*. has several weaknesses. In particular, ovarian cancer estimates are based upon a small sample size (n=21) and does not consider costs for patients not requiring a strong opioid. In addition, the analysis was carried out in 2000/2001 and may no longer reflect clinical practice. Therefore, in recognition of the uncertainty associated with the cost of palliative care, the TAG has tested this parameter in sensitivity analysis (Section 5.2.11).

Finally, in addition to the cost of further treatment and care, a one-off cost associated with a CT scan is applied at progression. This is to reflect that, during routine outpatient appointments in the stable period, a CA-125 test is typically carried out. If a CA-125 test indicates possible disease progression, a CT scan is then undertaken. The TAG acknowledges that some CT scans following raised CA-125 levels would not necessarily indicate disease progression; however, for simplicity, these additional scans have been excluded from the cost. The TAG considers it likely that such additional scans would be equally likely across treatments and therefore the variation is unlikely to materially impact upon results. The cost of a CT scan was estimated to be £109, based upon NHS Reference Costs 2012. It

was estimated as the weighted average of outpatient CT scans (RA08A, RA09A, RA10Z-RA14Z; weighted by activity).

5.2.10.4 Adverse event costs

As described in Section 5.2.8, following discussion with clinical experts, the key adverse events identified from the clinical review are: allergic reaction, alopecia, anaemia, fatigue, febrile neutropenia, nausea and vomiting, and neuropathy. The costs ascribed to each of these adverse events within the economic model are presented in Table 137.

Table 137. Adverse event costs included within the Technology Assessment Group's economic model

Adverse event	Mean cost	Source
Allergic reaction	£145	• Gynaecological oncology (503) outpatient attendance = £135 • Intramuscular epinephrine at 500 micrograms; Injection, adrenaline (as acid tartrate) 1 mg/mL, net price 0.5-mL amp = 52p • 10mg of chlorphenamine maleate at 10 mg/mL, net price 1-mL amp = £1.95 • Up to 120mg Injection (aqueous suspension), methylprednisolone acetate 40 mg/mL. 3-mL vial = £7.47
Alopecia	N/A	No cost ascribed to alopecia
Anaemia	£488	Weighted (by activity) average of NHS Reference Costs, SA13A *Single Plasma Exchange, Leucophoresis or Red Cell Exchange, with length of stay 2 days or less, 19 years and over*, SA14Z *Plasma Exchanges 2 to 9*, SA15Z *Plasma Exchanges 10 to 19*, SA16Z *Plasma Exchanges 20 or more*
Fatigue	N/A	No cost ascribed to fatigue
Febrile neutropenia	£1,077	NHS Reference Costs weighted mean HRG cost SA01F: Aplastic Anaemia without CC
Nausea and vomiting	£160	• Gynaecological oncology (503) outpatient attendance = £135 • 4mg three times a day for 5 days; 10mg dexamethasone; Injection, dexamethasone (as sodium phosphate) 4 mg/mL, net price 1-mL amp = 83p. Three amps £2.49, for five days, £12.45 • Granisetron 1mg twice a day for five days; Injection, granisetron (as hydrochloride) 1 mg/mL, for dilution before use, net price 1-mL amp = £1.20, £12.00
Neuropathy	N/A	No cost ascribed to neuropathy
Abbreviations used in table: HRG, healthcare resource group; mg, milligram; mL, millilitre.		

No costs were ascribed to alopecia, neuropathy or fatigue within the economic analysis. This is because, in practice, these adverse events are not easily treated and a cost to the NHS is not, in general, incurred. For alopecia and neuropathy, alternative therapies or a reduction in dose of chemotherapy would be more likely to be considered. The TAG recognises that, in particular, alopecia and fatigue can be distressing and problematic conditions for both patients and the clinicians treating

them. The TAG attempted to capture the impact of these conditions through a sensitivity analysis which included a quality of life decrement (Section 5.2.11).

The adverse event costs detailed in Table 137 are applied to the adverse event incidence (Section 5.2.8) to estimate a total cost of treating adverse events for each treatment regimen. For simplicity, it was assumed that these costs were incurred at the start of treatment within the economic model.

5.2.10.5 Cost summary

A summary of the costs, by treatment regimen, included within the TAG's *de novo* economic analysis is presented in Table 138.

Table 138. A summary of the costs included within the Technology Assessment Group's economic analysis

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 five, day 1 every 21 day cycle	£855	£363	£302	£78	£45	£796	£531
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.

5.2.11 Approach to uncertainty

The impact of parameter uncertainty upon model results has been investigated in both probabilistic sensitivity analyses (PSA) and deterministic (one-way) sensitivity analyses. In addition, (where possible) structural assumptions have been varied in deterministic scenario analyses. As a result of time constraints and the volume of sensitivity analysis carried out, deterministic rather than probabilistic analysis was selected to inform one-way sensitivity and scenario analysis. However, based on the consistency observed between probabilistic and deterministic base case results, the TAG considers that deterministic assessment of model sensitivity is reasonable.

5.2.11.1 Probabilistic sensitivity analyses

Within the TAG's economic model, PSA has been used to investigate the simultaneous impact of parameter uncertainty on the cost-effectiveness results. Probability distributions were assigned to each parameter (except drug acquisition costs) used within the model, from which values have been simultaneously sampled 1,000 times. 1,000 was chosen as the sample size for probabilistic analysis based on assessment of the stability of model results; assessed by comparing deterministic and probabilistic results obtained for sample sizes of 1,000; 2,000 and 5,000. There was assumed to be zero uncertainty associated with drug acquisition costs. Table 139 summarises the type of distribution, and rationale for selection of the distribution, used to inform each group of parameters; full details of distributional specifications are provided in Table 108.

Table 139. Probability distributions used for model parameters

Parameter type	Parameter description	Distribution(s) used	Rationale
Probability of PFS and OS associated with baseline curve	Parameters associated with selected distribution (Weibull in the base case)	Multivariate Normal	Each parameter is sampled from a multivariate normal distribution using the Cholesky decomposition method [145]
HRs	HRs estimated from TAG's NMA	N/A	The CODA output, from WinBUGS provides a list of all values generated from the full posterior distribution. Therefore, rather than re-sampling from the posterior distribution, the output itself has been used in PSA[146]
Costs	Unit costs of drug administration and delivery, unit costs of patient follow-up and care, cost of palliative care, unit costs associated with adverse events	Gamma or log normal	Either the Gamma or lognormal distribution may be considered suitable for the sampling of cost data.[145] Therefore, the distribution selected to inform each individual cost was dependent on the ability of that distribution to reproduce the inputted 95% confidence interval or standard error. Note: where 95% confidence intervals or standard errors were not available from the literature a standard error of 0.25 was assumed.
Odds ratio	Adverse events	Log normal	The CODA output, from WinBUGS provides a list of all values generated from the full posterior distribution. Therefore, rather than re-sampling from the posterior distribution, the output itself has been used in PSA[146]

Probability of:	Treatment selected for further lines of therapy. Baseline probability of adverse events. Probabilities of adverse events based on clinical opinion	Beta	Probabilities that are based on the proportion of observed outcomes (i.e. probability of event is 1-probability of non-event) may be assumed to follow a binomial distribution. Therefore, the beta distribution was used as it is the conjugate of the binomial distribution and is bounded by 0 and 1.[145] Note where 95% confidence intervals or standard errors were not available from the literature a standard error of 0.25 was assumed.
Utilities/disutilities	Stable disease, progressed disease utilities	Beta	The beta distribution was chosen based on the (0,1) boundary imposed by this distribution.[145]
Abbreviations used in table: CODA, Convergence Diagnostic and Output Analysis; HR, hazard ratio; N/A, Not applicable; NMA, network meta-analysis; OS, overall survival; PFS, progression free survival; PSA, probabilistic sensitivity analysis; TAG, Technology Assessment Group.			

5.2.11.2 One-way sensitivity analysis

For each therapy, by subgroup, all model parameters with the exception of drug costs were varied in one-way sensitivity analysis. Parameters were assigned low and high values according to the 95% confidence interval used in the PSA. The deterministic cost-effectiveness result was recorded for each one-way change in each parameter estimate. The variables associated with the greatest impact upon cost-effectiveness results are presented in tornado diagram format in Section 5.2.13.

5.2.11.3 Scenario analyses

A variety of structural assumptions have been made in the construction of the TAG's base case model. Where possible these have been tested in scenario analysis. Table 140 lists the scenario analyses carried out by the TAG, the parameters used to inform these scenarios, and the rationale for each analysis.

Table 140. Scenario analyses carried out by the Technology Assessment Group

Scenario analysis	Parameter definition	Rationale
Cost scenarios		
Costs associated with a 50 mg rather than 40 mg dose of PLDH	Cost per cycle for a 50 mg dose estimated to be £1,443 using the methods described in Section 5.2.10	To establish the impact of using the cost likely to be incurred in clinical practice in the base case
Patient weight (used to inform drug costs) estimated from the HSE, 2011	Estimating individual patient weight from Sacco *et al*[111]. using HSE 2011[142] based upon the patients age	To assess the potential impact of patient level data used to inform drug cost calculations
Branded costs of drugs	• Abraxane® (paclitaxel) • Taxol® (paclitaxel) • Gemzar® (gemcitabine) • Hycamtine® (topotecan)	To assess the potential impact of the use of branded drugs
Calculating cost based upon the selection of vials that resulted in the least number of vials used	For each chemotherapy, the combination of vials which resulted in the fewest number of vials used was investigated	To assess the robustness of the CE results of the calculation of drug costs
Vial sharing	For each chemotherapy, an average cost	To assess the potential impact

	per mg was estimated and applied to the dose (mg) required per patient	of wastage on the CE results
Efficacy scenarios		
Equivalent efficacy assumed for all therapies outlined within the NICE scope for patients with resistant/refractory disease with differences	• Efficacy for all pharmacotherapies set to the baseline PFS and OS for PLDH in resistant/refractory patients • Cost of etoposide both as monotherapy and in combination with a platinum therapy set as described in Section 5.2.10 • Cost of best supportive care set to £531 per month from start of model until death as described in Section 5.2.10	To reflect clinical advice that prognosis is often similar, and to investigate the cost impact associated with each therapy outlined in the NICE scope.
Baseline PS PFS survival curve network 1 using alternative functional forms	• Log logistic • Exponential • Log normal	To assess the impact of the data and functional form of the baseline PFS and OS estimates
Baseline PS PFS survival curve network 1 using Parmar[60]	Weibull curve fitted to the ICON4 data from Parmar *et al.*[60] using methods outlined in Hoyle *et al.*[110] rather than to the CALYPSO data from Pujade *et al.*[31] data	
Baseline PS OS survival curve network 1 using alternative functional forms for Wagner	• Log logistic • Exponential • Log normal	
Baseline PS OS survival curve network 1 using Parmar[60]	Weibull curve fitted to the ICON4 data from Parmar *et al.*([60]) using methods outlined in Hoyle *et al.*[110] rather than to the CALYPSO data from Wagner *et al.*[55]	
Baseline PS PFS survival curve network 2 using extrapolated estimates rather than KM data	• Weibull • Log logistic • Exponential • Log normal	
Baseline PS OS survival curve network 2 using alternative function forms for the KM data	• Log logistic • Exponential • Log normal	
Baseline PRR PFS survival curve using alternative functional forms for Monk 2010		
Baseline PRR OS survival curve using alternative functional forms for CSR data		
Head-to-head comparison of trabectedin plus PLDH with PLDH in platinum sensitive patients, using adjusted PFS and OS estimates from the PharmaMar submission	The manufacturer base case PFS and OS extrapolations were used within the TAG economic model	To assess the impact of using adjusted survival estimates within the TAG economic model, and to assess the face validity of the TAG and manufacturer ICERs for PLDH versus trabectedin when using the same efficacy data
Patient subgroups		
Analysis of the results considering the partially platinum sensitive subgroup alone (PFI 6-12 months)	Exploratory analysis using the OS NMA results for the partially platinum sensitive subgroup. Baseline survival for PLDH for the platinum sensitive population was used; this was because no numbers of patients at risk were available on published KM graphs. In addition, no PFS data was	To provide exploratory results for this patient subgroup; sufficient data was not available from the fully platinum sensitive subgroup in order to assess this comparison in addition

	inputted due to no possible network.	
Other		
Alternative discount rates for costs and benefits	Discount rate for costs and benefits assumed to be 1% and 6% alternately	As per NICE guides
Disutilities for adverse events applied	Disutilities from Havrilesky *et al.* (Section 5.2.9) for nausea and vomiting, fatigue, and febrile neutropenia; applied assuming: • AE duration of 1 month • AE during the first month of the model	To assess the potential impact of the different adverse event profiles associated with the treatments of interest
Nausea and vomiting probabilities for PS network 1 estimated from clinical expert opinion	Paclitaxel plus platinum 20% PLDH plus platinum 15% Gemcitabine plus carboplatin 15% Platinum 5%	To assess the potential impact of alternative sources of adverse event probabilities on model results
Half cycle correction	Half cycle correction was applied to the estimates of PFS and OS	To assess the potential impact of half cycle correction on model results
Abbreviations used in table: CE, cost-effectiveness; HSE, Health Survey for England; ICER, incremental cost-effectiveness ratio; KM, Kaplan Meier; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; OS, overall survival; PFI, platinum free interval; PFS, progression free survival; PLDH, pegylated liposomal doxorubicin hydrochloride; PRR, platinum resistant/refractory; PS, platinum sensitive; TAG, Technology Assessment Group.		

5.2.12 Base-case results

Fully incremental probabilistic and deterministic results for each of the subgroups analysed are presented in Tables 141 to 143. For each set of results, interventions are ordered with respect to their total cost. Interventions with higher incremental costs and lower incremental QALYs than their predecessor are considered to be strictly dominated, by their predecessor, and are therefore removed from consideration in the final ICER calculations. Similarly, interventions with higher incremental costs and lower incremental QALYs (vs the baseline treatment) than their predecessor are considered to be extendedly dominated, by their predecessor, and are removed from consideration in the final ICER calculations.

5.2.12.1 People with platinum sensitive disease

As described in Section 5.2.5, no single network comprising the interventions and comparators of interest as outlined in the NICE scope was possible from the data identified. Instead, two separate networks were constructed. Network one comprised: platinum; paclitaxel plus platinum; PLDH plus platinum; and gemcitabine plus carboplatin. Network two comprised: paclitaxel; PLDH, PLDH plus trabectedin and topotecan.

For network 1, base-case deterministic results indicated that PLDH plus platinum is strictly dominated by (is more costly and less effective than) paclitaxel plus platinum. Similarly, gemcitabine plus carboplatin was estimated to be extendedly dominated by paclitaxel plus platinum. Therefore, PLDH plus platinum and gemcitabine plus carboplatin are removed from consideration in the final ICER

calculation, leaving paclitaxel plus platinum vs platinum monotherapy as the only relevant comparison for this network. For this comparison, the incremental cost-effectiveness ratio (ICER) is estimated as £24,361; paclitaxel plus 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 monotherapy (Table 141).

Probabilistic results were largely consistent with deterministic results. That is, PLDH plus platinum and gemcitabine plus carboplatin are estimated to be strictly dominated and extendedly dominated by paclitaxel plus platinum, respectively. Similar to the deterministic base case result, the ICER of paclitaxel plus platinum versus platinum monotherapy has been estimated as £24,539 per QALY gained.

However, the TAG considers it important to note that the costs and QALYs associated with PLDH plus platinum and paclitaxel plus platinum are similar. Consequently, small changes in total costs or QALYs associated with either treatment, may alter the results (Section 5.2.13)

For network 2, base-case results (deterministic and probabilistic) indicate that topotecan is strictly dominated by PLDH. Topotecan was therefore removed from the analysis, leaving the relevant comparisons of PLDH vs paclitaxel, and trabectedin plus PLDH vs PLDH monotherapy. PLDH vs paclitaxel results in estimated ICERs of £23,733 and £25,931 in deterministic and probabilistic analyses, respectively. When compared with paclitaxel, PLDH was associated with incremental costs of approximately £3,900 and approximately 0.16 additional QALYs. The ICERs for trabectedin plus PLDH vs PLDH alone are estimated to be £85,212 and £81,353, deterministically and probabilistically, respectively. When compared with PLDH monotherapy, trabectedin plus PLDH is associated with approximately £13,000 incremental costs and 0.16 additional QALYs (Table 141).

Table 141. Results of the Technology Assessment Group analyses; platinum sensitive network 1

Treatment	Modelled regimen	Total cost (discounted)	Total QALYs (discounted)	Incremental cost (discounted)	Incremental QALYs (discounted)	Incremental ICER (cost/QALY)	Incremental ICER (cost/QALY) (excluding dominated options)
Probabilistic results							
Platinum	Carboplatin target AUC of five, on day 1 of every 21 day cycle	£15,935	1.805	–	–	–	–
Gemcitabine plus carboplatin	Gemcitabine 1,000 mg/m^2 on days 1 and 8 of every 21 day cycle, carboplatin target AUC of four on day 1 of every 21 day cycle	£20,426	1.852	£4,491	0.047	£94,984	Extendedly dominated
Paclitaxel plus platinum	Paclitaxel 175 mg/m^2 and carboplatin AUC five, on day 1 of every 21 day cycle	£21,604	2.036	£1,178	0.184	£6,411	£24,539
PLDH plus platinum	PLDH 30 mg/m^2; carboplatin target AUC of five, on day 1 of every 28 day cycle	£22,625	2.027	£1,021	-0.009	Strictly dominated	
Deterministic results							
Platinum	Carboplatin target AUC of five, on day 1 of every 21 day cycle	£15,949	1.799	–	–	–	–
Gemcitabine plus carboplatin	Gemcitabine 1,000 mg/m^2 on days 1 and 8 of every 21 day cycle, carboplatin target AUC of four on day 1 of every 21 day cycle	£20,381	1.837	£4,432	0.039	£114,410	Extendedly dominated
Paclitaxel plus platinum	Paclitaxel 175 mg/m^2 and carboplatin AUC five, on day 1 of every 21 day cycle	£21,643	2.032	£1,262	0.195	£6,472	£24,361
PLDH plus platinum	PLDH 30 mg/m^2; carboplatin target AUC of five, on day 1 of every 28 day cycle	£22,620	2.018	£977	-0.015	Strictly dominated	

Abbreviations used in table: AUC, area under the curve; m, metre; mg, milligram; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; PLDH, pegylated liposomal doxorubicin hydrochloride; vs, versus.

Table 142. Results of the Technology Assessment Group analyses; platinum sensitive network 2

Treatment	Modelled regimen	Total cost (discounted)	Total QALYs (discounted)	Incremental cost (discounted)	Incremental QALYs (discounted)	Incremental ICER (cost/QALY)	Incremental ICER (cost/QALY) (excluding dominated options)
Probabilistic results							
Paclitaxel	175 mg/m^2 on day 1 of every 21 day cycle	£15,777	1.421	–	–		
PLDH	40 mg/m^2 on day 1 of every 28 day cycle	£19,591	1.568	£3,814	0.147	£25,931	£25,931
Topotecan	1.5 mg/m^2, on days 1-5 of every 21 day cycle	£23,889	1.330	£4,298	-0.238	Strictly dominated	
Trabectedin plus PLDH	Trabectedin 1.1 mg/m^2; PLDH 30 mg/m^2, on day 1 of every 21 day cycle	£32,687	1.729	£8,798	0.399	£54,893	£81,353
Deterministic results							
Paclitaxel	175 mg/m^2 on day 1 of every 21 day cycle	£15,668	1.398	–	–	–	–
PLDH	40 mg/m^2 on day 1 of every 28 day cycle	£19,599	1.564	£3,931	0.166	£23,733	£23,733
Topotecan	1.5 mg/m^2, on days 1-5 of every 21 day cycle	£23,793	1.317	£4,194	-0.247	Strictly dominated	
Trabectedin plus PLDH	Trabectedin 1.1 mg/m^2; PLDH 30 mg/m^2, on day 1 of every 21 day cycle	£32,640	1.717	£8,847	0.400	£22,131	£85,212

Abbreviations used in table: AUC, area under the curve; m, metre; mg, milligram; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; PLDH, pegylated liposomal doxorubicin hydrochloride; vs, versus.

5.2.12.2 People with platinum resistant/refractory disease

The network of interventions and comparators identified for the platinum resistant/refractory subgroup was limited by the availability of data to three of the therapies outlined in the scope: paclitaxel, PLDH and topotecan (Section 5.2.5).

Base case deterministic and probabilistic results indicate that paclitaxel is strictly dominated by PLDH; resulting in topotecan vs PLDH being the only comparison considered in final cost-effectiveness results. The ICER for this comparison was estimated to be £449,553 and £324,188, deterministically and probabilistically, respectively. When compared with PLDH, topotecan was associated with approximately £7,000 incremental costs and 0.02 incremental QALYs (Table 143).

However, the TAG considers it important to note that the costs and QALYs associated with paclitaxel are similar to those associated with PLDH. Consequently, small changes in total costs or QALYs associated with either treatment may alter the results.

5.2.12.3 People with platinum allergic disease

Clinical advice indicated that response to therapy for patients with or without a platinum allergy was unlikely to differ for the same non-platinum containing therapy (Section 5.2.3). Moreover, given that the PS network 1 contained only platinum-based therapies, the TAG considers that the results for PS network 2, and the network identified in platinum resistant/refractory patients are applicable for the platinum allergic population (Table 142 and Table 143).

Table 143. Results of the Technology Assessment Group analyses; platinum resistant/refractory

Treatment	Modelled regimen	Total cost (discounted)	Total QALYs (discounted)	Incremental cost (discounted)	Incremental QALYs (discounted)	Incremental ICER (cost/QALY)	Incremental ICER (cost/QALY) (excluding dominated options)
Probabilistic results							
PLDH	40 mg/m^2 on day 1 of every 28 day cycle	£14,232	1.004	–	–	–	–
Paclitaxel	80mg/m^2 weekly for 18 weeks or until progression	£15,132	0.981	£901	-0.022	Strictly dominated	
Topotecan	1.5 mg/m^2, on days 1-5 of every 21 day cycle	£21,232	1.025	£6,100	0.044	£139,697	£324,188
Deterministic results							
PLDH	40 mg/m^2 on day 1 of every 28 day cycle	£14,320	1.004	–	–	–	–
Paclitaxel	80mg/m^2 weekly for 18 weeks or until progression	£15,095	0.971	£775	-0.033	Strictly dominated	
Topotecan	1.5 mg/m^2, on days 1-5 of every 21 day cycle	£21,271	1.020	£6,176	0.049	£127,117	£449,553

Abbreviations used in table: AUC, area under the curve; m, metre; mg, milligram; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; PLDH, pegylated liposomal doxorubicin hydrochloride.

5.2.13 Results of the sensitivity analysis

5.2.13.1 Probabilistic sensitivity analyses

Following consideration of the probabilistic base case results, some interventions have been excluded from final ICER calculations; based on strict or extended dominance by other interventions (Section 5.2.12). The remaining comparisons by subgroup are as follows:

- platinum sensitive – network 1:
    - paclitaxel plus platinum versus platinum monotherapy;
- platinum sensitive – network 2:
    - PLDH versus paclitaxel;
    - Trabectedin plus PLDH versus paclitaxel;
    - Trabectedin plus PLDH versus PLDH.
- platinum resistant/refractory patients:
    - topotecan versus PLDH.

For each of these comparisons, probabilistic results have been summarised in scatter plots on the cost-\effectiveness plane and cost-effectiveness acceptability curves (Figures 39 to 54).

However, as highlighted in Section 5.2.12, in PS network 1 and PRR there exist comparisons with highly similar total costs and total QALYs. In particular, in PS network 1, the comparison of PLDH plus platinum vs paclitaxel plus platinum. Also, in PRR, the comparison of paclitaxel vs PLDH. These similarities result in unstable estimates of mean cost-effectiveness. Therefore, to enable decision makers to assess the likelihood that the interventions considered in these unstable comparisons are cost-effective, probabilistic cost-effectiveness results (versus each other and versus the baseline treatment) have been summarised in scatter plots and CEACs (Figures 39 to 54).

Platinum sensitive network 1

For the subgroup of patients with platinum sensitive disease, probabilistic analysis of PS network 1 revealed that, for the majority of simulations, the addition of paclitaxel or PLDH to platinum therapy results in greater costs and greater QALYs than treatment with platinum alone. In particular, for a willingness-to-pay (WTP) threshold of £20,000 per additional QALY, the probabilities of paclitaxel plus platinum or PLDH plus platinum being considered cost-effective vs platinum monotherapy are 13% and 3%, respectively. At a WTP threshold of £30,000, the probabilities of being cost-effective vs platinum therapy increase to 78% and 48% for paclitaxel plus platinum and PLDH plus platinum, respectively.

Furthermore, the addition of PLDH to platinum therapy was estimated to be almost as likely to result in greater costs and QALYs as to be dominated by the addition of paclitaxel to platinum therapy. However, as discussed in Section 5.2.12, 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.

Figure 39. Scatter plot of cost-effectiveness results for paclitaxel plus platinum vs platinum monotherapy (dark blue line indicates threshold of £30,000 per additional QALY, light blue line indicates threshold of £20,000 per additional QALY)

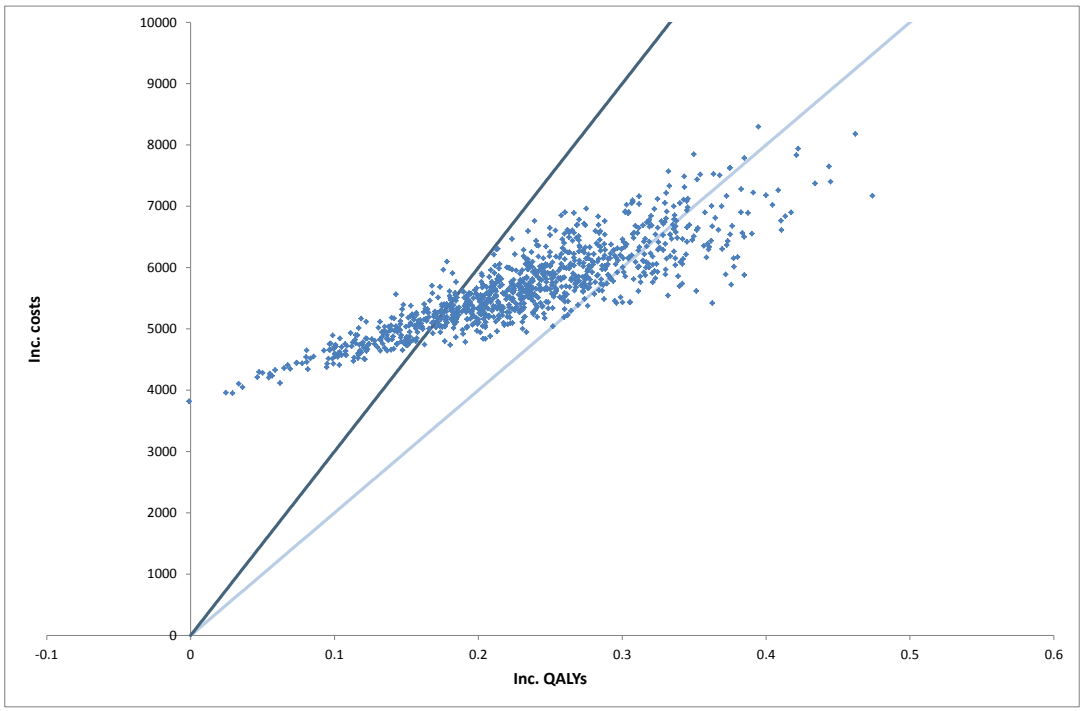


Figure 40. Cost-effectiveness acceptability curve for paclitaxel plus platinum vs platinum monotherapy

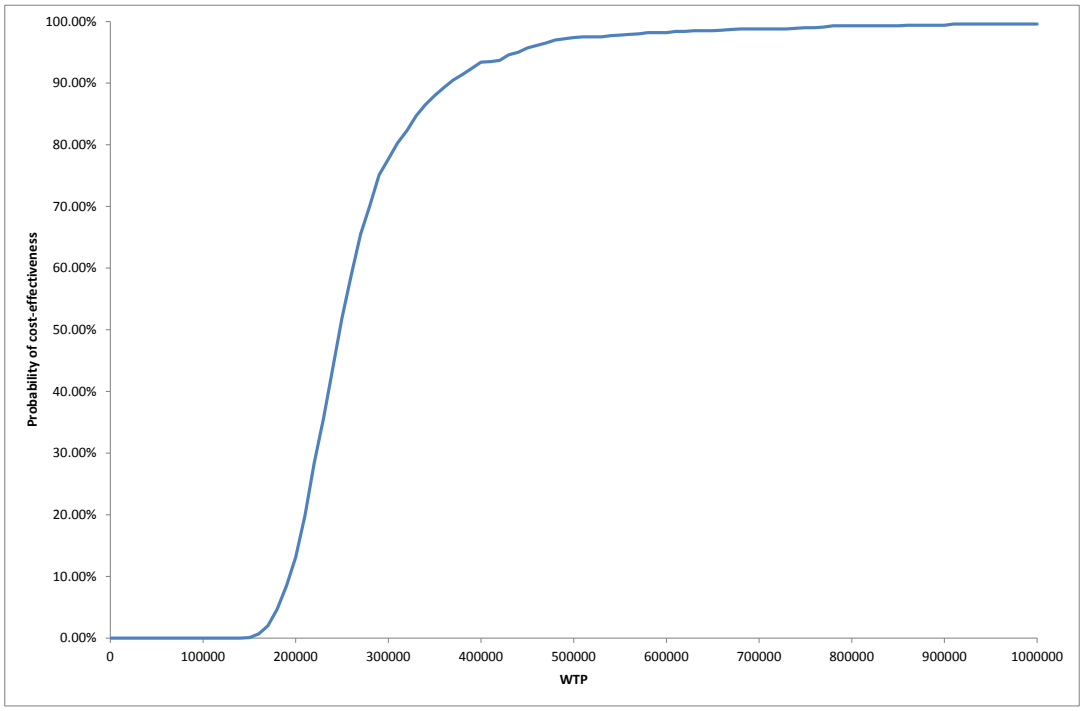


Figure 41. Scatter plot of cost-effectiveness results for PLDH plus platinum vs platinum monotherapy (dark blue line indicates threshold of £30,000 per additional QALY, light blue line indicates threshold of £20,000 per additional QALY)

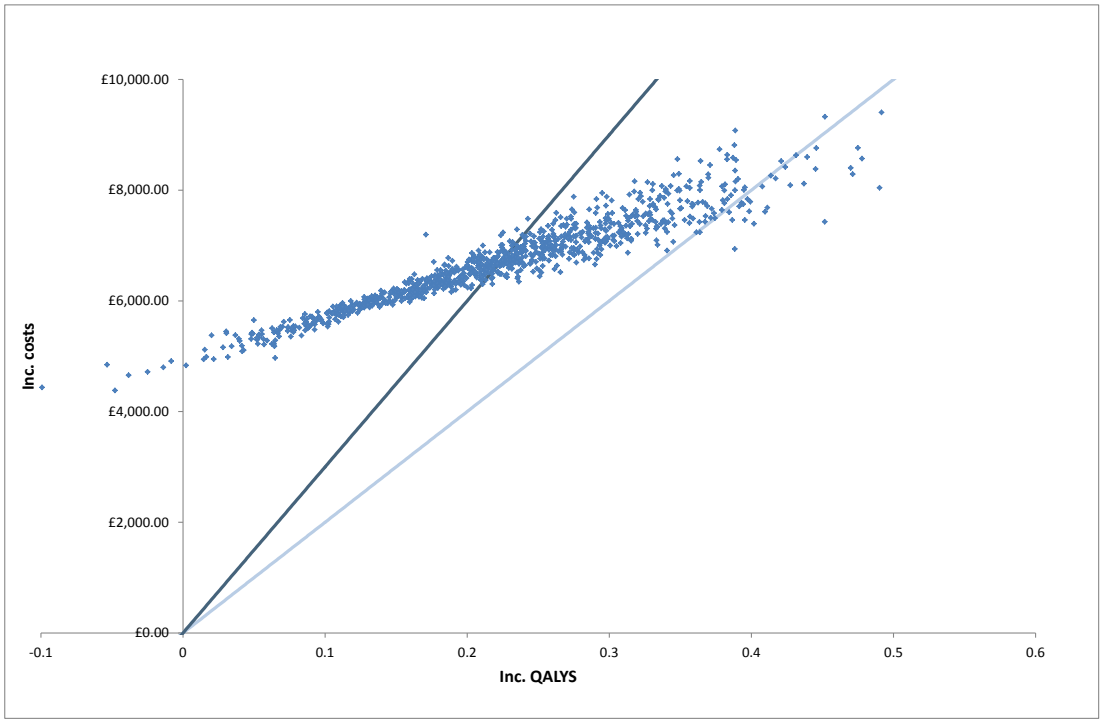


Figure 42. Cost-effectiveness acceptability curve for PLDH plus platinum vs platinum monotherapy

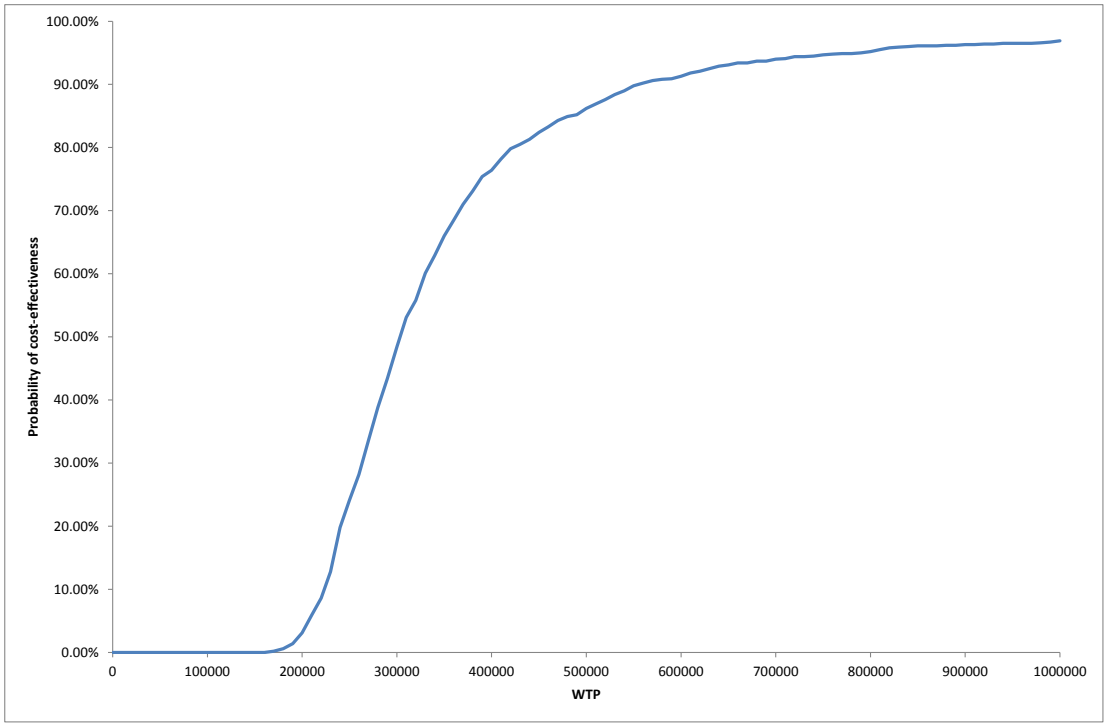


Figure 43. Scatter plot of cost-effectiveness results for PLDH plus platinum vs paclitaxel plus platinum (dark blue line indicates threshold of £30,000 per additional QALY, light blue line indicates threshold of £20,000 per additional QALY)

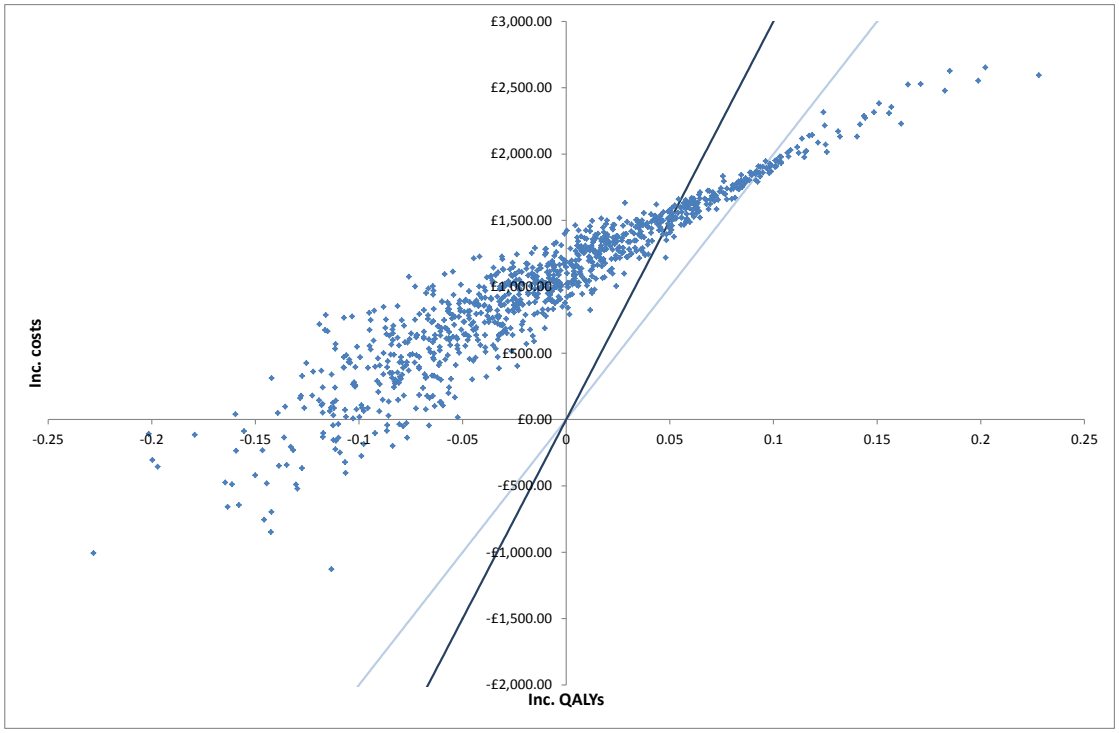
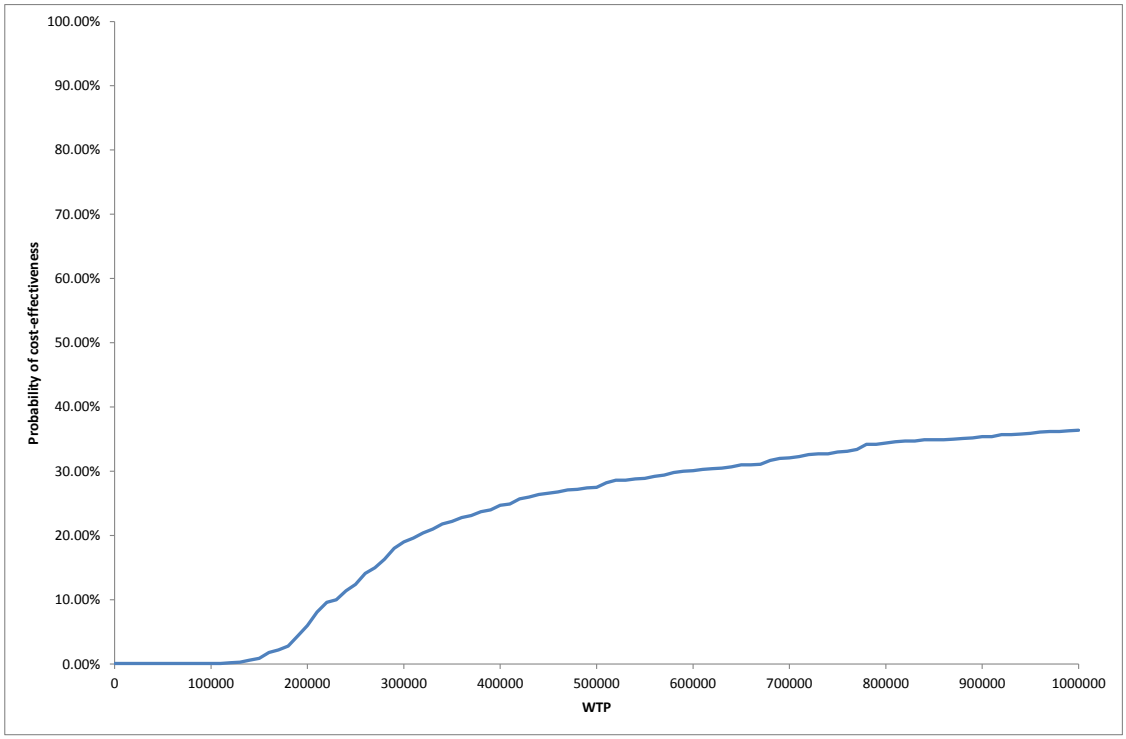


Figure 44. Cost-effectiveness acceptability curve for PLDH plus platinum vs paclitaxel plus platinum



Platinum sensitive network 2

For the subgroup of patients with platinum sensitive disease, probabilistic analysis of PS network 2 revealed that, at WTP thresholds of £20,000 and £30,000, treatment with PLDH (versus paclitaxel) is more likely to be cost-effective than treatment with trabectedin plus PLDH (versus paclitaxel). That is, treatment with PLDH has a 30% and 59% chance of being cost-effective at WTP thresholds of £20,000 and £30,000, respectively. Whereas, trabectedin plus PLDH has a 0.1% and 1.4% chance of being cost-effective at WTP thresholds of £20,000 and £30,000, respectively.

However, the TAG considers it important to note that 15% of PLDH versus paclitaxel simulations fall in the North-West quadrant (i.e., dominance by paclitaxel); whereas, 3% of simulations for trabectedin plus PLDH versus paclitaxel fall into this quadrant. This suggests that there is a greater degree of uncertainty associated with the benefit of PLDH over paclitaxel compared with the benefit of trabectedin plus PLDH over paclitaxel. This is emphasised further by considering the comparison of trabectedin plus PLDH versus PLDH alone in which 95% of simulations fall in the North-East quadrant suggesting that the addition of trabectedin to treatment with PLDH is likely to improve outcomes as well as increasing cost. However, according to the TAG analysis trabectedin plus PLDH has a 0% probability of being cost-effective over PLDH at WTP thresholds of £20,000 or £30,000.

Figure 45. Scatter plot of cost-effectiveness results for PLDH vs paclitaxel (dark blue line indicates threshold of £30,000 per additional QALY, light blue line indicates threshold of £20,000 per additional QALY)

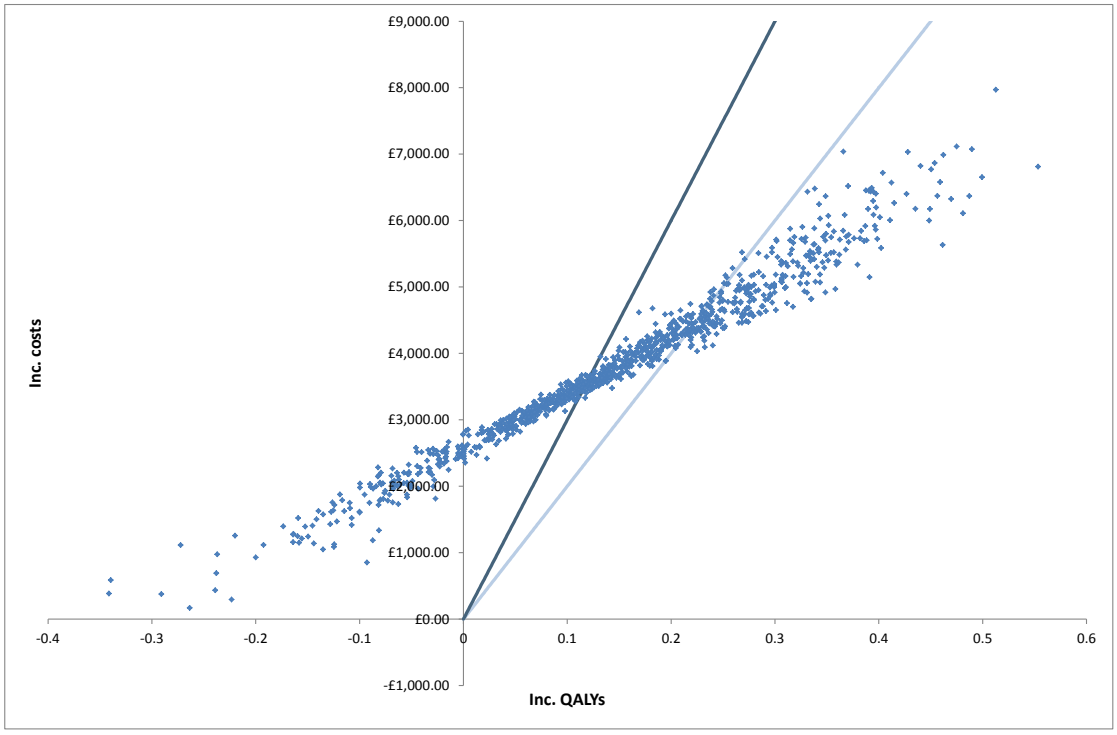


Figure 46. Cost-effectiveness acceptability curve for PLDH vs paclitaxel

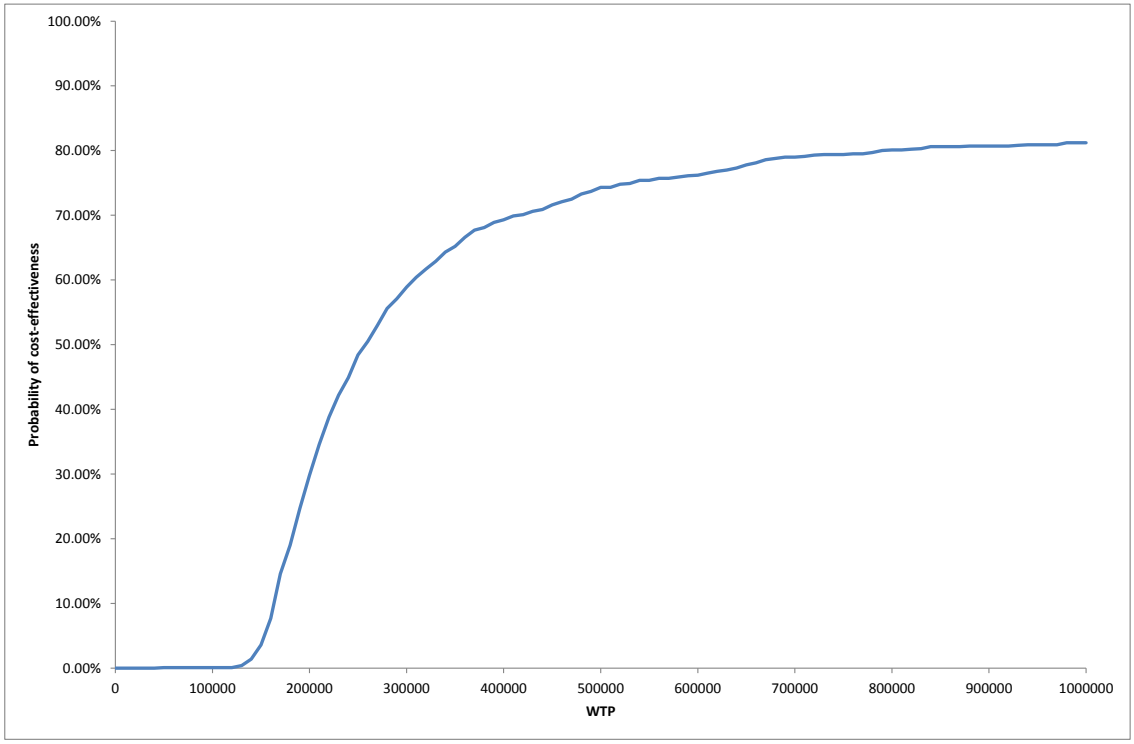


Figure 47. Scatter plot of cost-effectiveness results for trabectedin plus PLDH vs paclitaxel (dark blue line indicates threshold of £30,000 per additional QALY, light blue line indicates threshold of £20,000 per additional QALY)

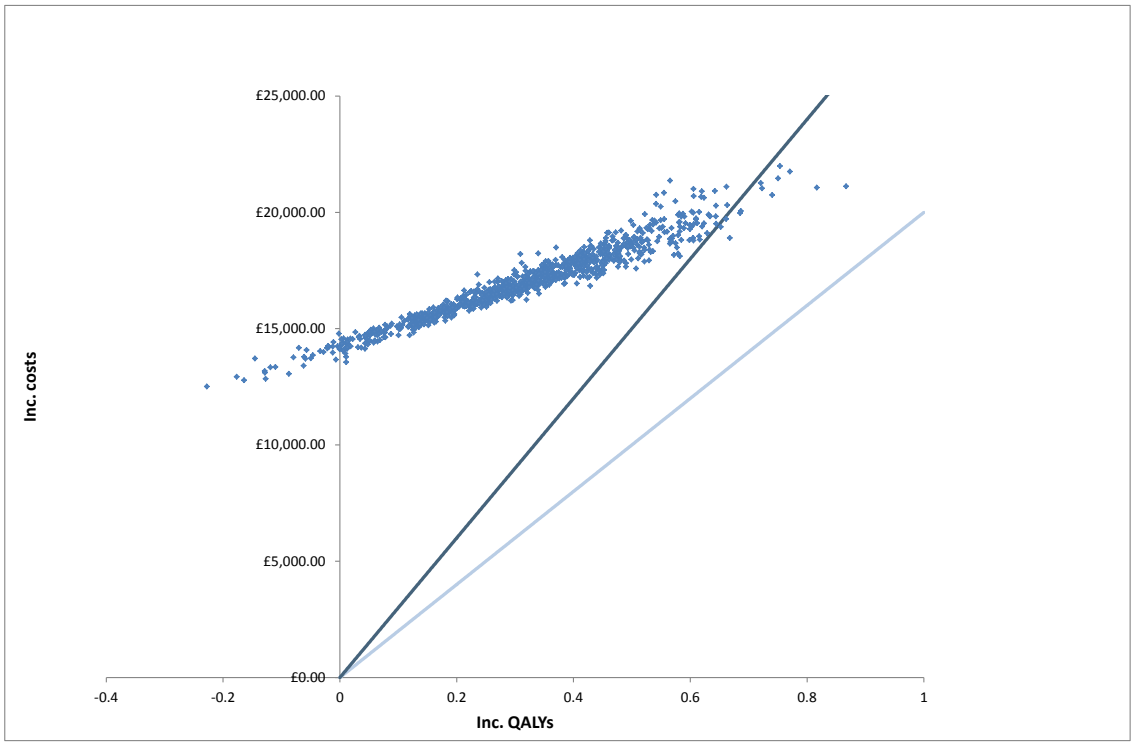


Figure 48. Cost-effectiveness acceptability curve for trabectedin plus PLDH vs paclitaxel

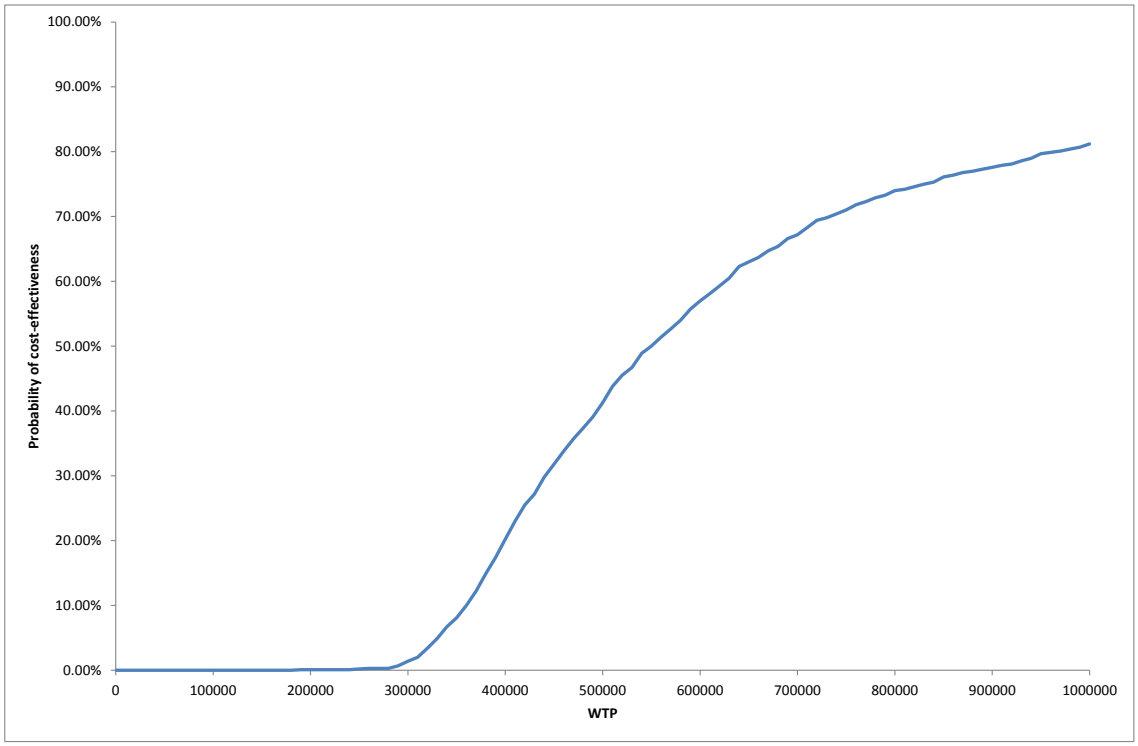


Figure 49. Scatter plot of cost-effectiveness results for trabectedin plus PLDH vs PLDH (dark blue line indicates threshold of £30,000 per additional QALY, light blue line indicates threshold of £20,000 per additional QALY)

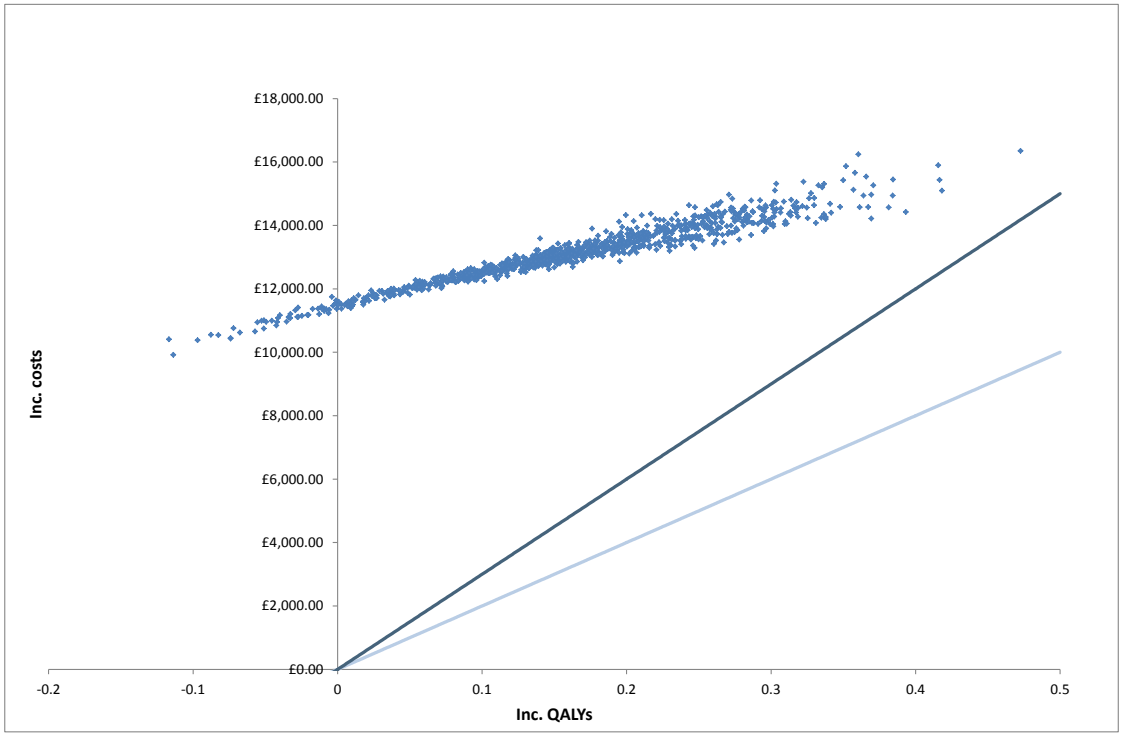
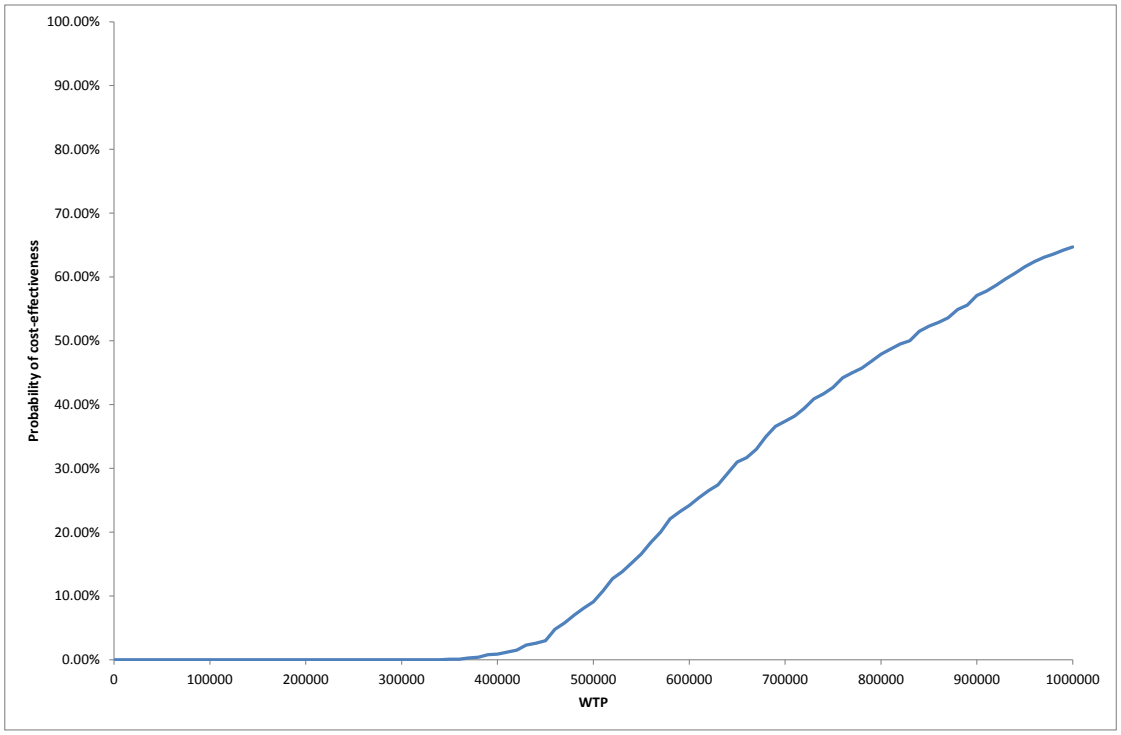


Figure 50. Cost-effectiveness acceptability curve for trabectedin plus PLDH vs PLDH



Platinum resistant/refractory network

For the subgroup of patients with platinum resistant or refractory disease, probabilistic analysis revealed that, on average, treatment with paclitaxel is dominated by treatment with PLDH. Therefore, based on mean estimates the key comparison in PRR patients is topotecan versus PLDH. However, at WTP thresholds of £20,000 and £30,000, topotecan has a 0% chance of being cost-effective. Whereas, in 39% of simulations paclitaxel provides greater QALYs at a higher cost (versus PLDH), with probabilities of being cost-effective of 3% and 14%, at WTP thresholds of £20,000 and £30,000, respectively. In addition, the TAG considers it important to note that in 23% of simulations paclitaxel was less expensive and less effective than PLDH.

Figure 51. Scatter plot of cost-effectiveness results for topotecan vs PLDH (dark blue line indicates threshold of £30,000 per additional QALY, light blue line indicates threshold of £20,000 per additional QALY)

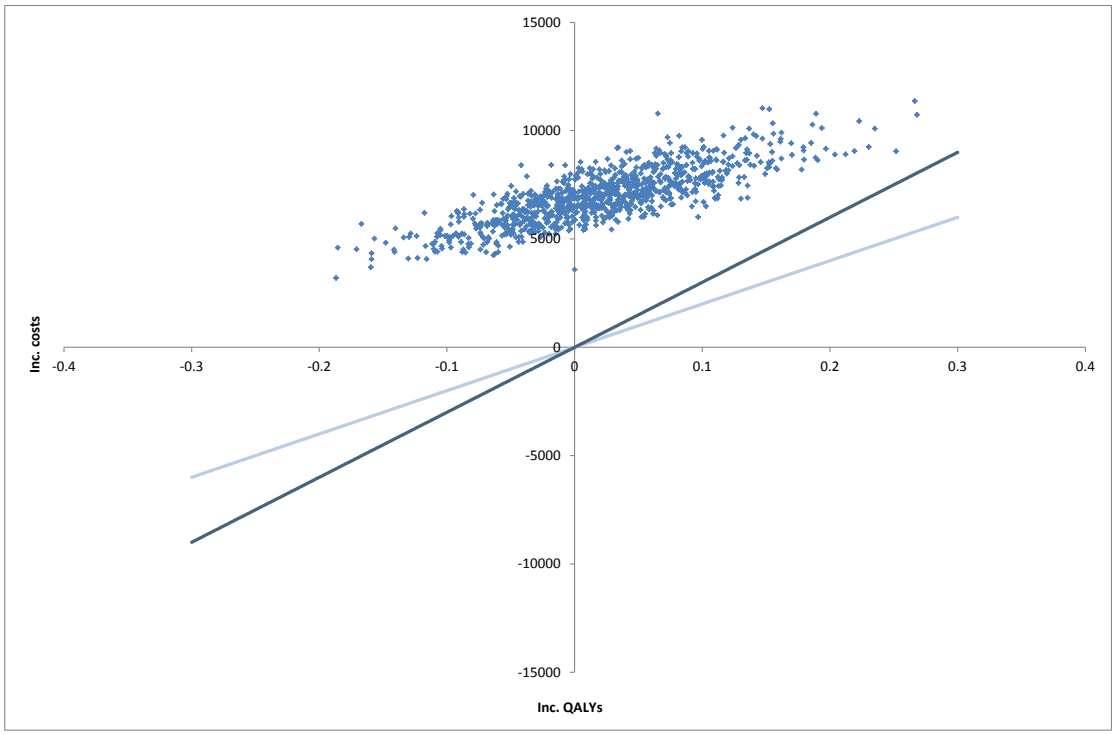


Figure 52. Cost-effectiveness acceptability curve for topotecan vs PLDH

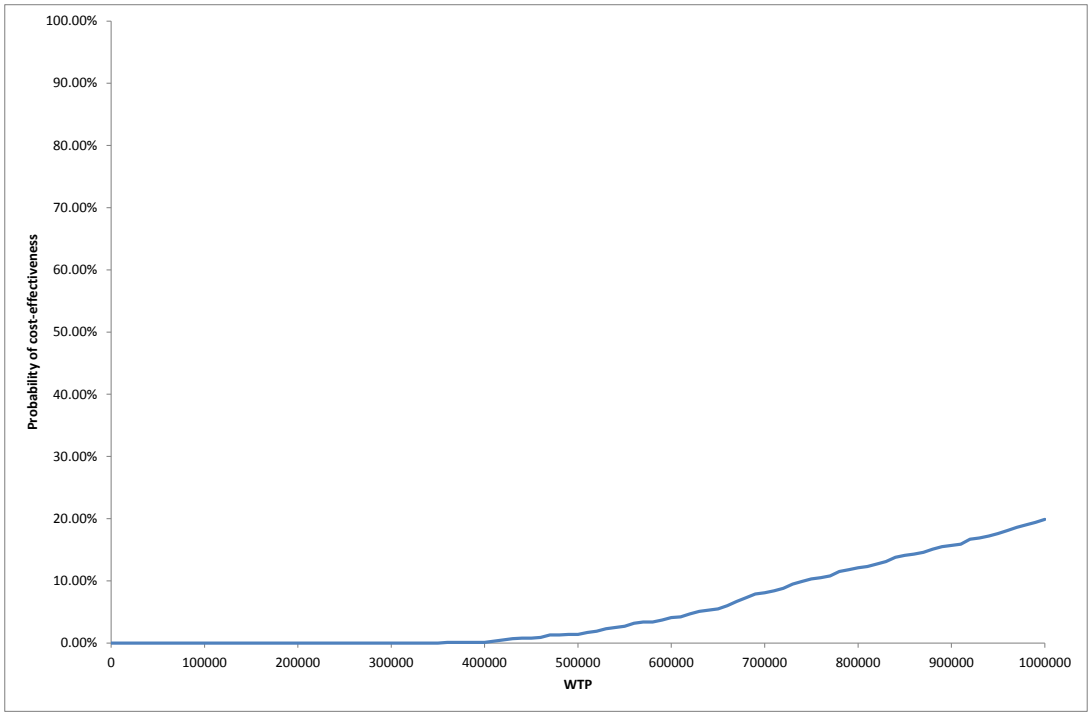


Figure 53. Scatter plot of cost-effectiveness results for paclitaxel vs PLDH (dark blue line indicates threshold of £30,000 per additional QALY, light blue line indicates threshold of £20,000 per additional QALY)

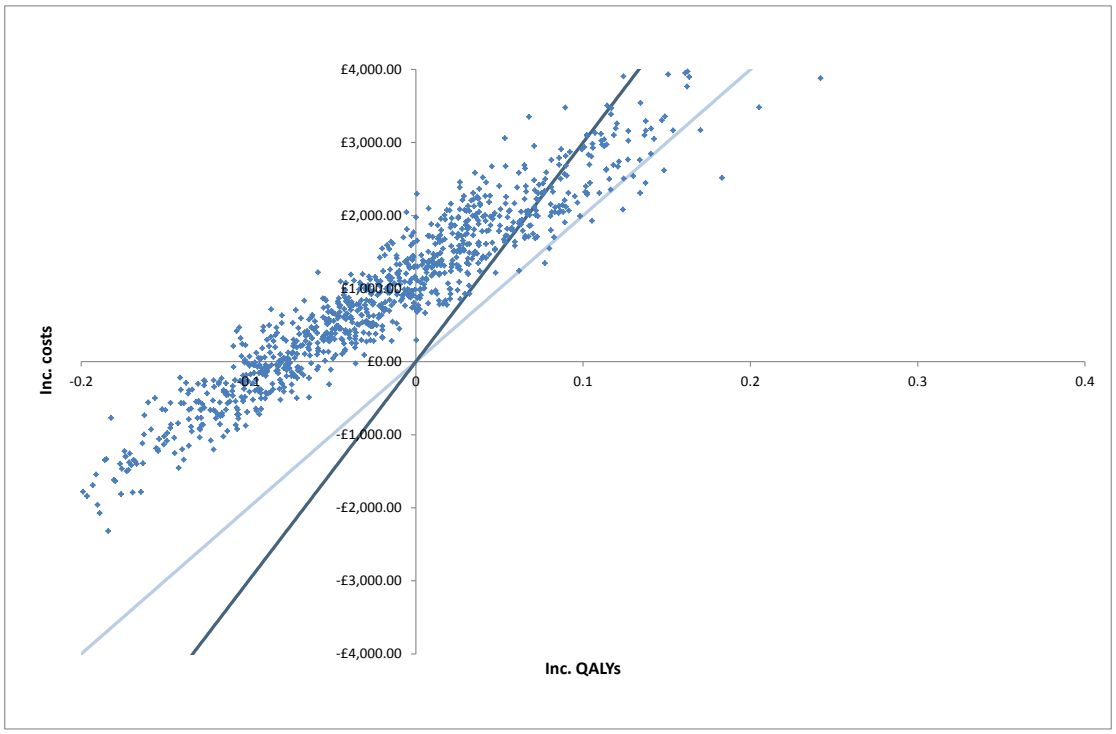
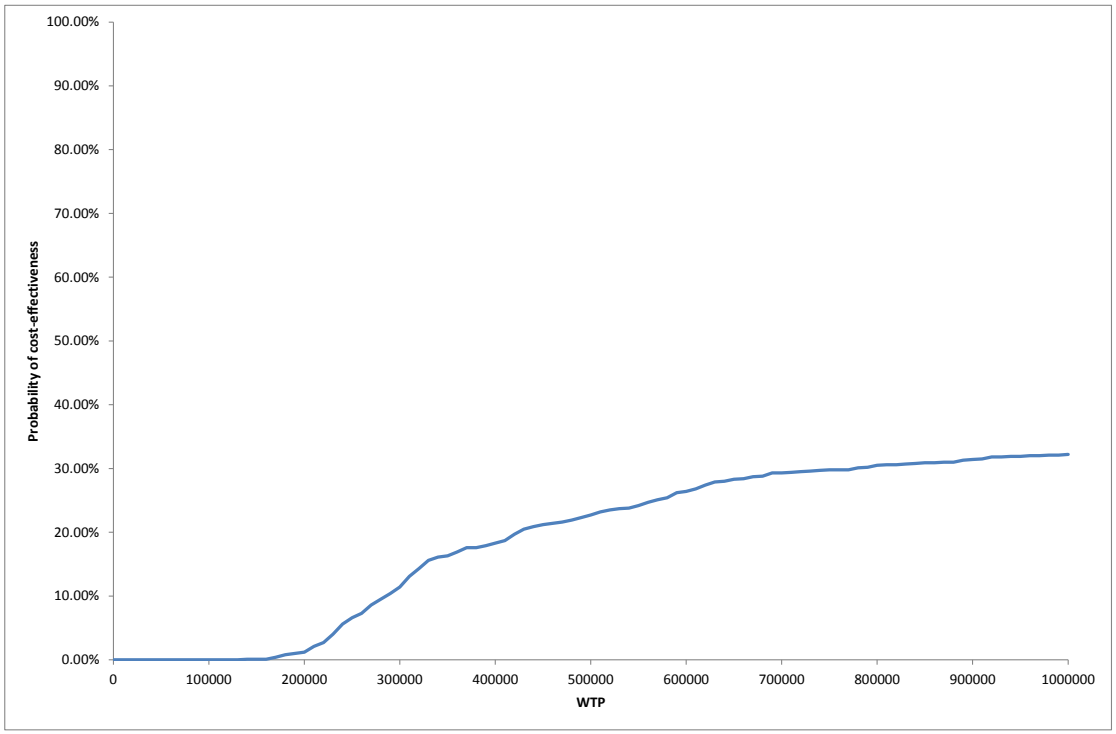


Figure 54. Cost-effectiveness acceptability curve for paclitaxel vs PLDH



5.2.13.2 One-way sensitivity analyses

As discussed in Section 5.2.12, in addition to probabilistic analysis, one-way sensitivity analysis has been carried out on all model parameters. The TAG notes that many of the parameters tested in sensitivity analysis had minimal impact on the deterministic cost-effectiveness results and therefore summaries of the most sensitive variables for each comparison are presented in Figures 55 to 62.

Platinum sensitive network 1

In patients considered to have platinum sensitive disease, one-way sensitivity analysis of PS network 1 revealed that the comparisons of paclitaxel plus platinum vs platinum (Figure 55) and PLDH plus platinum vs platinum (Figure 56) are most sensitive to the relative effect of treatment on OS. For example, use of the lower bound of the 95% credible interval (estimated from TAG NMA) for the HR of OS (platinum monotherapy vs paclitaxel plus platinum) increases the deterministic base case ICERs by over £20,000. This is because the base case value of the OS HR (platinum versus paclitaxel plus platinum) is 1.29, indicating that relative to paclitaxel plus platinum, platinum monotherapy increases the risk of death. Therefore assuming a lower value for this parameter directly results in a lower relative treatment effect for paclitaxel plus platinum and indirectly results in a lower relative treatment effect for PLDH plus platinum. The impact of other parameters, such as, the relative effect of treatment on PFS and the utility value associated with each health state, are relatively minimal.

Similarly, when considering the comparison of PLDH plus platinum with paclitaxel plus platinum, the relative effect of treatment on OS has the largest impact of all variables tested on the cost-effectiveness results (Figure 57). That is, when the lower bound of the OS HR (PLDH plus platinum vs paclitaxel plus platinum) is used to inform the cost-effectiveness analysis, the ICER moves from the dominance of PLDH plus platinum by paclitaxel plus platinum to an ICER of approximately £20,000 for PLDH plus platinum vs paclitaxel plus platinum. This is because lowering the HR (1.023 in the base case) reduces the relative benefit of paclitaxel plus platinum over PLDH plus platinum; however, the magnitude of change observed in this sensitivity analysis reflects the instability of the mean cost-effectiveness estimate for this comparison.

Figure 55. Tornado diagram of parameters to which the cost-effectiveness of paclitaxel plus platinum vs platinum monotherapy is most sensitive to

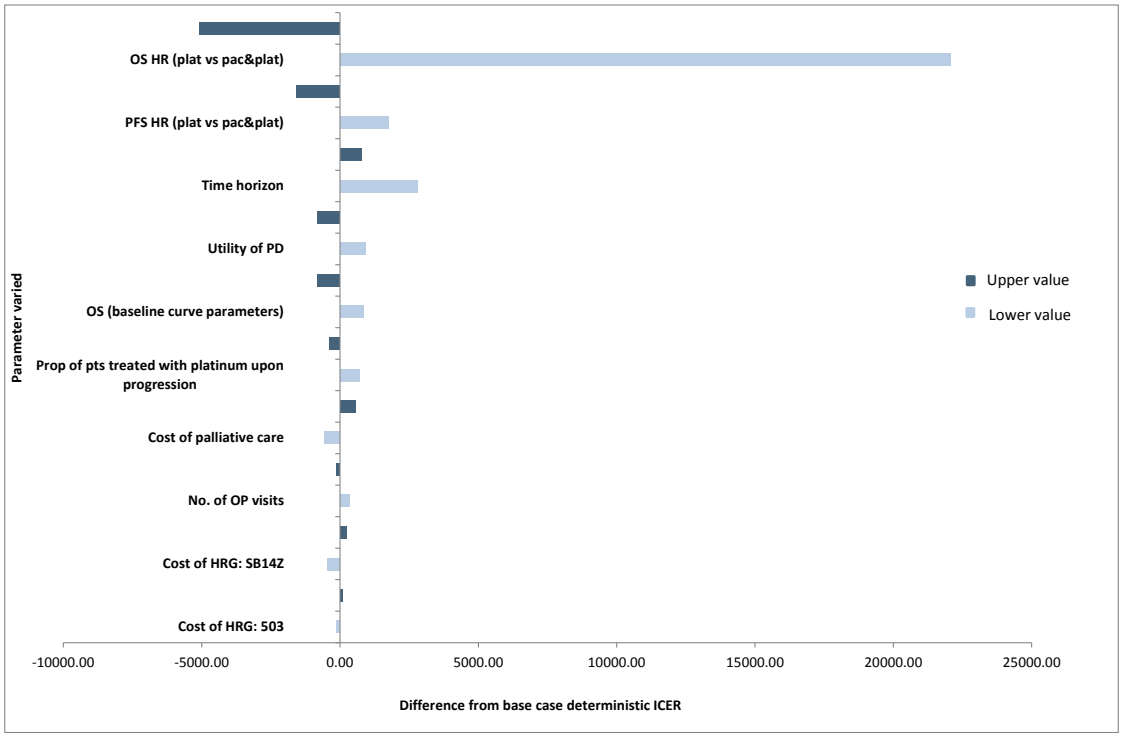


Figure 56. Tornado diagram of parameters to which the cost-effectiveness of PLDH plus platinum vs platinum monotherapy is most sensitive to

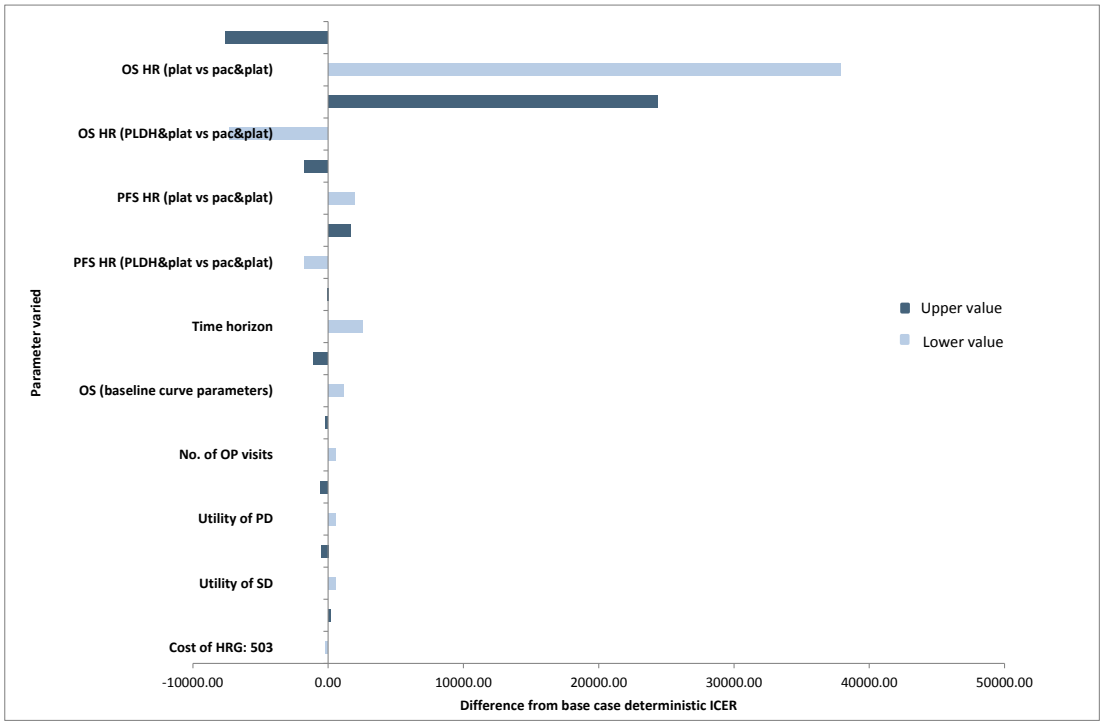
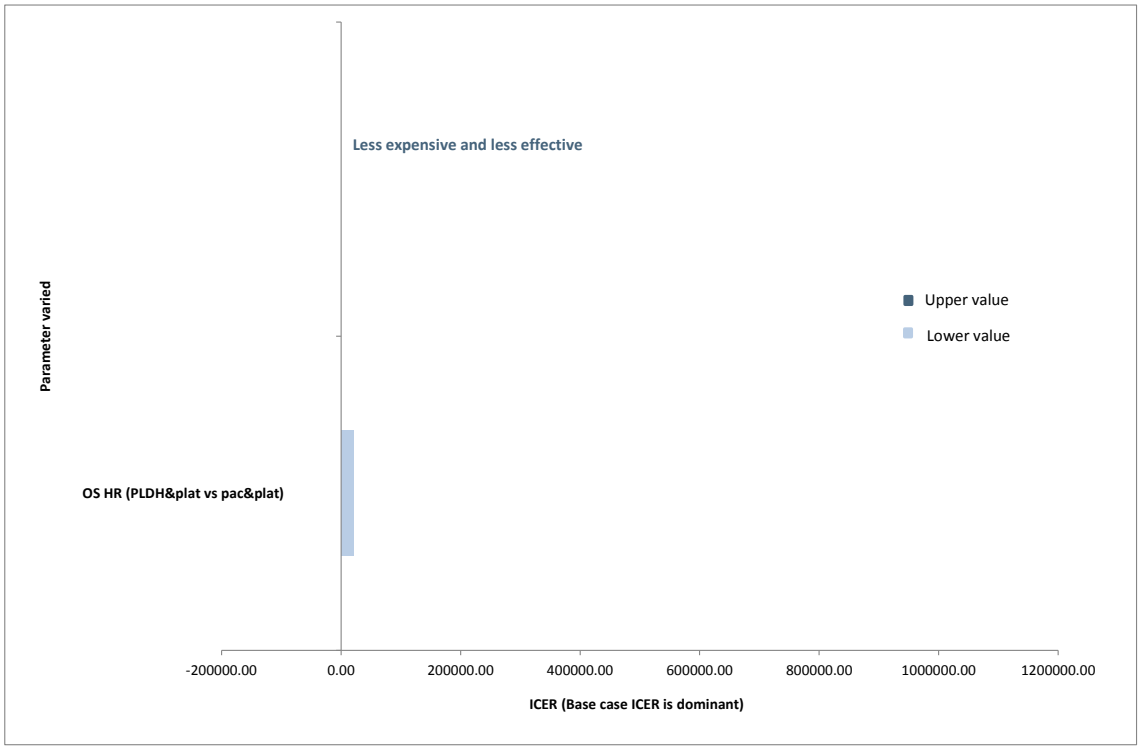


Figure 57. Tornado diagram of parameters to which the cost-effectiveness of PLDH plus platinum vs paclitaxel plus platinum is most sensitive to



Platinum sensitive network 2

Similar to the network of treatments for patients with platinum sensitive disease considered in PS network 1, the cost-effectiveness of treatments considered in PS network 2 appears to be driven by the relative effect of treatment on OS. For example, in the comparison of PLDH to paclitaxel, use of the lower bound of the 95% credible interval for the HR of OS (paclitaxel vs PLDH) results in a move from an ICER of approximately £25,000 (PLDH vs paclitaxel) to dominance of PLDH by paclitaxel (Figure 58). This is because the base case HR used to inform this comparison is 1.22 (paclitaxel vs PLDH), indicating that relative to PLDH, paclitaxel results in a higher risk of death. Therefore, assuming a lower value (0.80) for this parameter (i.e., representing a situation where, relative to PLDH, paclitaxel decreases the risk of death), results in a dramatic reversal of the cost-effectiveness results. As is the case in the comparison of paclitaxel plus platinum with PLDH plus platinum in PS network 1, the magnitude of change observed in this sensitivity analysis reflects the instability of the mean cost-effectiveness estimate for the comparison of PLDH with paclitaxel.

The relative effect of treatment on OS has a similar impact on the cost-effectiveness results of trabectedin plus PLDH versus PLDH (Figure 60). In this comparison, use of the lower bound of the OS HR (trabectedin plus PLDH versus PLDH) results in a £40,000 reduction in the ICER, whereas use of the upper bound of the OS HR (trabectedin plus PLDH vs PLDH) results in dominance of trabectedin plus PLDH by PLDH.

With respect to the comparison of trabectedin plus PLDH versus paclitaxel, the impact of treatment effect on OS remains high (Figure 59); although, it is not as influential as in the comparison of PLDH to paclitaxel (Figure 58). In particular, use of the lower bound of the OS HR (paclitaxel vs PLDH), increases the ICER from approximately £55,000 to £400,000; whereas, use of the upper bound of the OS HR (paclitaxel versus PLDH) decreases the ICER to approximately £35,000. This is because, in the base case, the OS HR (paclitaxel vs PLDH) is 1.22, and the OS HR (trabectedin plus PLDH vs PLDH) is 0.84; suggesting that compared with PLDH, paclitaxel increases the risk of death and trabectedin plus PLDH decreases the risk of death. Use of the lower 95% credible interval (0.85) of OS HR (paclitaxel vs PLDH) effectively removes the difference in OS benefit between trabectedin plus PLDH and paclitaxel and therefore increases the ICER. Conversely, a larger relative difference in the effect of treatment on OS (between trabectedin plus PLDH and paclitaxel), through use of the upper bound (1.69) of the OS HR (paclitaxel vs PLDH), decreases the ICER. However, unlike the comparison of PLDH vs paclitaxel (Figure 58), sensitivity analysis around the relative effect of treatment on OS does not alter the quadrant of the cost-effectiveness plane in which the result falls.

Figure 58. Tornado diagram of parameters to which the cost-effectiveness of PLDH vs paclitaxel is most sensitive to

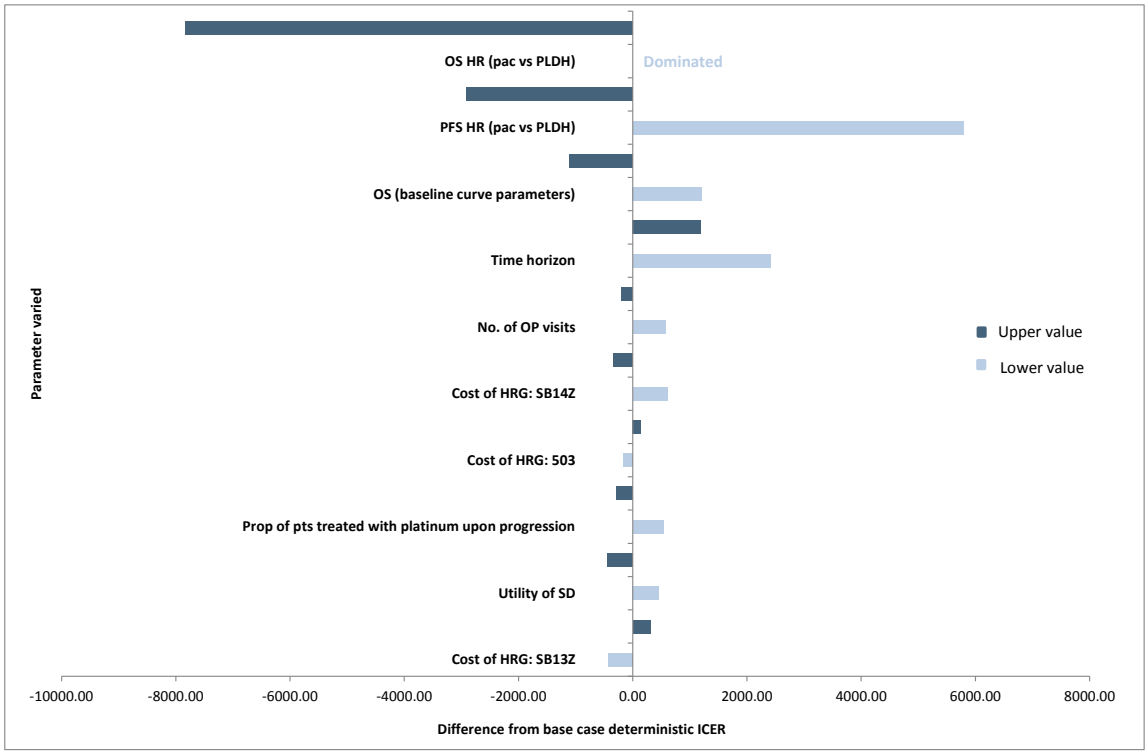


Figure 59. Tornado diagram of parameters to which the cost-effectiveness of trabectedin plus PLDH vs paclitaxel is most sensitive to

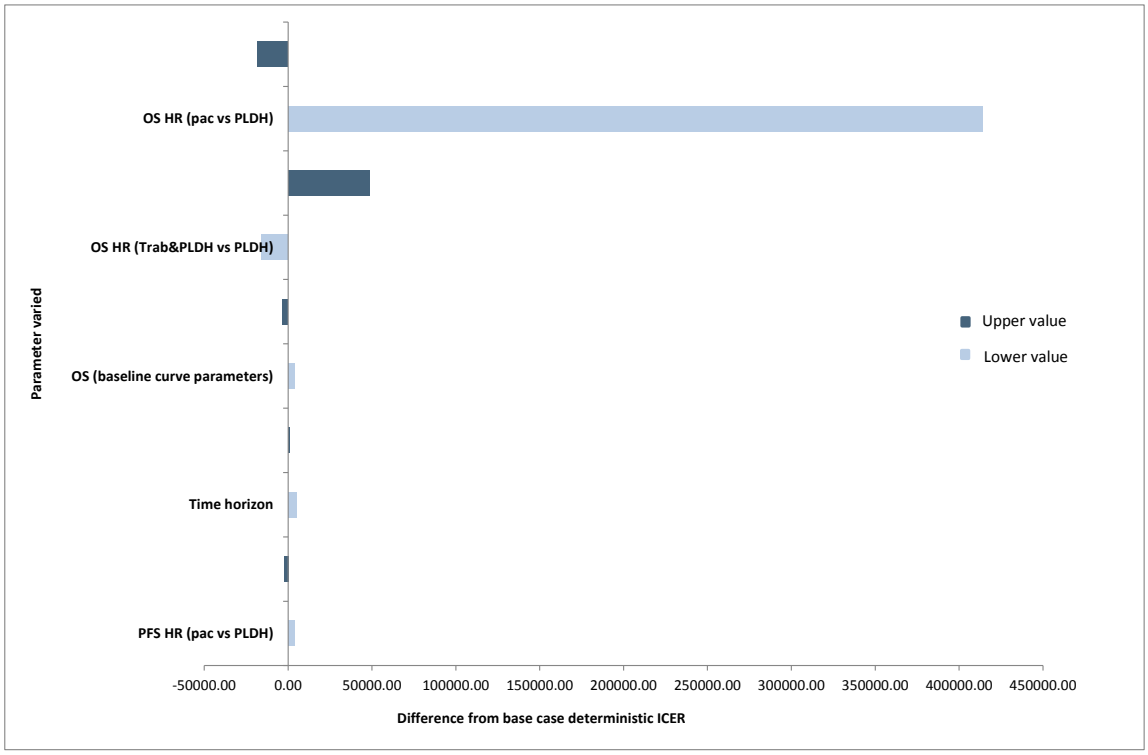
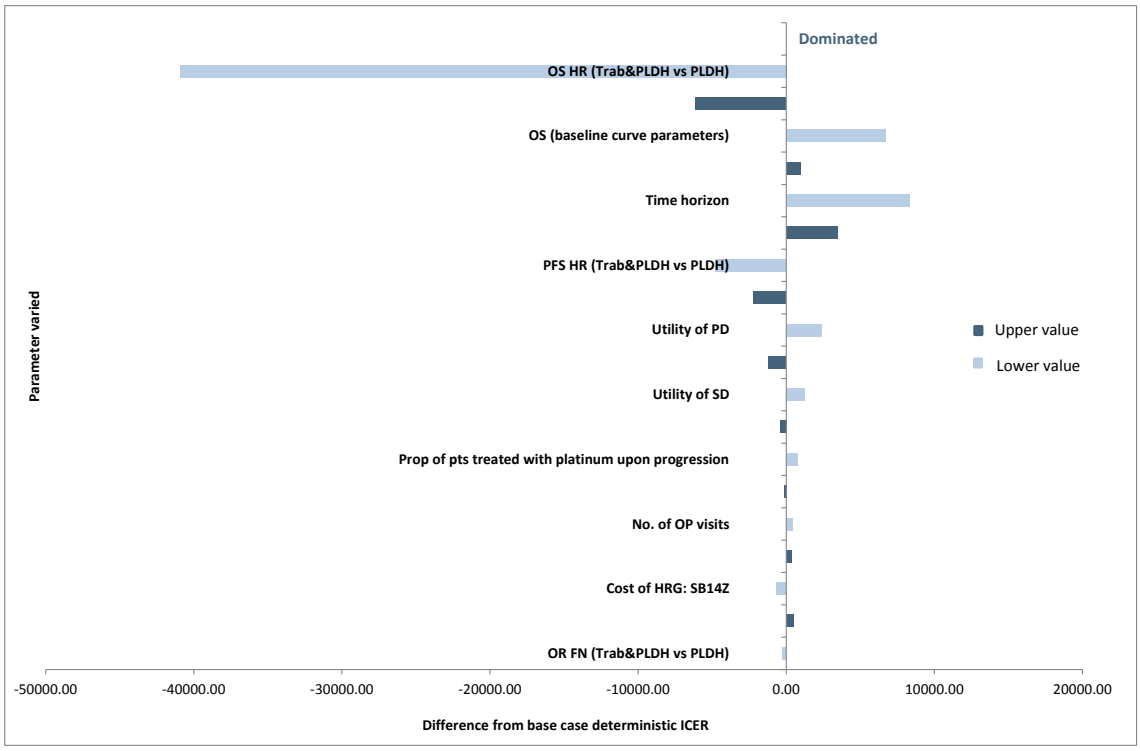


Figure 60. Tornado diagram of parameters to which the cost-effectiveness of trabectedin plus PLDH vs PLDH is most sensitive to



Platinum resistant/refractory network

In patients with resistant or refractory disease, the relative effect of treatment on OS continues to be a key driver of cost-effectiveness results. Moreover, one-way sensitivity analysis revealed that the comparisons of topotecan with PLDH (Figure 61) and paclitaxel with PLDH (Figure 62) are unstable. That is, for both comparisons, sensitivity analysis around the relative effect of treatment on OS altered the quadrant in which the cost-effectiveness result falls. In particular, when the lower bound of the OS HRs (topotecan vs PLDH and paclitaxel vs PLDH) were used, the ICERs of topotecan vs PLDH and paclitaxel vs PLDH were £53,288 and £17,903, respectively.

Figure 61. Tornado diagram of parameters to which the cost-effectiveness of topotecan versus PLDH is most sensitive to

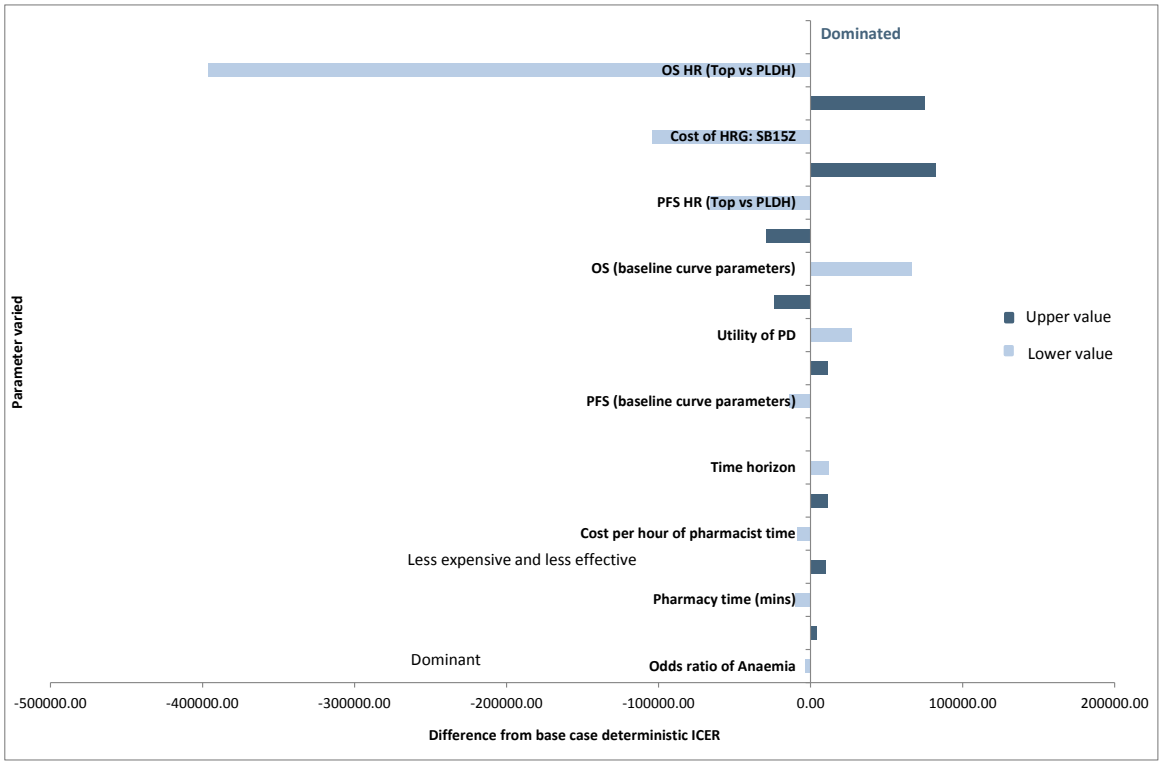
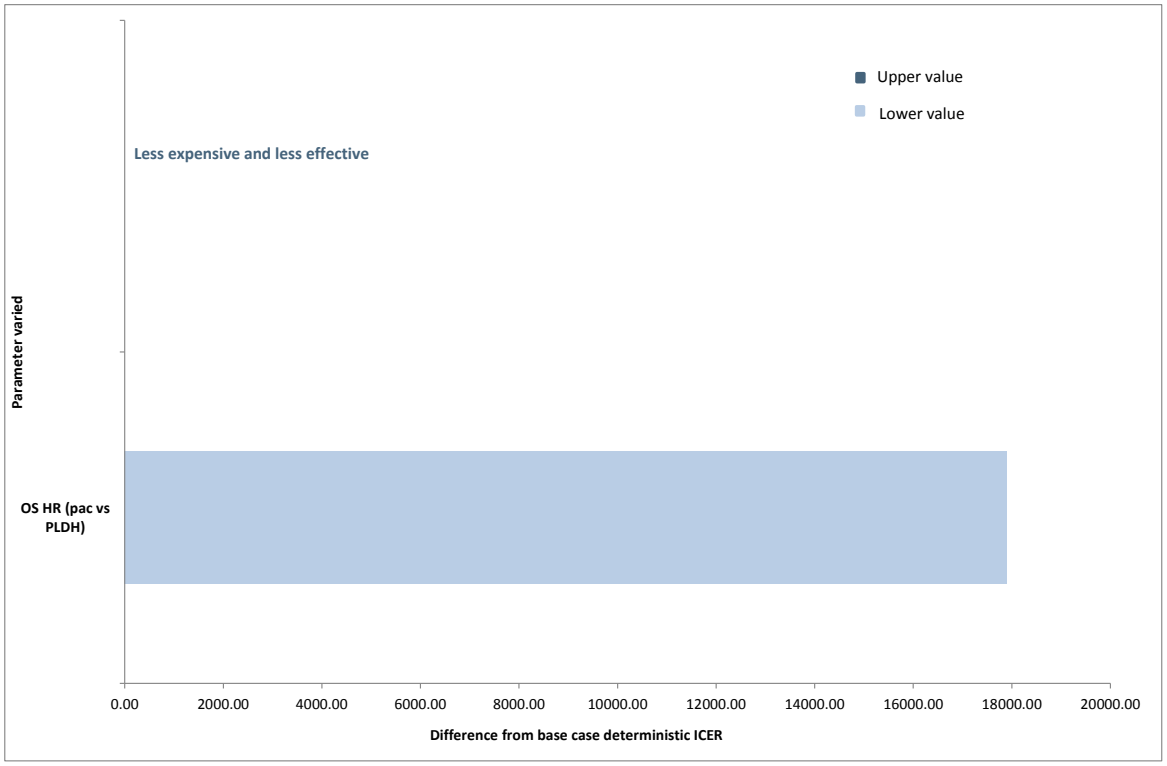


Figure 62. Tornado diagram of parameters to which the cost-effectiveness of paclitaxel versus PLDH is most sensitive to



5.2.13.3 Scenario analyses

In addition to probabilistic and one-way sensitivity analyses, several scenario analyses have been carried out to assess the sensitivity of the cost-effectiveness results to structural assumptions made. Full results of these analyses are presented in Appendix 11, with a summary of the key results, for each network, presented below.

Platinum sensitive network 1

For platinum sensitive network 1 (platinum; gemcitabine plus carboplatin; PLDH plus platinum; paclitaxel plus platinum) two scenarios materially impacted the results and conclusions of the base case analysis. These scenarios were those in which branded (Abraxane® and Taxol®) rather than non-proprietary drug acquisition costs of paclitaxel were used.

Using the cost associated with Abraxane®, the total discounted cost associated with paclitaxel plus platinum increases from £21,643 to £22,940. Increasing the ICER associated with paclitaxel plus platinum vs platinum from £24,361 to £29,912.This increase results in a shift from strict dominance of PLDH plus platinum by paclitaxel plus platinum, to extended dominance of PLDH plus platinum by paclitaxel plus platinum. That is, when Abraxane® is used, treatment with paclitaxel plus platinum results in higher costs than treatment with PLDH plus platinum. However, the additional benefit

provided by using paclitaxel rather than PLDH in combination with platinum therapy, may be considered to provide better value for money (i.e., results in a lower ICER vs platinum).

Use of Taxol® rather than non-proprietary paclitaxel produces very similar results and conclusions to the use of Abraxane®; PLDH plus paclitaxel switches from being strictly dominated by paclitaxel plus platinum to being extendedly dominated by paclitaxel plus platinum. The ICER associated with paclitaxel plus platinum vs platinum increases from £24,361 to £36,092.

For all other scenarios, results are robust to the changes made; gemcitabine plus carboplatin remains extendedly dominated, PLDH plus carboplatin remains strictly dominated, and the ICER for paclitaxel plus platinum vs platinum ranges between £19,113 and £30,084.

Platinum sensitive network 2

For platinum sensitive network 2 (paclitaxel; PLDH; PLDH plus trabectedin; topotecan) base case incremental results were robust to the majority of scenarios modelled. In particular, topotecan continued to be dominated by trabectedin plus PLDH, in every modelled scenario. In addition, with the exception of one scenario, the ICER associated with PLDH vs paclitaxel remained below £30,000; increasing the dose of PLDH (from 40 mg/m^2 to 50 mg/m^2) used in drug acquisition calculations, increased the ICER from £23,733 to £31,222. Furthermore, the ICER associated with trabectedin plus PLDH vs PLDH remained above £60,000 in all scenarios assessing incremental base case results.

In addition to scenario analyses of incremental base case results, a further two scenario analyses, examining the cost-effectiveness of a subset of comparisons of interest, were carried out. These were:

- exploratory analysis of the cost-effectiveness of PLDH, trabectedin plus PLDH and topotecan in patients with partially platinum sensitive (PFI 6-12 months) disease;
- head-to-head comparison of trabectedin plus PLDH vs PLDH using clinical effectiveness data from the PharmaMar submission (i.e. adjusted for baseline characteristics) within the TAG economic model.

Scenario analysis in the partially platinum sensitive patient population was carried out using OS HRs (trabectedin plus PLDH vs PLDH and topotecan, vs PLDH) estimated from TAG NMA (Section 4.2.2.1). For the following reasons, the TAG considers this analysis as highly uncertain and therefore exploratory. Firstly, as a result of data paucity, it was not possible to estimate baseline survival for the partially platinum sensitive (PFI 6 – 12 months) population; instead estimates of baseline survival from platinum sensitive (PFI $\geq$ 6 months) patients treated with PLDH were used. Secondly, HRs were only available for OS and not PFS; estimates of PFS from platinum sensitive patients were used as proxies. Results of this exploratory scenario analysis were dominance of topotecan by PLDH and an ICER of £37,691 for trabectedin plus PLDH versus PLDH.

Head-to-head comparison, in the platinum sensitive (PFI > 6 months) population, of trabectedin plus PLDH vs PLDH, based on PFS and OS from the PharmaMar submission (i.e. adjusted for baseline characteristics) within the TAG economic model, resulted in an ICER of £35,646. By contrast, the ICERs, of trabectedin plus PLDH versus PLDH in the platinum sensitive (PFI > 6) population, estimated by the TAG's and PharmaMar's base case analyses were £85,212 and £27,573, respectively. The deterministic incremental costs and QALYs associated with the TAG's base case and scenario analyses and the manufacturer's base case analysis are presented in Table 144.

Table 144. Head-to-head comparison of trabectedin plus PLDH versus PLDH using adjusted PFS and OS data from the PharmaMar submission; comparison of manufacturer and Technology Assessment Group analyses

Treatment	Total (discounted) costs	Total (discounted) QALYs	Incremental costs	Incremental QALYs	ICER
TAG base case estimates					
Trabectedin plus PLDH	£32,640	1.717	–	–	–
PLDH	£19,599	1.564	£13,041	0.15	£85,212
PharmaMar estimates					
Trabectedin plus PLDH	£38,206	2.33	–	–	–
PLDH	£24,809	1.85	£13,397	0.49	£27,573
TAG scenario analysis estimates					
Trabectedin plus PLDH	£34,569	2.08	–	–	–
PLDH	£21,063	1.70	£13,506	0.38	£35,646
Abbreviations used in table: ICER, incremental cost-effectiveness ratio; PLDH, pegylated liposomal doxorubicin hydrochloride; QALY, quality-adjusted life year.					

The TAG notes that, given both the TAG scenario analysis and the PharmaMar model utilise the same PFS, OS and utility data, it would be expected that the difference in the estimated ICERs would be explained through a difference in estimated incremental cost. However, incremental costs were similar between the TAG and PharmaMar analyses (£13,506 vs £13,397, respectively), with the difference in incremental QALYs (0.38 vs 0.49, respectively) the main driver of the difference in the ICER estimates. Therefore, the TAG investigated potential causes of this discrepancy and considers that it likely to be a result of the different methods used, within the model structures, to discount costs and benefits.

The manufacturer's model was based upon the model developed in TA91 (used in TA222), whereby the mean time to progression and mean time to death, to which costs and QALYs were applied, were estimated from survival data (Section 5.1.3). In order to apply discounting to costs and QALYs in this model structure, the manufacturer stated that: "the exponential discounting method was used whereby costs and QALYs were discounted continuously based on the time spent in the model health states.

The instantaneous rate of 3.44% (Ln[1.035]) was therefore considered" MS, page 31. Within TA222, a key critique of the manufacturer's model, by the ERG responsible for reviewing this STA, related to the method of discounting used as a result of the model structure: "discounting cannot be easily implemented in such a model structure. Ideally a state transition-type Markov trace element should be constructed to facilitate the implementation of discounting."[(90)] The TAG economic analysis did not rely upon mean estimates of PFS or OS. Instead, costs and QALYs were estimated monthly for each health state; these costs and QALYs were then discounted depending upon the year in which they fell.

The TAG considers that, as a result of the discounting methodology used, the manufacturer may have overestimated the QALY gain. This is because, application of discounting to average estimates is unlikely to be as accurate as discounting based on monthly estimates, as the granularity of patient proportions, by health state, over time, is not captured.

However, the TAG considers that the difference in the ICER between the TAG's and manufacturer's base case analyses is predominantly a consequence of the use of adjusted clinical effectiveness data; adjusted for baseline characteristics such as PFI (as a continuous variable). The TAG notes that adjustment of clinical effectiveness data for key prognostic factors such as PFI is likely to result in more accurate estimates of PFS and OS.

For these reasons, the TAG considers that the ICER estimated in the TAG's scenario analysis is likely to be the most accurate reflection of the cost-effectiveness of trabectedin plus PLDH versus PLDH.

Platinum resistant/refractory network

For the platinum resistant/refractory network (paclitaxel; PLDH; topotecan) results are robust to the majority of scenarios modelled. The ICER for topotecan vs PLDH ranges between £374,963 and £503,885. Paclitaxel is dominated in all but one scenario; where costs associated with a 50 mg dose of PLDH, rather than costs associated with a dose of 40 mg are used. In this scenario, paclitaxel becomes the least costly treatment option and therefore represents the baseline for incremental assessment of cost-effectiveness results. In this scenario, the ICER associated with PLDH vs paclitaxel is estimated to be £10,480.

The TAG modelled a scenario in which only the costs associated with treatment for platinum resistant/refractory patients differed between chemotherapy regimens. In this scenario, PFS and OS were set equal to the baseline treatment (PLDH). The purpose of this scenario was twofold; firstly, to provide a comparison including all interventions and comparators of interest as listed in the NICE scope and secondly, to reflect clinical advice that the prognosis of patients with platinum resistant/refractory disease is often poor across available treatment options. In this scenario, the cost of etoposide 50 mg (oral) days 1-21 every 28 days for a maximum of six cycles followed by

maintenance with oral etoposide, was estimated to be the cheapest treatment option (£8,194), followed by best supportive care (£12,622). The TAG considers that the cost associated with best supportive care may have been overestimated. The palliative cost associated with ovarian cancer was estimated by Guest *et al.* to be £4,789 (at 2000/2001 prices) for an average time period of 399 days.[114] This cost predominantly consisted of hospitalisation costs (71% of costs). Updating the estimate of palliative care for ovarian cancer patients from Guest *et al*. to current prices using the Hospital & Community Health Services index results in a cost of £6,963;[112] equating to £531 per month. This cost is applied monthly to all platinum resistant/refractory patients following entry into the progressed disease health state, and all platinum sensitive patients following six months of residence in the progressed disease health state.

The TAG notes that the analysis carried out by Guest *et al*. has several weaknesses. In particular, ovarian cancer estimates are based upon a small sample size (n=21) and does not consider costs for patients not requiring a strong opioid. In addition, the analysis was carried out in 2000/2001 and may no longer reflect clinical practice.

This is because the data from which the estimated monthly cost of palliative care is taken (Guest *et al.*) is subject to a number of limitations. In particular, ovarian cancer estimates are based upon a small sample size (n=21) and does not consider costs for patients not requiring a strong opioid. In addition, the analysis was carried out in 2000/2001 and may no longer reflect clinical practice. To establish the impact of this uncertainty, the TAG varied this cost in sensitivity analysis for the base case; however, the TAG considers that future research into the cost of best supportive care for women with ovarian cancer may be warranted (Section 8.1).

5.2.14 Summary of the Technology Assessment Group *de novo* economic evaluation

Following review of the economic literature and manufacturer submissions, the TAG developed a *de novo* economic model to address the decision problem outlined for this MTA. The economic model was based upon the model structure for TA91 in which three health states were modelled; stable disease, progressed disease and death. Within the TA91 model, the proportions of patients within each health state were calculated from estimates of mean time to progression and mean time to death, available from the literature. Utilities and costs were then applied to mean estimates of time spent within each health state. The ERG responsible for appraisal of a subsequent STA (TA222) in which the same model structure was applied, commented that the use of mean estimates resulted in difficulties in the application of discounting; this is because the proportion of patients in each health state over time is not explicitly modelled. Therefore, in order to address this concern, the model used in TAG analyses incorporates monthly estimates of PFS and OS over time (Section 5.2.7).

Furthermore, based on the data identified in the clinical systematic review and consultation with clinical experts, the TAG carried out separate analyses of patients with platinum sensitive disease (PFI ≥ 6 months) and platinum resistant/refractory disease (PFI < 6 months). Moreover, as no single trial, assessing the full range of interventions and comparators, was identified in the platinum sensitive or platinum resistant/refractory patient populations; NMAs were used to synthesis the available clinical effectiveness data (Section 4.2). However, as a result of the trials available, for patients with platinum sensitive disease, it was not possible to construct a single complete network comparing all interventions with all comparisons and with one another. Instead, two separate, disconnected networks form the basis of analyses in the platinum sensitive subgroup. For patients with platinum resistant/refractory disease, the trials available enabled the TAG to analyse a subset of the interventions and comparators listed within the scope. Finally, following consultation with clinical experts, the TAG considers that patients who are platinum allergic are likely to respond to non-platinum therapies in a similar way to patients without a platinum allergy. Therefore, a separate analysis of platinum allergic patients has not been carried out; however, treatment options for platinum allergic patients are assumed to exclude platinum-based therapies (Section 5.2.3).

Within the TAG's economic model, costs associated with drug acquisition and administration; patient care (health state costs) and adverse events are accounted for. Quality adjusted life years (QALYs) are used to assess the benefit of each treatment to patients. QALYs are calculated by the application of health state utility values, identified from the published literature, to the proportion of patients in each health state over time. Adverse events, which following consultation with clinical experts, are considered to be associated with a noteworthy cost are included in the base case analyses. However, the impact of treatment related toxicity on quality of life is not explicitly assessed in the TAG's base case analysis. The rationale for exclusion of utility decrements associated with adverse events is twofold. In particular, the TAG notes that the impact of adverse events on patient quality of life associated with trabectedin plus PLDH and PLDH monotherapy is implicitly included within the health state utility estimates used (health state utility estimates are sourced from TA222). Furthermore, the reliability of the estimates identified for quality of life decrements is uncertain. Finally, in line with the NICE reference case, analysis is carried out from the perspective of the NHS and Personal social services (PSS), costs and benefits are discounted at a rate of 3.5% per annum over a 15 year time horizon.

A summary of the results of the TAG's base case analyses is presented in Table 145.

Table 145. Summary of results, by network, from the Technology Assessment Group analyses

Platinum sensitive network 1				Platinum sensitive network 2 (including platinum allergic patients)				Platinum resistant/refractory (including platinum allergic patients)			
Treatment	**Incremental ICER probabilistic (deterministic)**	**Prob. cost-effective at threshold of:[a]**		**Treatment**	**Incremental ICER probabilistic (deterministic)**	**Prob. cost-effective at threshold of:[a]**		**Treatment**	**Incremental ICER probabilistic (deterministic)**	**Prob. cost-effective at threshold of:[a]**	
		£20,000	**£30,000**			**£20,000**	**£30,000**			**£20,000**	**£30,000**
Platinum	–	–	–	**Paclitaxel**	–	–	–				
Gemcitabine plus carboplatin	Extendedly dominated			**PLDH**	£25,931 (£23,733)	30%	59%	**PLDH**	–	–	–
Paclitaxel plus platinum	£24,539 (£24,361)	13%	78%	**Topotecan**	Strictly dominated			**Paclitaxel**	Strictly dominated		
PLDH plus platinum	Strictly dominated			**Trabectedin plus PLDH**	£81,353 (£85,212)	0%	0%	**Topotecan**	£324,188 (£449,553)	0%	0%

[a] The probability each therapy would be considered cost-effective at a willingness to pay threshold of £20,000 or £30,000 per additional QALY gained

Abbreviations used in table: ICER, incremental cost-effectiveness ratio; PLDH, pegylated liposomal doxorubicin hydrochloride; prob, probability.

5.2.15 Discussion

As highlighted in Section 5.2.14, economic analysis has been carried out separately for patients with platinum sensitive (PFI ≥ 6 months) and platinum resistant/refractory (PFI < 6 months) disease. In addition, as a result of the limited number of trials identified, two separate networks, of interventions and comparators outlined in the scope of this MTA, have been constructed in patients with platinum sensitive disease. Consequently, cost-effectiveness is assessed for three networks of treatment, of which, two consider a population of patients with platinum sensitive disease and one considers a population of patients with platinum resistant/refractory disease.

For each network, OS and PFS data, synthesised in NMA, are used to inform the economic model. In the absence of IPD of sufficient granularity to allow IPD NMA, these data were synthesised from summary measures, available in the literature, of relative treatment effect in the form of hazard ratios (HRs). Furthermore, although some of the clinical trials, identified for inclusion in the NMAs, reported HRs adjusted for particular baseline characteristics, unadjusted HRs are used within the NMAs and therefore economic analyses. This is because adjusted HRs were not available for all included trials, and of those trials reporting adjusted HRs, adjustments for different factors had been carried out. Therefore, the TAG considers the synthesis of unadjusted HRs to be the most equitable way to compare therapies.

Within each network, the TAG selected a baseline treatment for which monthly estimates of PFS and OS could be obtained from submitted or published Kaplan-Meier data. Where Kaplan-Meier data were incomplete (i.e., when a proportion of patients remained at risk at the end of trial follow-up), parametric survival distributions were fitted to allow extrapolation beyond the trial duration. HRs obtained from the TAG's NMAs are applied to baseline estimates of PFS and OS.

However, by using this methodology, the TAG implicitly makes three key assumptions. Firstly, that data combined within the NMAs were homogenous or, that any differences between the trials included in the analysis would not bias estimates of relative treatment effect. Secondly, that the relative effect of treatment (relative to the baseline treatment) is constant over time; namely the assumption of proportional hazards. Thirdly and perhaps most importantly, as a result of using a consistent dataset (i.e., unadjusted HRs rather than a combination of adjusted and unadjusted HRs), the methodology used assumes that estimates of relative treatment effect based on unadjusted data would not meaningfully differ from estimates of relative treatment effect based on adjusted data.

The homogeneity or otherwise, of the trials included in the TAG's NMAs was assessed from a clinical perspective. That is, baseline characteristics of key prognostic indicators were compared both within and across included trials. Where differences were identified, expert clinical advice was sought to determine the potential magnitude of impact (on estimates of relative treatment effect) that imbalances

in these characteristics was likely to have. However, statistical assessment of heterogeneity was not possible, as a result of the low number of trials identified and the predominantly linear nature of the networks constructed.

Furthermore, for each network, the pertinence of assuming that the relative effect of treatment (relative to the baseline treatment) is constant over time was investigated through assessment of the hazards (of progression or death) associated with each treatment. In particular, log-cumulative hazard (LCH) plots based on submitted or published Kaplan-Meier data were constructed and visually examined to determine the presence or absence of hazards that were proportional between treatments.

Finally, the potential impact of adjustments for baseline characteristics on estimates of relative treatment effect was assessed by considering individual trial comparisons for which HRs calculated from adjusted and unadjusted data were presented. For example, in the evidence submitted by PharmaMar as part of this MTA, OS HRs (trabectedin plus PLDH vs PLDH) calculated from unadjusted Kaplan-Meier data and from Kaplan-Meier data which adjusted for PFI (as a continuous variable), ECOG PS score, race, baseline CA-125, age, baseline liver/lung involvement and prior taxane therapy were presented; the HRs obtained from these analyses were 0.83 (95% CI: 0.67 to 1.04; p = 0.106) and 0.78 (95% CI: 0.62 to 0.98; p = 0.0319), respectively. This suggests that use of unadjusted data in the NMAs and therefore economic analyses may introduce bias into estimates of relative treatment effect. However, in the absence of consistently adjusted data for all treatments of interest the TAG is unable to account for the magnitude or direction of any bias introduced from the use of unadjusted data.

In the sections that follow, the results of the TAG's base case and sensitivity analyses are discussed. In addition, the potential impact, with respect to the magnitude and direction of bias, that may have been introduced as a result of non-proportional hazards or potential clinical heterogeneity within the network of trials informing the TAG's NMAs, is discussed.

5.2.15.1 Patients with platinum sensitive disease

For patients with platinum sensitive disease, a single network linking all the interventions and comparators of interest was not identified from the literature; instead, two independent networks were constructed. Platinum sensitive – network 1, which compared regimens containing platinum, in particular: platinum plus paclitaxel, PLDH plus platinum, gemcitabine plus carboplatin, and platinum. Platinum sensitive – network 2, which compared therapies not containing platinum, in particular: PLDH, trabectedin plus PLDH, paclitaxel and topotecan. The TAG notes that the ICERs estimated from these two networks are not comparable with each other and should be interpreted as independent analyses. Furthermore, the TAG acknowledges that the use of two independent analyses to inform this aspect of the decision problem (i.e., the comparative cost-effectiveness of treatments in patients with

platinum sensitive disease) is a limitation. However, following consultation with clinical experts, the TAG considers that the use of separate analyses for platinum and non-platinum therapies may not be unreasonable. This is because, it is generally accepted that in clinical practice, patients who are platinum sensitive and able to (and willing to) tolerate further platinum treatment would be treated with platinum. Therefore, for these patients, PS network 1 may be considered to provide information on the network of therapies most likely to be considered in clinical practice. Similarly, PS network 2, (PLDH, trabectedin plus PLDH, paclitaxel and topotecan) may be considered to provide information on the network of treatments suitable for platinum sensitive patients who are unable or unwilling to tolerate further platinum based therapy.

As a result of limited data, in particular PFS data, available for patients with partially platinum-sensitive (PFI 6-12 months) and fully platinum-sensitive (PFI > 12 months) disease, base case analyses were not carried out for these subgroups. Furthermore, the TAG notes that, identified trials which reported subgroup analyses in patients with partially and fully platinum sensitive disease were not sufficiently powered.

Platinum sensitive – network 1

Of the treatments considered in platinum sensitive – network 1 (platinum, gemcitabine plus carboplatin, paclitaxel plus platinum and PLDH plus platinum), base case probabilistic and deterministic analysis estimated that treatment with gemcitabine plus carboplatin was extendedly dominated by treatment with paclitaxel plus platinum. That is, for the additional costs associated with paclitaxel plus platinum, the additional benefit was such that paclitaxel plus platinum may be considered better value for money than treatment with gemcitabine plus carboplatin.

Probabilistic analysis of the addition of paclitaxel or PLDH to platinum therapy resulted in similar estimates of mean total costs and QALYs. However, on average, treatment with paclitaxel plus platinum appeared to offer greater benefit than treatment with PLDH plus platinum. In addition, on average, treatment with PLDH plus platinum incurred higher costs than treatment with paclitaxel plus platinum; resulting in the dominance of PLDH plus platinum by paclitaxel plus platinum in probabilistic and deterministic analysis. The ICER associated with paclitaxel plus platinum vs platinum was estimated from probabilistic analysis as £24,539.

However, the TAG considers it important to note, that expert clinical advice highlighted that increased risk of neurotoxicity as a result of prior taxane therapy means that not all patients may tolerate further treatment with paclitaxel. With this in mind, the TAG consider it important to highlight that, at a WTP threshold of £30,000, the addition of PLDH to platinum therapy was associated with a 48% likelihood of being cost-effective vs platinum monotherapy (probabilistic ICER vs platinum was estimated to be £30,188).

Furthermore, one way sensitivity analysis revealed that the relative effective of treatment on OS was the key driver of the cost-effectiveness results. However, visual inspection of the LCH plots for the outcome of OS (Appendix 10) indicated that relative to the hazard of death associated with platinum therapy, the hazard of death associated with paclitaxel plus platinum may not be proportional. In fact, the relative hazard between these treatments appears to non-monotonically decrease over time. A similar relative hazard is observed between PLDH plus platinum vs platinum monotherapy. With regards to the cost-effectiveness analysis, hazards that initially increase and then decrease over time are likely to lead to an initial underestimation of treatment effect, followed by an overestimation of treatment effect. However, it is unclear whether estimation of treatment effect will balance out over the time horizon of the economic model.

Furthermore, as discussed in Section 4.2.1.4, there exists an imbalance in baseline performance score (ECOG) within one of the trials included in the OS NMA. In particular, the trial carried out by Gonzalez-Martin *et al*., in which paclitaxel plus carboplatin is compared with platinum monotherapy; the proportion of patients with a baseline ECOG score of 2 that were randomised to treatment with platinum monotherapy was 17.9% vs 5.6% of patients randomised to treatment with paclitaxel plus carboplatin. The TAG notes that this imbalance is likely to result in an overestimation of the relative treatment effect of paclitaxel plus carboplatin vs platinum monotherapy.

In addition, the TAG notes the presence of clinical heterogeneity in the duration of PFI between trials. In particular, patients enrolled in the ICON-4 trial had a comparably longer PFI than patients enrolled in the other trials included in NMA of OS and PFS data. Similarly, a comparatively high proportion of patients enrolled in the trial carried out by Gonzalez-Martin *et al*. were diagnosed as recurrent based on assessment of CA125 levels; therefore these patients are likely to be more susceptible to platinum therapy than patients enrolled in the other included trials. However, the TAG notes that although patients in ICON-4 and Gonzalez-Martin *et al*. may be expected to experience greater benefit than patients enrolled in the other trials, the magnitude of this difference is unlikely to affect estimates of the relative effect of treatment.

For these reasons (non-proportional hazards and within trial heterogeneity) the TAG considers that it is unclear whether the relative effect of treatment with platinum monotherapy is overestimated or underestimated, particularly when compared with treatment with paclitaxel plus platinum.

Platinum sensitive – network 2

For PS network 2 (PLDH, trabectedin plus PLDH, paclitaxel and topotecan), base case probabilistic and deterministic analysis estimated that treatment with topotecan was strictly dominated by (more expensive and less effective than) treatment with PLDH. Treatment with PLDH and treatment with trabectedin plus PLDH were estimated to provide benefit over treatment with paclitaxel. The

existence of this benefit is more certain for trabectedin plus PLDH, than for PLDH. However, based on the TAG's probabilistic analysis the cost per QALY of trabectedin plus PLDH vs paclitaxel is £54,893 and the ICER associated with trabectedin vs PLDH is £81,353. Whereas the ICER associated with PLDH versus paclitaxel is £25,931.

The key driver of the cost-effectiveness results in PS – network 2 was identified in one-way sensitivity analysis as the relative effect of treatment on OS. As discussed above, the relative effect of treatment on OS has been estimated in NMA under the assumptions of proportional hazards and homogeneity of included trials. However, as a result of the absence of Kaplan-Meier data, it was not possible to construct LCH plots examining the hazards of OS associated with PLDH vs paclitaxel; therefore, the proportionality or otherwise of these hazards is unknown. Furthermore, as a result of insufficient reporting, the TAG was not able to assess the baseline characteristics of included trials; trials were generally carried out in a mixed population of patients with platinum resistant or platinum sensitive disease, therefore, baseline characteristics were not disaggregated by the subgroups of platinum sensitivity.

The TAG consider it important to highlight that the manufacturer of trabectedin, PharmaMar, submitted an analysis considering the head-to-head comparison of trabectedin plus PLDH vs PLDH based on clinical effectiveness data that had been adjusted for baseline characteristics. Of particular importance within this analysis was the adjustment of PFS and OS data using PFI as a continuous variable. Following consultation with clinical experts, the TAG considers the use of adjusted data, in particular data adjusting for PFI as a continuous variable, to be appropriate. This is because, platinum sensitivity, as indicated by PFI, is a continuum related to the prognosis of the patient. That is, the longer the PFI, the more favourable the patient's prognosis is. The ICER of trabectedin plus PLDH versus PLDH, estimated by the manufacturer, is £27,573 (including PAS [Section 5.1.3]).

However, as discussed in Section 6.1.3, previous appraisal of the manufacturer's model, by the ERG responsible for critical appraisal of the evidence submitted as part of TA222, highlighted limitations associated with the model used; in particular, the difficulty in applying discounting. Therefore, in order to assess the impact of using adjusted survival estimates within the TAG's economic model, and to assess the validity of the manufacturer's ICER, the TAG carried out a head-to-head comparison of trabectedin plus PLDH vs PLDH. That is, adjusted PFS and OS data presented within the manufacturer's model were used in the TAG's model; costs, utilities and discounting applied within the TAG's model were not altered. The ICER of trabectedin plus PLDH vs PLDH, estimated by the TAG's scenario analysis, is £35,646. Following inspection of the manufacturer's model, the TAG notes that the difference in ICERs between the TAG's scenario and manufacturer's base case analyses is likely to be a result of the method with which discounting is applied. The TAG considers that the method used in TAG analysis is likely to be more accurate as a result of a model structured around

monthly rather than mean estimates of PFS and OS. However, as efficacy data used in the TAG's base case model was unadjusted (to provide a consistent dataset), the TAG notes that the head-to-head ICER generated from using adjusted efficacy data is not comparable with ICERs estimated for other treatments in the TAG's base case analyses

5.2.15.2 Patients with platinum resistant/refractory disease

The network of interventions and comparators considered for the platinum resistant/refractory subgroup was limited by the availability of data to three of the therapies, paclitaxel, PLDH and topotecan, outlined in the scope. However, based on expert clinical opinion, that the prognosis of patients with platinum resistant/refractory disease is often poor across available treatment options, a sensitivity analysis assuming equivalent efficacy between all treatments was carried out. Sensitivity analysis estimated that treatment with etoposide resulted in the lowest overall cost. However, the TAG notes that the cost associated with BSC may have been overestimated as only patients requiring strong opioid treatment were accounted for in the cost calculations.

Platinum resistant/refractory network

Of the treatments considered in the platinum resistant/refractory network base case probabilistic and deterministic analysis estimated that treatment with paclitaxel is strictly dominated by treatment with PLDH. However, probabilistic analysis estimated that the ICER of topotecan vs PLDH as £324,188, with 0% probability of being cost-effective at WTP of £30,000. Furthermore, the costs and QALYs associated with paclitaxel are similar to those associated with PLDH, with paclitaxel being dominated by PLDH in 39% of probabilistic simulations. As highlighted for patients with platinum sensitive disease, increased risk of neurotoxicity following prior taxane therapy means that not all patients may tolerate further treatment with paclitaxel.

One way sensitivity analysis revealed that the relative effective of treatment on OS was the key driver of the cost-effectiveness results. Assessment of the LCH plots for the outcome of OS (Appendix 10) indicated that the hazard of death associated with topotecan is generally proportional to the hazard of death associated with PLDH. However, as a result of the absence of Kaplan-Meier data, it was not possible to construct LCH plots examining the hazards of OS associated with paclitaxel vs PLDH; therefore, the proportionality or otherwise of these hazards is unknown. Furthermore, as a result of insufficient reporting, the TAG was not able to assess the baseline characteristics of included trials; trials were generally carried out in a mixed population of patients with platinum resistant or platinum sensitive disease, therefore, baseline characteristics were not disaggregated by the subgroups of platinum sensitivity.

6 ASSESSMENT OF FACTORS RELEVANT TO THE NHS AND OTHER PARTIES

6.1 End of life criteria

Tables 146 to 148 assess the treatments against the NICE end of life criteria, by network. The TAG considers that it is likely that the criteria for end of life have not been met by any treatment. For the platinum sensitive networks (platinum sensitive network 1 and platinum sensitive network 2) life expectancy for the baseline treatments are estimated by the TAG to be greater than 24 months. For the platinum resistant population, no evaluable treatment offers a survival gain of greater than three months.

Table146. Assessment of treatments in platinum sensitive network 1 against NICE end of life criteria

	Gemcitabine plus carboplatin	**Paclitaxel plus platinum**	**PLDH plus platinum**
Life expectancy on current standard care <24 months	Mean OS for platinum monotherapy estimated from the TAG *de novo* analysis to be approximately 34 months. Median OS for platinum monotherapy estimated from the TAG *de novo* analysis to be approximately 30 months.		
Treatment provides extension to life expectancy compared to current standard care of >3 months	Mean OS estimated by TAG to be 35 months; gain in estimated mean OS < 1 month Median OS estimated by TAG to be 30 months; no gain in estimated median OS.	Mean OS estimated by TAG to be 38 months; gain in estimated mean OS > 4 months Median OS estimated by TAG to be 35 months; gain in estimated median OS of approximately 5 months.	Mean OS estimated by TAG to be 38 months; gain in estimated mean > 4 months Median OS estimated by TAG to be 34 months; gain in estimated median OS of approximately 4 months.
The treatment is licensed or otherwise indicated for small populations	The incident population with platinum sensitive disease was estimated by the manufacturer for trabectedin to be 2,617 (Table 102); however, this population does not include prevalent patients who relapse or take into account multiple relapses that may increase the number of treatable patients. The TAG estimates that including prevalent patients who may relapse and require treatment, would result in approximately 3,379 patients.		
The estimates of the extension to life are robust	The HR for OS versus platinum monotherapy was estimated by the TAG to be non-statistically significant. Therefore, the extension to life may not be considered to be robust	The HR for OS versus platinum monotherapy was estimated by the TAG to be statistically significant. Therefore, the extension to life may be considered to be robust	The HR for OS versus platinum monotherapy was estimated by the TAG to be statistically significant. Therefore, the extension to life may be considered to be robust
Overall assessment	All criteria not met Current life expectancy >24 months; gain in OS <3 months; gain in OS not statistically significant	All criteria not met Current life expectancy >24 months	All criteria not met Current life expectancy >24 months
Abbreviations used in table: HR, hazard ratio; OS, overall survival; PLDH, pegylated liposomal doxorubicin hydrochloride; TAG, Technology Assessment Group.			

Table 147. Assessment of treatments in platinum sensitive network 2 against NICE end of life criteria

	PLDH	Topotecan	Trabectedin plus PLDH
Life expectancy on current standard care <24 months	Mean OS for paclitaxel estimated from the TAG *de novo* analysis to be approximately 26 months. Median OS for paclitaxel estimated from the TAG *de novo* analysis to be approximately 21 months.		
Treatment provides extension to life expectancy compared to current standard care of >3 months	Mean OS estimated by TAG to be 29 months; gain in estimated mean OS approximately 3 months Median OS estimated by TAG to be 25 months; gain in estimated median OS of approximately 4 months.	Mean OS estimated by TAG to be 25 months; reduction in estimated mean OS Median OS estimated by TAG to be 19 months; reduction in estimated median OS.	Mean OS estimated by TAG to be 32 months; gain in estimated mean > 6 months versus paclitaxel (approximately 3 months vs PLDH) Median OS estimated by TAG to be 28 months; gain in estimated median OS of approximately 7 months (approximately 3 months vs PLDH).
The treatment is licensed or otherwise indicated for small populations	The incident population with platinum sensitive disease was estimated by the manufacturer for trabectedin to be 2,617 (Table 102); however, this population does not include prevalent patients who relapse or take into account multiple relapses that may increase the number of treatable patients. The TAG estimates that including prevalent patients who may relapse and require treatment, would result in approximately 3,379 patients. The number of eligible patients may be greater than this if multiple relapses are taken into account. The TAG notes that the manufacturer for trabectedin is requesting consideration for a subset of this population, and the manufacturer estimates the patient population to be 491 in 2014. The TAG considers that this number is likely to be an underestimate if prevalent and multiple relapses were taken into consideration.		
The estimates of the extension to life are robust	The HR for OS versus paclitaxel monotherapy was estimated by the TAG to be non-statistically significant. Therefore, the extension to life may not be considered to be robust	N/A	The HR for OS versus platinum monotherapy or PLDH monotherapy was estimated by the TAG to be non-statistically significant. Therefore, the extension to life may not be considered to be robust
Overall assessment	All criteria not met Current life expectancy >24 months; gain in OS not statistically significant	All criteria not met Current life expectancy >24 months; no gain in OS	All criteria not met Current life expectancy >24 months; gain in OS not statistically significant
Abbreviations used in table: HR, hazard ratio; OS, overall survival; PLDH, pegylated liposomal doxorubicin hydrochloride; TAG, Technology Assessment Group.			

Table 148. Assessment of treatments in the platinum resistant/refractory network against NICE end of life criteria

	Paclitaxel	**Topotecan**
Life expectancy on current standard care <24 months	Mean OS for PLDH estimated from the TAG *de novo* analysis to be approximately 18.5 months. Median OS for PLDH estimated from the TAG *de novo* analysis to be approximately 14 months.	
Treatment provides extension to life expectancy compared to current standard care of >3 months	Mean OS estimated by TAG to be 18 months; reduction in estimated mean OS. Median OS estimated by TAG to be 14 months; no gain in estimated median OS	Mean OS estimated by TAG to be 19 months; gain in mean OS <1 months Median OS estimated by TAG to be 15 months; gain in estimated median OS of approximately 1 month.
The treatment is licensed or otherwise indicated for small populations	The incident population with recurrent advanced ovarian cancer was estimated by the manufacturer for trabectedin to be 3,272 (Table 102); given that the manufacturer estimated that 80% of these patients would be platinum sensitive disease, this implies that 20% patients would have platinum resistant refractory disease approximately 654 patients. However, this population does not include prevalent patients who relapse or take into account multiple relapses that may increase the number of treatable patients. The TAG estimates that including prevalent patients who may relapse and require treatment, would result in approximately 845 patients.	
The estimates of the extension to life are robust	N/A	The HR for OS versus PLDH monotherapy was estimated by the TAG to be non-statistically significant. Therefore, the extension to life may not be considered to be robust
Overall assessment	All criteria not met No gain in OS	All criteria not met Gain in OS <3 months; gain in OS not statistically significant
Abbreviations used in table: HR, hazard ratio; OS, overall survival; PLDH, pegylated liposomal doxorubicin hydrochloride; TAG, Technology Assessment Group.		

7 DISCUSSION

The systematic review of clinical effectiveness evidence carried out to address the decision problem that is the focus of this MTA identified 16 randomised controlled trials (RCTs), evaluating 14 pair wise comparisons. Furthermore, 21 economic evaluations considering patients with recurrent ovarian cancer were identified in the TAG's review of the economic literature. However, the scope of the evidence identified was insufficient to fully address the decision problem; therefore, where possible the TAG has carried out synthesis of the evidence within network meta-analyses and *de novo* economic analyses.

Following consideration of the data identified and consultation with clinical experts, separate analyses have been carried out for patients with platinum sensitive disease (platinum free interval [PFI] ≥6 months) and platinum resistant/refractory disease (PFI <6 months). The identified RCTs facilitated the construction of three distinct networks for the outcomes of overall survival (OS) and progression-free survival (PFS), two of which considered patients with platinum sensitive disease; the remaining network considered patients with disease that is platinum-resistant/refractory. As the systematic review was conducted in such a way as to identify all trials with at least one intervention of interest, a wider selection of treatments were assessed, but unfortunately this did not uncover trials that could link the disconnected networks, in patients with platinum sensitive disease, together. Furthermore, due to time constraints, the decision was taken not to search for non-randomised trials.

The two networks constructed in patients with platinum sensitive disease were, platinum sensitive – network 1, which compared regimens containing platinum, in particular: platinum plus paclitaxel, PLDH plus platinum, gemcitabine plus carboplatin, and platinum alone. Platinum sensitive – network 2, which compared non-platinum based therapies, in particular: PLDH, trabectedin plus PLDH, paclitaxel and topotecan.

7.1 Statement of main findings

Patients with platinum sensitive disease

OS and PFS data were identified for eight and seven different head-to-head comparisons of interventions and comparators of interest, respectively. Of these, three reported a statistically significant difference in OS between the treatments considered. In particular, Parmar *et al*. reported a statistically significant difference in OS between paclitaxel plus platinum vs conventional platinum treatment (HR [95% CI]: 0.82 [0.69 to 0.97]), observed in the ICON4/AGO-OVAR trial. Gonzalez Martin *et al.* reported a statistically significant difference between paclitaxel plus carboplatin vs carboplatin alone (HR [95% CI]: 0.31 [0.14 to 0.68]) and Gordon *et al*. present a statistically

significant difference between PLDH and topotecan (HR [95% CI]: 1.43 [1.07 to 1.92]). Six of the identified head-to-head comparisons identified a statistically significant difference in PFS. These were:

- CALYPSO: PLDH plus carboplatin vs paclitaxel plus carboplatin (HR [95% CI]: 0.82 [0.72 to 0.94]);
- ICON4/AGO-OVAR 2.2: Paclitaxel plus platinum vs conventional platinum treatment (HR [95% CI]: 0.76 [0.66 to 0.89]);
- Gonzalez Martin *et al*.: Paclitaxel plus carboplatin vs carboplatin alone (HR [95% CI]: 0.54 [0.32 to 0.92]);
- Alberts *et al*.: PLDH plus carboplatin vs carboplatin alone (HR [95% CI]: 0.54 [0.32 to 0.93]);
- OVA-301: Trabectedin plus PLDH vs PLDH (HR [95% CI]: 0.73 [0.56 to 0.95]);
- Pfisterer *et al*.: Gemcitabine plus carboplatin vs carboplatin alone (HR [95% CI]: 0.72 [0.58 to 0.90]).

In the NMA evaluating platinum-based chemotherapies, PLDH plus carboplatin and paclitaxel plus carboplatin were found to significantly improve OS compared with platinum monotherapy. However, no statistically significant differences in OS were identified between the remaining treatments considered in the network. When compared with platinum monotherapy, PFS was estimated to significantly improve in patients treated with paclitaxel plus carboplatin, gemcitabine plus carboplatin or PLDH plus carboplatin. In addition a statistically significant difference in PFS was estimated for paclitaxel plus carboplatin vs PLDH plus carboplatin.

NMA of non-platinum based therapies indicated that PLDH monotherapy and trabectedin plus PLDH are both significantly more effective at prolonging OS than topotecan monotherapy. No other significant OS differences were identified. Analysis of non-platinum-based regimens indicates that trabectedin plus PLDH statistically significantly improves PFS compared with PLDH, paclitaxel and topotecan when given as monotherapies. No statistically significant differences were identified among the monotherapies evaluated (PLDH, topotecan, and paclitaxel).

Overall response rate (ORR) was reported for eleven different head-to-head comparisons of interventions and comparators of interest. Of these, only two were statistically significant: trabectedin plus PLDH vs PLDH from OVA-301 (OR [95% CI]: 1.57 [1.04 to 2.35]); gemcitabine plus carboplatin vs carboplatin alone from Pfisterer *et al*. (OR [95% CI]: 1.527 [1.025 to 2.275]).

Based on the trials identified, it was not possible to construct a complete network informing relative ORR. Akin to analyses of OS and PFS, two discrete networks were generated, one evaluating platinum-based therapies (paclitaxel plus carboplatin, gemcitabine plus carboplatin, PLDH plus carboplatin and platinum monotherapy) and the second comparing non-platinum-based regimens

(PLDH, trabectedin plus PLDH, topotecan (intravenous), paclitaxel (every 3 weeks), topotecan (oral) and paclitaxel weekly).

In the network evaluating platinum-based chemotherapies, paclitaxel plus carboplatin and gemcitabine plus carboplatin were found to have a significantly higher ORR than platinum monotherapy. There was no significant difference between PLDH plus carboplatin vs any of the chemotherapeutic treatments assessed. Analysis of non-platinum-based regimens indicates that trabectedin plus PLDH significantly improves ORR compared with PLDH, and oral topotecan. Compared with oral topotecan, intravenous topotecan was found to be associated with a significant increase in the proportion of patients achieving CR or PR. No other statistically significant differences were identified.

Probabilistic economic analyses of platinum sensitive – network 1 indicated that treatment with gemcitabine plus platinum was extendedly dominated by treatment with paclitaxel plus platinum. That is, for the additional costs associated with paclitaxel plus platinum, the additional benefit was such that paclitaxel plus platinum may be considered better value for money than treatment with gemcitabine plus platinum.

Furthermore, the addition of paclitaxel or PLDH to platinum therapy resulted in similar estimates of mean total costs and QALYs. However on average PLDH plus platinum was strictly dominated by (more expensive and less effective than) paclitaxel plus platinum. However, the increased risk of neurotoxicity as a result of prior taxane therapy means that not all patients may tolerate further treatment with paclitaxel. The ICERs associated with paclitaxel plus platinum vs platinum and PLDH plus platinum vs platinum are £24,539 and £30,188, respectively.

In platinum sensitive – network 2, probabilistic economic analysis estimated that topotecan was strictly dominated by treatment with PLDH. In addition, treatment with PLDH and treatment with trabectedin plus PLDH were estimated to provide benefit over treatment with paclitaxel. However, based on the TAG's probabilistic analysis the ICER associated with trabectedin plus PLDH vs paclitaxel is £54,893 and the ICER associated with trabectedin vs PLDH is £81,353. Whereas the ICER associated with PLDH versus paclitaxel is £25,931.

However, the TAG considers it important to note that head-to-head comparison of trabectedin plus PLDH vs PLDH, submitted by PharmaMar, estimated the ICER of trabectedin plus PLDH vs PLDH as £27,573 (including PAS). This analysis was based on adjusted efficacy data, adjusted for, amongst other factors, PFI as a continuous variable. When efficacy data from the manufacturer's model were used in the TAG's model, the head-to-head ICER became £35,646. The TAG notes that the discrepancy in ICERs (between the manufacturer's and the TAG's analyses) is likely to be a result of

the different methodologies used in the application of discounting. Furthermore, the TAG considers that the method used in TAG analysis is likely to be more accurate as a result of a model structured around monthly rather than mean estimates of PFS and OS. Moreover, the TAG considers that the ICER of £35,646 estimated using adjusted data is more likely to represent the cost-effectiveness of trabectedin plus PLDH vs PLDH. However, as efficacy data used in the TAG's base case model was unadjusted (to provide a consistent dataset), the TAG notes that the head-to-head ICER generated from using adjusted efficacy data is not comparable with ICERs estimated for other treatments in the TAG's base case analyses.

Patients with platinum resistant/refractory disease

OS and PFS data were reported for five and four different head-to-head comparisons in PRR patients, respectively. Two RCTs enrolled only patients with PRR, with the remaining RCTs reporting results from a subgroup of patients within the trial. None of the trials identified a significant difference in OS or PFS between the two treatment groups evaluated. Furthermore, no statistically significant differences in ORR were reported in the eight different head-to-head comparisons involving PRR patients. Similarly, no statistically significant differences in OS or PFS were identified in NMA of treatment with paclitaxel, PLDH and topotecan. However, NMA of ORR estimated that PLDH significantly increased ORR compared with paclitaxel (175 mg/m^2) every 21 days and with an alternative regimen in which paclitaxel was given weekly at a dose of 67 mg/m^2. PLDH monotherapy was also significantly more effective than an unconventional regimen of topotecan in which topotecan was administered weekly at a dose of 4 mg/m^2.

Probabilistic economic analysis estimated that similar costs and QALYs were accrued from treatment with PLDH and treatment with paclitaxel; however, on average treatment with PLDH was dominated by treatment with paclitaxel. As highlighted for patients with platinum sensitive disease, increased risk of neurotoxicity following prior taxane therapy means that not all patients may tolerate further treatment with paclitaxel.

7.2 Strengths and limitations of the assessment

Strengths

- The evidence used to inform the decision problem that is the focus of this MTA has been identified following the general principles published by the Centre for Reviews and Dissemination (CRD).
- The methods used for the NMA followed the guidance described in the NICE Decisions Support Unit's (DSU's) Technical Support Documents (TSDs) for Evidence Synthesis.
- Economic analyses have been carried out in accordance with NICE guide to methods of technology appraisal, ISPOR guidance and where possible, recommendations made by NICE DSU have been adhered to.

- The economic model used to provide a framework for analysis has been widely used in the indication that is the focus of this MTA. In addition, amendments to the structure based on previous critiques have been made.
- Expert clinical input has been sought and received throughout the project, in particular with respect to assumptions made in clinical and economic analyses and the face validity of final results and conclusions.

Weaknesses

The key weaknesses of the evidence synthesis used to address the decision problem are related to the limitations of the data available from the literature.

- The absence of data linking the networks of treatment identified in patients with platinum sensitive disease prevented consistent appraisal of the clinical and cost-effectiveness of therapies of interest to patients with platinum sensitive disease.
- Limited data available for treatments of interest to patients with platinum resistant/refractory disease led to assessment of the clinical and cost-effectiveness of a subset of therapies of interest.
- Clinical heterogeneity identified within the Gonzalez-Martin *et al.* trial included in NMA of platinum sensitive – network 1 may have introduced bias into the estimates of relative treatment effect.
- The use of clinical effectiveness data unadjusted for key prognostic indicators such as the PFI (measured continuously) may have introduced bias into the relative estimates of treatment effectiveness estimated from NMAs. Confounding from the use of post-progression therapy may have introduced bias into relative estimates of OS benefit. In particular, in trials in which all patients cross over to the alternative group after progression or in trials in which the "new" therapy is available as a post-progression treatment in the control group. The assumption of proportional hazards may have introduced bias into clinical and economic analyses.

7.3 Uncertainties

The magnitude and direction of potential bias introduced from use of unadjusted clinical effectiveness data, the assumption of proportional hazards and the potential clinical heterogeneity amongst trials included within the NMAs is uncertain. However, based on expert clinical opinion the TAG considers that the trials included in NMA were sufficiently homogenous to facilitate the comparison of the clinical effectiveness of treatments. Furthermore, the TAG considers that the identified heterogeneity is unlikely to significantly impact estimates of relative treatment effect.

As a result of the absence of Kaplan-Meier data, the validity or otherwise of the assumption of proportional hazards is unknown for all comparisons considered in clinical and economic analysis. However, for the treatments identified in platinum sensitive – network 1, the TAG think it is likely that underestimates and overestimates of the relative effect of treatment may balance out over the time horizon of the economic model.

7.4 Other relevant factors

Based on criteria outlined by NICE, the TAG considers that none of the treatments identified within the scope of this MTA are eligible for consideration as end-of-life treatments.

8 CONCLUSIONS

8.1 Suggested research priorities

Provided that this was thought to be of interest to the wider clinical community, randomised controlled trial evidence comparing platinum containing regimens with non-platinum containing regimens should be sought. Furthermore, RCT evidence of the efficacy of etoposide and best supportive care in patients with resistant/refractory disease may be desirable.

Assessment of the impact of treatments on patient quality of life may be of interest to the wider clinical community, particularly in patients with resistant/refractory disease.

Future trials in recurrent ovarian cancer should endeavour to carry out analysis on patient level data that has been adjusted for a consistent array of variables; of particular importance is the adjustment of clinical effectiveness data for platinum free interval (measured as a continuous rather than categorical variable).

Further research into the cost of best supportive care for women with ovarian cancer may also be warranted.

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10 APPENDICES

Appendix 1. Literature search strategies

Clinical searches

OVID MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to present (initially searched 18 January 2013 and updated 23 May 2013)

#	Term
1	exp ovarian neoplasms/
2	(ovar$ adj4 (cancer$ or tumo?r$ or malignan$ or oncolog$ or carcinoma$ or neoplas$ or mass$ or growth$ or cyst$)).mp.
3	(adenexa$ adj4 mass$).mp.
4	1 or 2 or 3
5	exp Topotecan/
6	topotecan.mp.
7	(hycam$ or potactasol).mp.
8	exp Doxorubicin/
9	(doxorubicin hydrochloride or doxorubicin hcl).mp.
10	liposomal doxorubicin.mp.
11	liposome encapsulated doxorubicin.mp.
12	doxil.mp.
13	caelyx.mp.
14	exp Paclitaxel/
15	paclitaxel.mp.
16	taxol.mp.
17	trabectedin.mp.
18	yondelis.mp.
19	gemcitabine.mp.
20	gemzar.mp.
21	or/5–20
22	4 and 21
23	Randomized Controlled Trials as Topic
24	randomized controlled trial
25	Random Allocation
26	Double Blind Method/
27	Single Blind Method/
28	clinical trial/
29	clinical trial, phase i.pt.
30	clinical trial, phase ii.pt.
31	clinical trial, phase iii.pt.
32	clinical trial, phase iv.pt.
33	controlled clinical trial.pt.
34	randomized controlled trial.pt.
35	multicenter study.pt.
36	clinical trial.pt.
37	exp Clinical Trials as topic/
38	(clinical adj trial$).tw.
39	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.
40	PLACEBOS/
41	placebo$.tw.
42	randomly allocated.tw.
43	(allocated adj2 random$).tw.
44	or/23–43
45	case report.tw.
46	letter/ (795094)
47	historical article
48	45 or 46 or 47

49	44 not 48
50	22 and 49

OVID: EMBASE (searched from inception to 18 January 2013 and updated 23 May 2013)

#	Term
1	exp ovary cancer
2	(ovar$ adj4 (cancer$ or tumo?r$ or malignan$ or oncolog$ or carcinoma$ or neoplas$ or mass$ or growth$ or cyst$)).mp.
3	(adenexa$ adj4 mass$).mp.
4	1 or 2 or 3
5	exp topotecan/
6	topotecan.mp.
7	(hycam$ or potactasol).mp.
8	exp doxorubicin/
9	(doxorubicin hydrochloride or doxorubicin hcl).mp.
10	liposomal doxorubicin.mp.
11	liposome encapsulated doxorubicin.mp.
12	doxil.mp.
13	caelyx.mp.
14	exp paclitaxel/
15	paclitaxel.mp.
16	taxol.mp.
17	exp trabectedin/
18	trabectedin.mp.
19	yondelis.mp.
20	exp gemcitabine/
21	gemcitabine.mp.
22	gemzar.mp.
23	or/5–22
24	4 and 23
25	Clinical trial/
26	Randomized controlled trial/
27	Randomization/
28	Single blind procedure/
29	Double blind procedure/
30	Crossover procedure/
31	Placebo/
32	Randomi?ed controlled trial$.tw.
33	Rct.tw.
34	Random allocation.tw.
35	Randomly allocated.tw.
36	Allocated randomly.tw.
37	(allocated adj2 random).tw.
38	Single blind$.tw.
39	Double blind$.tw.
40	((treble or triple) adj blind$).tw.
41	Placebo$.tw.
42	Prospective study/
43	or/25–42
44	Case study/
45	Case report.tw.
46	Abstract report/ or letter/
47	44 or 45 or 46
48	43 not 47
49	24 and 48

Cochrane Controlled Trials Register (initially searched 18 January 2013 and updated 23 May 2013)

#	Term
1	OVARIAN NEOPLASMS explode all trees (MeSH)
2	(ovar* near cancer*)
3	(ovar* near tumor*)
4	(ovar* near tumour*)
5	(ovar* near malignan*)
6	(ovar* near oncolog*)
7	(ovar* near carcinoma)
8	(ovar* near neoplas*)
9	(ovar* near mass*)
10	(ovar* near growth*)
11	(ovar* near cyst*)
12	(adenexa* near mass*)
13	(#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12)
14	TOPOTECAN explode all trees (MeSH)
15	(topotecan or hycamtin or hycamptamine or potactasol)
16	(#14 or #15)
17	DOXORUBICIN explode all trees (MeSH)
18	(doxil or (doxorubicin next hydrochloride) or (doxorubicin next hcl))
19	(liposomal next doxorubicin)
20	(caelyx or adriamycin or rubex)
21	(liposome next encapsulated next doxorubicin)
22	(#17 or #18 or #19 or #20 or #21)
23	PACLITAXEL explode all trees (MeSH)
24	(paclitaxel or taxol or taxotere or abraxane)
25	(#23 or #24)
26	(trabectedin or yondelis or ecteinascidin or ET-743 or ecteinascidin 743)
27	(gemcitabine or gemzar)
28	(#16 or #22 or #25 or #26 or #27)
29	(#13 and #28)

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP®) (initially searched 18 January 2013 and updated 23 May 2013)

Field	Term
Substance:	Topotecan or paclitaxel or pegylated liposomal doxorubicin hydrochloride, trabectedin or gemcitabine
Medical condition:	Ovarian cancer
Status of study:	Planned; ongoing; finalised
No limits placed on:	Study type
	Coordinating entity of study
	Research network
	Population age
	Scope of study

Appendix 2. Data abstraction

Data abstraction of clinically relevant details from included studies

Alberts *et al*.[20]

Item	Details
Study	Alberts *et al*.
Location	USA (number of institutions not reported)
Trial sponsor	Grant awarded by the National Cancer Institute and supported in part by Ortho Biotech
Patient enrolment	Between August 2002 and December 2004

Trial design	Phase II (initially designed as Phase III but deemed to be Phase II due to low patient accrual), randomised controlled trial with an active control Level of masking is unclear	
Line of therapy	Second line (all)	
Inclusion criteria	• Histologically diagnosed Stage III or IV disease consistent with epithelial carcinoma of the ovary, peritoneal carcinoma or mixed mullerian tumours; • Relapse or progression of disease within 6–24 months of completing front-line platinum-based chemotherapy (either single agent or combination therapy); • Progressive disease according to RECIST criteria or GCIG CA125 progression criteria; • Performance status of 0–1 by Zubrod; • Consolidation therapy (i.e., up to 12 courses of non-platinum containing, continuing chemotherapy or biological therapy following first-line platinum-based chemotherapy) during the 6–24 month progression-free and platinum-free interval was allowed, provided it was completed at least 28 days prior to registration; • Surgical debulking for recurrent/progressive disease was allowed with recovery from side effects prior to registration; • No prior cumulative anthracycline (e.g., doxorubicin, daunorubicin, epirubicin) dose in excess of 240 mg/m^2 and no prior therapy with PLDH; • No prior abdominopelvic irradiation; • Free from class 2 or greater cardiac problems as defined by New York Heart Association Criteria; • No evidence of active or uncontrolled infection; • No known brain metastases, severe gastrointestinal symptoms or grade 2 or greater sensory neuropathy per CTC 2.0 criteria at the time of registration.	
Exclusion criteria	None in addition to above	
Outcomes reported	OS, PFS, tumour response, and toxicity	
Subgroups	None	
Stratification	Disease measurability, number of disease sites and serous histology	
Measure of disease response or progression	Objective response and disease progression were defined according to standard RECIST criteria. GCIG CA125 progression criteria were also implemented in defining disease progression.	
Ethnicity	Not reported	
Disease classifications according to platinum sensitivity	All platinum sensitive (PFI 6–24 months)	
Other definitions	OS, PFS, and confirmed response rate not defined	
Treatment	**Intervention: PLDH + carboplatin**	**Comparator: Carboplatin alone**
Randomised, n	31	30
Withdrawals, n (%)	Not reported	Not reported
Treatment	Intravenous infusion: PLDH 30 mg/m^2 as a 1 hr IV infusion plus carboplatin (AUC 5 mg/mL × min) administered over a minimum of 15 minutes every 4 weeks	Carboplatin alone (AUC 5 mg/mL × min) administered over a minimum of 15 minutes every 4 weeks
Treatment duration	Median number of cycles: 7 (range 1–18)	Median number of cycles: 6 (range 2–16)
Treatment discontinuation	Treatment was given until progression, intolerable toxicity or physician/patient desire for removal from study. The maximum cumulative dose allowed for PLDH was 600 mg/m^2. Any patient with a compromised left ventricular ejection fraction (<45% or decreases by a relative 20% from baseline) was removed from PLDH and continued on the carboplatin treatment. For PPE or stomatitis and bilirubin toxicity a dose reduction schedule was created based on grade and previous history in order to minimize this side effect.	Treatment was given until progression, intolerable toxicity or physician/patient desire for removal from study. Patients with persistently greater than equal to grade 2 peripheral neuropathy, despite dose reduction, were permanently taken off carboplatin treatment

	For all other grade 3 and 4 events, PLDH was withheld for up to 4 weeks until the toxicity resolved to less than or equal to a grade 2, after which treatment resumed at a one-level dose reduction (level −1 = 25 mg/m^2, level −2 = 20 mg/m^2). If treatment was delayed greater than 4 weeks PLDH was permanently discontinued. Patients with persistently greater than equal to grade 2 peripheral neuropathy, despite dose reduction, were permanently taken off carboplatin treatment	
Concomitant medications	Prophylactic use of G-CSF or GM-CSF was not allowed, but was allowed to treat neutropenia according to ASCO guidelines	
Duration of follow up	Median 22.4 months	
Baseline patient characteristics		
Age, years (range)	Median 66.9 (range 43–87)	Median 62.5 (range 31–80)
Previous treatment	Not reported	Not reported
Duration of platinum-free interval	Median 430 (range 253–774) days Proportion with PFI >365 days: 57%	Median 382 (range 192–790) days Proportion with PFI >365 days: 57%
Prior chemotherapy, n (%) One regimen	 31 (100%)	 30 (100%)
Primary site of disease	Not reported	
Number of sites of lesions, n (%) ≤2 ≥3	 24 (77%) 7 (23%)	 22 (73%) 8 (27%)
Histologic type, n (%) Serous Non-serous (not broken down further)	 25 (81%) 6 (19%)	 25 (83%) 5 (17%)
Histologic grade	Not reported	
Tumour size, cm	Not reported	
Disease measurability Measurable disease Elevated CA125 Other non-measurable disease	 19 (61%) 4 (13%) 8 (26%)	 20 (67%) 2 (7%) 8 (27%)

FIGO stage at diagnosis	Not reported	
Performance status	Zubrod Performance Status at Study Entry	
0	20 (65%)	16 (53%)
1	11 (35%)	14 (47%)
Comments	Study closed early because of slow patient accrual	
Abbreviations used in table: ASCO, American Society of Clinical Oncology; AUC, area under curve; GCIG, Gynecologic Cancer InterGroup; GSCF, granulocyte colony-stimulating factor; GMCSF, granulocyte-macrophage colony-stimulating factor; IV, intravenous; OS, overall survival; PFI, platinum-free interval; PFS, progression-free survival; PLDH, pegylated liposomal doxorubicin hydrochloride; PPE, palmar–plantar erythrodysaesthesia; RECIST, Response Evaluation Criteria for Solid Tumors.		

Bafaloukos *et al*.[26]

Item	Details
Study	Bafaloukos *et al*.
Location	Greece; number of institutions not reported
Trial sponsor	Not reported
Patient enrolment	Between October 1999 and December 2005
Trial design	Phase II, randomised controlled trial with an active control Level of masking unclear
Line of therapy	Predominantly second line
Inclusion criteria	• Women ≥18 years old; • Histologically confirmed recurrent ovarian cancer; • ≥6 months after platinum-based chemotherapy; • Bidimensionally measurable disease or only elevated serum tumour marker CA125 (≥twice the upper limit of normal); • ECOG performance status 0–2; • Life expectancy of at least 3 months; • Adequate bone marrow, hepatic and renal functions
Exclusion criteria	• History of malignancy other than completely excised in situ carcinoma of the cervix or basal carcinoma of the skin; • Prior or recurrent central nervous system metastases; • Serious cardiac disease; • Other serious medical illness; • Inability to comply with the treatment plan and follow-up visits; • Residual neurotoxicity from previous platinum and/or taxane chemotherapy
Outcomes reported	Primary endpoints: RR and toxicity of the two treatment regimens Secondary endpoints: TTP and OS.
Subgroups	None
Stratification	No stratification criteria applied at randomisation
Measure of disease response or progression	WHO criteria for those with measurable disease and CA125 according to Rustin's criteria for those without measurable disease
Ethnicity	Not reported
Disease classifications according to platinum sensitivity	Platinum-sensitive: patients with ovarian cancer relapsing ≥6 months after first-line platinum based therapy
Other definitions	OS was estimated from the initiation of treatment to the date of last follow-up or until the patient's death. TTP was calculated from the initiation of treatment to the first disease progression

Treatment	Intervention: PLDH plus carboplatin	Comparator: Paclitaxel plus carboplatin
Randomised, n	93	96
Withdrawals, n (%)	20 (21.5%)	24 (25%)
Treatment	Intravenous infusion: PLDH 45 mg/m^2 as a 90 min IV infusion followed by carboplatin AUC 5	Intravenous infusion: Paclitaxel 175 mg/m^2 as a 3 h IV infusion followed by carboplatin at an AUC 5, on day 1
Treatment duration	Median number of cycles: 6 (range 1–8) Median length per cycle: 28 days	Median number of cycles: 6 (range 1–9) Median length per cycle: 21 days
Treatment discontinuation	Maximum of 2 weeks delay was allowed for toxicity and treatment was discontinued if longer toxicity-related delays occurred. In cases of prolonged neutropenia (>7 days with ANC <0.5 × 109/L) despite G-CSF use or febrile neutropenia, a 25% dose reduction for all drugs was applied additionally to G-CSF. For grade 3 and 4 thrombocytopenia, a 25% and a 50% dose reduction, respectively, was recommended for all drugs. If creatinine clearance was calculated as <30 ml/min, treatment was delayed for a maximum of 2 weeks until recovery; otherwise the patient was withdrawn from the study. For cardiac arrhythmia, grade 3 hypersensitivity reactions and any non-haematological toxicity grade >2 treatment was discontinued. Specifically, for grade 2 PPE, treatment was delayed for a maximum of 2 weeks until recovery to Grade 0 or 1.	
Concomitant medications	All patients received standard premedication of dexamethasone, diphenhydramine and ranitidine prior to PLDH infusion	All patients received standard premedication of dexamethasone, diphenhydramine and ranitidine prior to paclitaxel, orally 12 h prior to and again intravenously 30 min prior to paclitaxel infusion
Duration of follow up	Median 43.6 (range 0.1–74.8) months	Median 43.6 (range 0.1–74.8) months
Baseline patient characteristics		
Age, years (range)	Median 62 (range 38–89)	Median 63 (range 37–81)
Previous treatment	Surgery: 76 (82%) Taxane-containing therapy: 86/93 (92%)	Surgery: 85 (89%) Taxane containing therapy: 84/96 (88%)
Platinum-free interval from last therapy		
Median	17.3 (6–119) months	14.8 (6–96) months
6–12 months	22 (23%)	32 (33%)
12.1–24 months	38 (41%)	32 (33%)
>24 months	29 (31%	23 (24%)
Unknown	4 (4%)	9 (9%)
Previous chemotherapy, n (%)		
One regimen	89/93 (96%)	92/96 (96%)
Two or more regimens	4/93 (4%)	4/96 (4%)
Primary site of disease	Not broken down by affected site	
Number of sites of lesions, n (%)	Not reported	
Histologic type, n (%)		
Serous	72 (77%)	71 (74%)
Mucinous	3 (3%)	0 (0%)
Endometroid	7 (8%)	6 (6%)
Clear cell	3 (3%)	3 (3%)
Other	5 (5%)	9 (9%)
Unknown	3 (3%)	7 (7%)

Histologic grade		
I	5 (5%)	8 (8%)
II	30 (32%)	27 (28%)
III	44 (47%)	48 (50%)
IV	2 (2%)	1 (1%)
Unknown	12 (13%)	12 (13%)
Tumour size, cm	Not reported	
Disease measurability		
Elevated CA125 only	9 (10%)	7 (7%)
FIGO stage at diagnosis:		
I	5 (5%)	9 (9%)
II	7 (8%)	9 (9%)
III	62 (67%)	56 (58%)
IV	13 (14%)	15 (16%)
Unknown	6 (7%)	7 (7%)
Performance status	ECOG score	
0	55 (59%)	62 (65%)
1	30 (32%)	27 (28%)
2	1 (1%)	0 (0%)
Unknown	7 (8%)	7 (7%)
Comments	None	
Abbreviations used in table: ANC, absolute neutrophil count; AUC, area under curve; ECOG, Eastern Cooperative Oncology Group; G-CSF, granulocyte colony stimulating factor; OS, overall survival; PLDH, pegylated liposomal doxorubicin hydrochloride; PPE, palmar-plantar erythrodysesthesia; RR, response rate; TTP, time to progression; WHO, World Health Organization.		

Gonzalez-Martin *et al*.[27]

Item	Details
Study	Gonzalez-Martin *et al*.[27]
Location	Spain; number of institutions not reported
Trial sponsor	Not specified
Patient enrolment	Between May 2000 and December 2002
Trial design	Phase II randomised controlled trial, “pick the winner” design (no formal statistical analysis between the treatment arms was planned)
Line of therapy	Second and third
Inclusion criteria	• ≥18 years of age; • Recurrent, histologically confirmed epithelial ovarian cancer; • Platinum-sensitive disease (defined as tumour progression >6 months following the completion of platinum-based chemotherapy); • No more than 2 lines of previous chemotherapy; • Last regimen must have contained a platinum-based treatment; • Bidimensionally measurable disease as measured by computed tomography scan or clinically evident but non-measurable disease evaluated by CA125 Rustin’s criteria; • ECOG performance status ≤2; • Life expectancy of at least 12 weeks; • Adequate bone marrow (granulocytes ≥2,000/mm^3, platelets ≥100,000/mm^3), renal (creatinine clearance ≥40 ml/min) and liver (serum bilirubin and transaminases <1.5 x upper limit) function
Exclusion criteria	No additional criteria listed

Outcomes reported	Response rate, overall survival, time to progression, tolerability and quality of life	
Subgroups	None specified	
Stratification	Stratification by platinum-free interval (6–12 months versus >12months) and number of previous lines of therapy (one versus two)	
Measure of disease response or progression	WHO criteria for those with measurable disease and CA125 according to Rustin's criteria for those without measurable disease	
Ethnicity	Not reported	
Disease classifications according to platinum sensitivity	Platinum sensitive	
Other definitions	OS: date of randomisation to death TTP: date of randomisation to date of documentation of tumour progression.	
Treatment	**Intervention: Paclitaxel plus carboplatin**	**Comparator: Carboplatin**
Randomised, n	41	40
Withdrawals, n (%)	Not reported	Not reported
Treatment	Paclitaxel 175 mg/m^2 over 3 hours plus carboplatin (AUC 5) every 3 weeks for a minimum of six cycles unless there was progression, unacceptable toxicity or patient refusal	Carboplatin AUC 5 every three weeks for a minimum of six cycles unless there was progression, unacceptable toxicity or patient refusal
	In both groups, therapy was continued after six cycles if, in the opinion of the attending physician, further clinical benefit could be expected	
Treatment duration	Median number of cycles 6 (range 1–8)	Median number of cycles 6 (range 2–9)
Treatment discontinuation	Progression, unacceptable toxicity or patient refusal	Progression, unacceptable toxicity or patient refusal
Concomitant medications	Premedication of dexamethasone, diphenhydramine and ranitidine approximately 30 minutes before infusion of paclitaxel	None
Duration of follow up	Median 67.7 weeks	
Baseline patient characteristics		
Age, years (range)	Median 59 (range 40–77)	Median 61 (range 35–77)
Previous treatment	Previous paclitaxel: In any regimen: 35/38 (92.1%) In last regimen: 32/38 (84.2%)	Previous paclitaxel: In any regimen: 33/40 (82.5%) In last regimen: 33/40 (82.5%)
Treatment-free interval, months Median (range) 6–12 months >12 months	 13.5 (7–147) 17 (45%) 21 (55%)	 14 (6–60) 16 (40%) 24 (60%)
Previous chemotherapy, n (%) One regimen Two regimens	 31 (81.6%) 7 (18.4%)	 35 (87.5%) 5 (12.5%)
Primary site of disease	Not reported	
Number of involved sites, n (%) 1–2 >2	 25 (65.8%) 13 (34.2%)	 33 (82.5%) 7 (17.5%)

Histologic type, n (%)		
Serous	29 (76.3%)	27 (67.5%)
Mucinous	2 (5.3%)	–
Endometroid	2 (5.3%)	2 (5.0%)
Clear cell	2 (5.3%)	5 (12.5%)
Undifferentiated	1 (2.6%)	5 (12.5%)
Other	2 (5.3%)	1 (2.5%)
Histologic grade: Poorly differentiated grade	16 (48.5%)	20 (54.1%)
Tumour size, cm	>5 cm: 8 (21.1%)	>5 cm: 5 (12.5%)
Disease measurability		
WHO criteria	27 (71%)	25 (62.5%)
CA125 criteria	11 (28.9%)	15 (37.5%)
FIGO stage at diagnosis:	Not reported	
Performance status	ECOG	
0	17 (47.2%)	14 (35.9%)
1	17 (47.2%)	18 (46.2%)
2	2 (5.6%)	7 (17.9%)
Not reported	2	1
Comments	None	
Abbreviations used in table: AUC, area under curve; ECOG, Eastern Cooperative Oncology Group; OS, overall survival; PLDH, RR, response rate; TTP, time to progression; WHO, World Health Organization.		

Gordon *et al*.[30;31]

Item	Details
Study	Gordon *et al*. (2001)
Location	United States, Canada, and Europe (104 sites)
Trial sponsor	Alza Corporation, Mountain View, CA, Johnson & Johnson Pharmaceutical, Raritan, NJ, and Tibotec Theraputics, a division of Biotech Products.
Patient enrolment	Between May 1997 and March 1999
Trial design	Multicentre
Line of therapy	Second line
Inclusion criteria	• ≥18 years of age; • Measurable, or measurable and assessable, disease that recurred or failed first line platinum-based therapy; • Adequate bone marrow function (platelets ≥100,000/mm^2, haemoglobin ≥9 g/dL, absolute neutrophil count ≥1,500 cells/mm^3, renal function (serum creatinine ≤2.5 mg/dL), liver function (AST ≤two times the upper limit of normal, bilirubin ≤ upper limit of normal), cardiac function (LVEF ≥50% or the institutional normal), Karnofsky performance status ≥60%; • Disease-free period of more than 5 years from prior malignancies (except curatively treated basal cell carcinoma, squamous cell carcinoma of the skin, or carcinoma in situ of the cervix).

Exclusion criteria	• Women pregnant or breast-feeding; • Life expectancy ≤3 months; • Prior radiation therapy to greater than a third of hematopoietic sites; • History of cardiac disease that met the New York State Heart Association Classification class 2 or greater; • Uncontrolled systemic infection; • Investigational agent within 30 days of the first dose of study drug; • Prior PLDH or topotecan therapy; • Chemotherapy within 29 days of the study drug (or within 42 days if patient had received a nitrosourea or mitomycin)	
Outcomes reported	OS, PFS, and ORR	
Subgroups	None specified	
Stratification	Stratified by platinum sensitivity (platinum refractory versus platinum sensitive); presence or absence of bulky disease (tumour mass >5 cm).	
Measure of disease response or progression	CR: complete disappearance of all measurable and assessable disease, no new lesions, and no disease-related symptoms. PR: ≥50% decrease in the sum of the products of bidimensional perpendicular diameters of all measurable lesions. Progression of assessable disease and new lesions were not allowed. PD: ≥50% increase in the sum of the products of bidimensionally measured lesions over the smallest sum obtained at best response or reappearance of any lesion that had disappeared, or clear worsening of any assessable disease, or failure to return for evaluation because of death or deteriorating condition, or the appearance of any new lesion or site. Stable disease: If the patient did not qualify for CR, PR, or PD. Objective tumour assessments CR and PR were confirmed by radiologic assessment at least four weeks later.	
Ethnicity	Not reported	
Disease classifications according to platinum sensitivity	Platinum refractory: progressed during initial platinum-based chemotherapy, demonstrated stable disease, or relapsed within 6 months after completing platinum-based chemotherapy. Platinum sensitive: PFS >6 months after first-line platinum therapy	
Other definitions	Measurable disease was defined as bidimensionally measurable lesion(s) with clearly defined margins by plain X-ray with at least one lesion of diameter ≥0.5 cm (excluding bone lesions) or computer tomography, magnetic resonance imaging, or another imaging scan with both diameters greater than distance between cuts of imaging study or palpation with both diameters ≥2 cm. Assessable disease included unidimensionally measurable lesion(s), mass(es) with margins not clearly defined, lesion(s) with both diameters ≤2cm, and malignant ascites or pleural effusion in conjunction with serum CA125 levels more than 100 U/mL in absence of cirrhosis.	
Treatment	**Intervention: PLDH**	**Comparator: Topotecan**
Randomised, n	239	235
Withdrawals, n (%)	7 patients didn't receive study drug but number not given by arm.	
Treatment	PLDH 50 mg/m^2 via 1 hour infusion every 28 days	Topotecan administered at 1.5 mg/m^2/d as 30-minute infusion daily for 5 consecutive days every 21 days, beginning on day 1 of a 21 day cycle
Treatment duration	Median number of cycles: 6 Median cycle length 30 (range 27–56) days	Median number of cycles: 8 Median cycle length 24 (range 20–38) days

Treatment discontinuation	Treatment was temporarily suspended or discontinued if a person: had disease progression, developed serious or intolerable adverse events precluding further treatment, was unable to tolerate study drug despite dose modification, had LVEF <45% or 20% decrease from baseline, decided to withdraw participation. Patients requiring radiation were removed from treatment.	Treatment was temporarily suspended or discontinued if a person: had disease progression, developed serious or intolerable adverse events precluding further treatment, was unable to tolerate study drug despite dose modification, had LVEF <45% or 20% decrease from baseline, decided to withdraw participation. Patients requiring radiation were removed from treatment.
Concomitant medications	Prophylactic cytokine administration was not recommended during the first cycle of either study drug. However, growth factor support was allowed in subsequent cycles for any patient with grade 4 neutropenia lasting more than 7 days or failure of absolute neutrophil count to recover within 22 days. All patients who developed febrile neutropenia were also eligible for prophylactic growth factor administration in the next cycles.	
Duration of follow up	Not reported	Not reported
Baseline patient characteristics		
Age, years (range)	Median 60 (range 27–87)	Median 60 (range 25–85)
Previous treatment Prior platinum and taxane	 74%	 72%
Treatment-free interval Median, months Platinum-sensitive Platinum refractory	 7.0 (range 0.9–82.1) 109 (45.6%) 130 (54.4%)	 6.7 (range 0.5–109.6) 110 (46.8%) 125 (53.2%)
Previous chemotherapy, n (%) One regimen	 100%	 100%
Primary site of disease	Not reported	
Number of lesions, median (range)	Median of 20 (1–441)	Median of 20 (1–296)
Histologic type, n (%)	Not reported	
Histologic grade:	Not reported	
Tumour size Bulky disease Present Absent	 111 (46%) 128 (54%)	 111 (47%) 124 (53%)
Disease measurability	Breakdown of measurable disease versus assessable disease at baseline not reported	
FIGO stage at diagnosis I II III IV	 11 (5%) 13 (5%) 175 (73%) 40 (17%)	 15 (6%) 8 (3%) 164 (70%) 48 (20%)
Performance status	Baseline Karnofsky performance status, n (%)	
<80 ≥80 Unknown:	39 (16.3%) 199 (83.3%) 1 (0.4%)	37 (15.7%) 195 (83.0%) 3 (1.3%)
Comments	None	

Abbreviations used in table: AST, aspartate transaminase; CR, complete response; LVEF, left ventricular ejection fraction; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PLDH, pegylated liposomal doxorubicin hydrochloride; PR, partial response.

Gore *et al*.[34]

Item	Details	
Study	Gore *et al*.	
Location	Europe, South Africa and North America; multicentre	
Trial sponsor	SmithKlineBeecham	
Patient enrolment	Not reported	
Trial design	Open-label, multicentre	
Line of therapy	Second line	
Inclusion criteria	• ≥18 years; • Measurable disease with one lesion ≥2 cm in diameter (or ≥1 cm for skin lesions); • ECOG performance status ≤2; • Life expectancy of at least 3 months; • Adequate bone marrow, renal and hepatic function – haemoglobin ≥90 g/L, white blood cell ≥3.5 x 109/L, platelets ≥100 x 109/L, creatinine ≤132.6 µmol/L (or creatinine clearance >1 ml/s), serum bilirubin ≤34.2 µmol/L and liver enzymes ≤2 times the upper limit of normal (or ≤5 times the upper limit of normal if liver metastases were present).	
Exclusion criteria	• Received surgery, radiotherapy or hormone therapy for 4 weeks prior to study, or 60 days in case of prior immunotherapy; • Presence of malignancies at other sites (except for basal and squamous cell carcinoma of the skin and carcinoma in situ of the cervix), brain or leptomeningeal metastases; • Uncontrolled infection or other severe medical problems; • Peptic ulcers or other gastrointestinal conditions affecting absorption or motility, or concomitant treatment for gastric or duodenal ulcers.	
Outcomes reported	ORR, OS, adverse events	
Subgroups	None specified	
Stratification	Stratification by response to previous platinum chemotherapy, tumour size (< or ≥5 cm in diameter) and whether or not the previous regimen had included a taxane	
Measure of disease response or progression	Based on WHO criteria, confirmed by independent, blinded radiological review. Time to response, TTP and OS measured from time of first dose and response duration measured from time of first documented complete response or partial response. Response also measured by serial CA125 values. Response defined as 50% decrease in two samples, confirmed by third, or serial decrease over three samples of >75%. Final sample at least 25 days after previous sample.	
Ethnicity	Not reported	
Disease classifications according to platinum sensitivity	Platinum refractory: progressive or stable disease during initial chemotherapy Platinum resistant: responded and subsequently relapsed within 6 months of discontinuing initial chemotherapy Platinum sensitive: responded to initial therapy, but subsequently relapsed >6 months	
Other definitions	Measurable disease was defined as one lesion ≥2 cm in diameter (or ≥1 cm for skin lesions). Complete response: complete disappearance of all known measurable and evaluable disease determined by two measurements not less than 4 weeks apart. Partial response: >50% decrease in measurable lesion size for at least 4 weeks with no simultaneous increase in a known lesion or appearance of new lesions or increase in evaluable disease.	
Treatment	**Intervention: Oral topotecan**	**Comparator: Intravenous topotecan**
Randomised, n	135	131
Withdrawals, n (%)	0	0
Treatment	Oral topotecan 2.3 mg/m^2/day. Duration of therapy depended on response to	Intravenous topotecan 1.5 mg/m^2/day for 5 days every 21 days dependent on

	treatment and at discretion of investigator.	response to treatment and at discretion of investigator.
Treatment duration	Median number of cycles 4 (1–23)	Median number of cycles 6 (1–26)
Treatment discontinuation	Not reported	
Concomitant medications	Not reported	
Duration of follow up	Not reported	
Baseline patient characteristics		
Age, years (range)	Median 60 (23–80)	Median 60 (27–80)
Previous treatment		
First-line platinum/paclitaxel	53	54
Treatment-free interval		
Median	Not reported	Not reported
Platinum sensitive	58 (43%)	56 (43%)
Platinum resistant	37 (27%)	36 (27%)
Platinum refractory	40 (30%)	39 (30%)
Previous chemotherapy, n (%)		
One regimen	100%	100%
Primary site of disease	Not reported	
Number of sites of lesions, n (%)	Not reported	
Histologic type, n (%)	Not reported	
Histologic grade:	Not reported	
Tumor size, cm		
<5	66 (49%)	65 (50%)
5–10	58 (43%)	50 (38%)
>10	10 (7%)	11 (8%)
Missing data	1 (1%)	5 (4%)
Disease measurability	Patients all had measurable disease at baseline	
FIGO stage at diagnosis		
III	84 (62%)	82 (63%)
IV	43 (32%)	42 (32%)
Missing	8 (6%)	7 (5%)
Performance status	ECOG score	
0	59 (45%)	47 (35%)
1	60 (46%)	77 (57%)
2	12 (9%)	11 (8%)
Comments	None	
Abbreviations used in table: ECOG, Eastern Cooperative Oncology Group; LVEF, left ventricular ejection fraction; ORR, overall response rate; OS, overall survival; TTP, time to progression; WHO, World Health Organization.		

CARTAXHY (Lortholary *et al*.[23])

Item	Details
Study	CARTAXHY
Location	Not reported; patients randomized at the 'GINECO' (Groupe d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens) data centre
Trial sponsor	Not reported
Patient enrolment	Between April 2004 and August 2008
Trial design	Phase II, multicenter, open-label.

	Three-armed trial; third arm evaluated weekly paclitaxel plus weekly topotecan, which is outside of the scope of the review.	
Line of therapy	Second/third line	
Inclusion criteria	• ≥18 years of age; • Histologically proven epithelial ovarian cancer, primary carcinoma of the peritoneum, or fallopian tube cancer; • Progressive disease during or relapse within 6 months of completing platinum-containing therapy; • Received at least one prior regimen; • Received both a platinum and taxane agent with the last chemotherapy regimen containing platinum; • Measurable disease (according to RECIST or CA125-assessable disease); • ECOG performance status of ≤2; • Life expectancy >12 weeks	
Exclusion criteria	• Prior treatment with weekly paclitaxel; • Presence or history of other malignancy, central nervous system metastases, cardiovascular illness, neurologic toxicity of grade 2 or higher, active infection; • Inadequate hematologic, hepatic, or renal function.	
Outcomes reported	Primary end point: comparison of PFS Secondary end points: ORR, OS, QoL, and safety	
Subgroups	None specified	
Stratification	Not reported	
Measure of disease response or progression	Response determined according to RECIST for measurable disease and Rustin criteria for nonmeasurable disease. Progression determined according to the definition of the Gynecologic Cancer Intergroup. Objective response: radiologically confirmed at least 4 weeks after baseline assessments.	
Ethnicity	Not reported	
Disease classifications according to platinum sensitivity	Progression during or within 6 months of platinum-containing therapy: progression during treatment, relapse between 0 and 3 months, or relapse >3 months and ≤6 months	
Other definitions	No other definitions	
Treatment	**Intervention: Weekly paclitaxel plus carboplatin**	**Comparator: Weekly paclitaxel**
Randomised, n	51	57
Withdrawals, n (%)	Progressive disease 20 (39.2%) Toxicity 15 (29.4%) Other 2 (3.9%)	Progressive disease 29 (50.8%) Toxicity 1 (1.8%) Other 3 (5.3%)
Treatment	Weekly paclitaxel plus carboplatin dosed to an AUC 5 mg/ml/min on day 1 of a 4-week cycle given for six to nine cycles or until progression	Paclitaxel 80 mg/m^2 days 1, 8, and 15 of a 4-week cycle given for six to nine cycles or until progression
Treatment duration	Median number of cycles 3 (1–23)	Median number of cycles 3 (1–23)
Treatment discontinuation	On progression, patients treated with weekly paclitaxel plus carboplatin received treatment per the investigator	On progression, patients treated with weekly paclitaxel received carboplatin (AUC 5)
Concomitant medications	Not reported	Not reported
Duration of follow up	Median 15 months	Median 15 months
Baseline patient characteristics		
Age, years (range)	Median 60 (43–77)	Median 60 (30–80)
Previous treatment	Not reported	Not reported
Disease-free interval:		

Progression during treatment	0%	4%
<3 months	47%	42%
>3months	53%	54%
Previous chemotherapy, n (%) One regimen Two regimens >2 regimens	 71% 29% 0%	 74% 19% 7%
Primary site of disease	Not reported	
Number of sites of lesions, n (%)	Not reported	
Histologic type, n (%) Serous Clear cell Other Unknown	 76% 2% 18% 4%	 79% 2% 18% 2%
Histologic grade	Not reported	
Tumour size, cm	Not reported	
Disease measurability Measurable (RECIST) Elevated CA-125 only (GCIG)	 68% 28%	 57% 37%
FIGO stage at diagnosis	Not reported	
Performance status 0–1 2	 92% 8%	 95% 5%
Comments	None	
Abbreviations used in table: ECOG, Eastern Cooperative Oncology Group; ORR, overall response rate; OS, overall survival; QoL, quality of life; PFS, progression-free survival; QoL, quality of life; RECIST, Response Evaluation Criteria for Solid Tumors.		

OVA-301 (Monk *et al*. [2010][(21)])

Item	**Details**
Study	OVA-301
Location	124 centres in 21 countries
Trial sponsor	Johnson and Johnson
Patient enrolment	Between April 2005 and May 2007
Trial design	Phase III, open-label, international, multicentre
Line of therapy	Second line
Inclusion criteria	• ≥18 years of age; • Histologically confirmed epithelial ovarian, fallopian tube, or primary peritoneal carcinoma; • Received one prior platinum-based chemotherapy and experienced persistence, recurrence or progression. Included people with platinum-resistant (platinum-free interval <6 months) and platinum-sensitive disease (platinum-free interval ≥6 months); • Measurable disease by RECIST; • ECOG performance status ≤2; • Haemoglobin ≥9 g/dL, absolute neutrophil count ≥1,500 µm, platelets ≥100,000 µm, serum creatinine ≤1.5 mg/dL or creatinine clearance ≥60 mL/min, creatinine phosphokinase ≤ ULN, total bilirubin ≤1.5 x ULN, direct bilirubin ≤ ULN, total ALP ≤1.5 x ULN (if > 1.5 x ULN, ALP liver fraction or 5’ nucleotidase ≤ULN), AST and

	ALT ≤2.5 X ULN, and left ventricular ejection fraction within institutional limits.	
Exclusion criteria	• Platinum refractory patients (disease progression during front-line therapy). • Women of childbearing age not using adequate contraception.	
Outcomes reported	OS, PFS, ORR duration of response.	
Subgroups	None specified	
Stratification	Stratified by ECOG PS (0 to 1 versus 2) and platinum sensitivity (sensitive versus resistant)	
Measure of disease response or progression	PFS by independent radiology assessment based on only RECIST criteria. Secondary analyses of PFS based on independent oncologist (radiological evaluation in conjunction with prespecified clinical data) and investigator's assessments.	
Ethnicity	PLDH plus trabectedin	PLDH alone
White	265 (79%)	259 (77%)
Asian	66 (20%)	71 (21%)
Black	2 (1%)	3 (1%)
Other	4 (1%)	2 (1%)
Disease classifications according to platinum sensitivity	Platinum sensitive or resistant but not refractory	
Other definitions	ORR: response maintained ≥4 weeks by the RECIST criteria Duration of response: date of first documentation of response to date of progressive disease or death due to progressive disease.	
Treatment	**Intervention: PLDH plus trabectedin**	**Comparator: PLDH**
Randomised, n	337	335
Withdrawals, n (%)	Lost to follow-up (N = 2) Discontinued trabectedin/PLDH (N = 325): Disease progression (N = 139); Patient choice (N = 57); Adverse event (N = 69); Other (N = 28); CR (confirmed) (N = 24).	Did not receive PLDH (N = 6) Lost to follow-up (N = 0) Discontinued PLDH (N = 322): Disease progression (N = 178); Patient choice (N = 50); Adverse event (N = 39); Other (N = 33); CR (confirmed) (N = 14).
Treatment	PLDH 30 mg/m^2 followed immediately by trabectedin 1.1 mg/m^2 (3-hour infusion) through a central venous catheter every 3 weeks	PLDH 50 mg/m^2 every 4 weeks
Treatment duration	Not reported	Not reported
Treatment discontinuation	Treatment continued until disease progression or confirmation of complete response and could be continued for two or more cycles beyond confirmed complete response.	Treatment continued until disease progression or confirmation of complete response and could be continued for two or more cycles beyond confirmed complete response.
Concomitant medications	Before treatment with PLDH, patients were given intravenous dexamethasone 20 mg (or equivalent) followed by treatment regimen after 30 minutes. Colony-stimulating factors were permitted after cycle 1 per ASCO guidelines; additional antiemetics were permitted at investigator's discretion.	Colony-stimulating factors were permitted after cycle 1 per ASCO guidelines; additional antiemetics were permitted at investigator's discretion.
Duration of follow up	Not reported	Not reported

Baseline patient characteristics		
Age, years (range)	Median 56.0 (26–82)	Median 58.0 (27–87)
Previous treatment		
Prior taxane use, %	269 (80%)	271 (81%)
Prior consolidation chemotherapy	27 (8%)	32 (10%)
Platinum-free interval, months		
<6	115/333 (35%)	117/330 (35%)
6 to <12	123/333 (37%)	91/330 (28%)
≥12	95/333 (28%)	122/330 (37%)
Previous chemotherapy, n (%)		
One regimen	100%	100%
Primary site of disease	Not reported	
Number of sites of lesions		
0	6 (2%)	3 (1%)
1–3	278 (82%)	295 (88%)
>3	53 (16%)	37 (11%)
Histologic type		
Papillary/serous	225 (67%)	230 (69%)
Endometrioid	23 (7%)	17 (5%)
Clear cell carcinoma	13 (4%)	16 (5%)
Mucinous	5 (1%)	4 (1%)
Transitional-cell carcinoma	2 (1%)	2 (1%)
Mixed epithelial tumour	4 (1%)	5 (1%)
Peritoneal carcinoma	11 (3%)	9 (3%)
Fallopian tube carcinoma	3 (1%)	3 (1%)
Other	50 (15%)	49 (15%)
Histologic grade		
1	18 (5%)	10 (3%)
2	58 (17%)	59 (18%)
3	175 (52%)	174 (52)
Unknown	85 (25%)	91 (27%)
Tumour size, cm	Not reported	
Disease measurability	All patients had measurable disease at baseline	
FIGO stage at diagnosis	Not reported	
Performance status	ECOG score	
0	230 (68%)	192 (57%)
1	98 (29%)	132 (39%)
2	9 (3%)	11 (3%)
Comments	None	

Abbreviations used in table: ALP, alkaline phosphatise; ALT, alanine transaminase; AST, aspartate transaminase; CR, complete response; ECOG, Eastern Cooperative Oncology Group; ORR, overall response rate; OS, overall survival; QoL, quality of life; PFS, progression-free survival; PLDH, pegylated liposomal doxorubicin; RECIST, Response Evaluation Criteria for Solid Tumors; ULN, upper limit of normal; WHO, World Health Organization.

ICON4/AGO-OVAR2.2 (Parmar *et al*.[33])

Item	Details
Study	ICON4/AGO-OVAR-2.2
Location	199 hospitals in UK, Norway, Switzerland, Italy.
Trial sponsor	Bristol-Myers-Squibb
Patient enrolment	ICON4 MRC CTU: Between May 1996 and March 2002 ICON4 Italy: Between January 1996 and March 2002 AGO: Between October 1996 and September 1999.
Trial design	Parallel RCTs, 3 different protocols: Medical Research Council's Clinical Trials Unit (MRC CTU) protocol Istituto Mario Negri, Milan, Italy (IRFMN) protocol AGO, Karlsruhe, Germany (AGO-OVAR-2.2) protocol
Line of therapy	MRC CTU: Second line and greater AGO: Second line ICON4: Second line
Inclusion criteria	• Relapse epithelial ovarian cancer requiring chemotherapy; • Previously received platinum-based chemotherapy; • Treatment free for >6 months (>12 months in ICON4); • No concomitant or previous malignant disease likely to interfere with treatment or outcomes; • Measurable disease was required for patients in Italian protocols, but not in the MRC CTU or AGO protocol; • Patients randomised in the AGO protocol must have previously received cisplatin plus paclitaxel or carboplatin plus paclitaxel; all patients in ICON 4 were required to have had previous platinum-based chemotherapy, with or without paclitaxel. AGO patients had previously received cisplatin plus paclitaxel or carboplatin plus paclitaxel; • ICON4 all patients had previous platinum-based chemotherapy
Exclusion criteria	None apart from above
Outcomes reported	OS, PFS
Subgroups	OS and PFS results were reported by trial and by pre-specified subgroups.
Stratification	Stratification by centre, age, last chemotherapy received, time since completion of last chemotherapy, and intended platinum treatment.
Measure of disease response or progression	Progressive disease defined by clinical or radiological evidence. Raised CA125 concentrations alone (in the absence of clinical or radiological evidence of progressive disease) were not deemed to show disease progression.
Ethnicity	Not reported
Disease classifications according to platinum sensitivity	Platinum sensitivity: treatment free (following platinum therapy) for greater than 6 months.
Other definitions	OS: time from randomisation to death from any cause; patients known to be alive at the time of analysis were censored at the time of their last follow-up. PFS: time from randomisation to first appearance of progressive disease or death from any cause; patients known to be alive and without progressive disease at the time of analysis were censored at their last follow-up.

Treatment	Intervention: Paclitaxel plus platinum chemotherapy	Comparator: Conventional platinum-based chemotherapy
Randomised, n	392	410
Withdrawals, n (%)	1 (treatment never began); 7 (missing details)	2 (treatment didn't begin); 16 (missing details)
Treatment	**Paclitaxel** **AGO:** 185 mg/m^2 paclitaxel (3 hour infusion) followed by carboplatin. ICON4: 175 mg/m^2 paclitaxel (3 hour infusion) plus platinum followed by carboplatin or cisplatin. **Carboplatin** If determined by method of Calvert and Colleagues, AUC was a minimum of 5. If the dose was assessed by Cockcroft formula, the AUC was 6. The planned minimum dose of cisplatin, in ICON4 patients only, was 50 mg/m^2 if given in combination.	Platinum-based treatment **Carboplatin** If determined by method of Calvert and Colleagues, AUC was a minimum of 5. If the dose was assessed by Cockcroft formula, the AUC was a minimum of 6. **Cisplatin** The planned minimum dose of cisplatin, in ICON4 patients only, was 75 mg/m^2 if given as a single agent.
Treatment duration	309 received ≥6 cycles 75 received <6 cycles	271 received ≥6 cycles 121 received <6 cycles
Treatment discontinuation	Reasons for not completing 6 cycles were: disease progression or death (109; 56%); toxicity 77 (39%); patient preference 9 (5%) (not shown separately by group)	
Concomitant medications	Not reported	Not reported
Duration of follow up	Median 42 months	Median 42 months
Baseline patient characteristics		
Age, years:		
Median	60	59.2
<55	127/392 (32%)	123/410 (30%)
55-65	151 (39%)	162 (40%)
>65	114 (29%)	125 (30%)
Previous treatment Last chemotherapy received:		
Paclitaxel and carboplatin	133/392 (34%)	141/410 (34%)
Carboplatin	119 (30%)	128 (31%)
CAP	62 (16%)	72 (18%)
Paclitaxel and cisplatin	27 (7%)	20 (5%)
Docetaxel and carboplatin	7 (2%)	14 (3%)
Other platinum-based	34 (9%)	30 (7%)
Other non-platinum	10 (3%)	5 (1%)
Treatment-free interval (months)		
≤12	92 (23%)	111 (27%)
>12	300 (77%)	299 (73%)
Previous chemotherapy, n (%)		
1	354 (90%)	380 (93%)
2 (MRC CTU patients only)	22 (6%)	22 (5%)
>2 (MRC CTU patients only)	15 (4%)	15 (4%)
Not yet known	1 (0.2%)	1 (0.2%)
Primary site of disease	Not reported	
Number of sites of lesions	Not reported	

Histologic type, n (%)	Not reported	
Histologic grade	Not reported	
Tumour size, cm	Not reported	
Disease measurability	Not reported	
FIGO stage at diagnosis	Not reported	
Performance status	WHO score	
0	246 (63%)	262 (64%)
1	121 (31%)	122 (30%)
2–3	25 (6%)	26 (6%)
Comments	None	
Abbreviations used in table: ORR, overall response rate; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria for Solid Tumors; WHO, World Health Organization.		

Pfisterer *et al*.[24]

Item	Details
Study	Pfisterer *et al*.
Location	Germany
Trial sponsor	AGO-OVAR, National Cancer Institute of Canada Clinical Trials Group, and European Organisation for Research and Treatment of Cancer (EORTC) Gynecologic Cancer Group; supported by Lily Deutchland GmbH
Patient enrolment	Between September 1999 and April 2002
Trial design	Phase III, randomised controlled trial, active-controlled
Line of therapy	Second-line
Inclusion criteria	• Women at least 18-years-old; • Recurrent ovarian cancer at least 6 months after completion of first-line, platinum-based therapy; • Measurable or assessable lesions per SWOG criteria; • ECOG performance status of 0 to 2; • Adequate bone marrow reserve (ANC ≥1.5 ×109/L and platelets ≥100 ×109/L), an estimated GFR greater than 50 mL/min, no serious concomitant systemic disorders incompatible with the study; • Estimated life expectancy 12 weeks or longer; • Written informed consent
Exclusion criteria	No others reported
Outcomes reported	PFS (primary), ORR, duration of response, OS QoL, and toxicity
Subgroups	Age (>60 *vs* ≤60) Performance status (0 *vs* 1–2) Prior platinum therapy (platinum plus non-paclitaxel *vs* platinum plus paclitaxel) Disease status (bidimensionally measurable *vs* assessable) Duration of platinum-free interval (6 to 12 months *vs* >12 months)
Stratification	Stratified according to platinum-free interval (6 to 12 months *vs* ≥12 months), first-line therapy (platinum paclitaxel *vs* other platinum-based therapy), and bidimensionally measurable disease (yes *vs* no)
Measure of disease response or progression	Progressive disease was based on clinical and/or radiologic evaluation according to SWOG criteria. Categorisation of progressive disease was not based on CA125 elevation without other clinical or radiologic evidence of disease progression.
Ethnicity	Not reported
Disease classifications according to platinum sensitivity	Platinum-sensitive recurrent ovarian cancer: recurrent ovarian cancer at least 6 months after completion of first-line, platinum-based therapy

Other definitions	PFS was defined as the time from the date of random assignment to the date of disease progression or death from any cause. OS was measured from the date of random assignment to the date of death from any cause. Overall survival was assessed when 71% of the study population had died	
Treatment	**Intervention: Gemcitabine plus carboplatin**	**Comparator: Carboplatin alone**
Randomised, n	178	178
Withdrawals, n (%)	1 ineligible after randomisation 2 withdrew consent	3 withdrew consent 1 thrombocytopenia
Treatment	Gemcitabine (1,000 mg/m^2) on days 1 and 8 plus carboplatin AUC 4 on day 1 every 21 days	Carboplatin AUC 5, based on the Calvert formula, on day 1 every 21 days
	Treatments were given for six cycles in the absence of progressive disease or unacceptable toxicity. Patients showing benefit could receive up to 10 cycles, based on the discretion of the investigator	
Treatment duration	Median number of cycle: 6	Median number of cycles: 6
Treatment discontinuation	Day 8 gemcitabine was reduced by 50% if ANC ≥1.0 to 1.4 ×109/L and/or platelets 75 to 99 ×109/L, and it was omitted if below these values. For grade 3 non-haematologic toxicities (excluding nausea/vomiting), dose modifications and/or study discontinuation were at the investigator's discretion. Successive reductions by one dose level were required for treatment delays 1 week or longer due to toxicity, ANC less than 0.5 ×109/L for more than 5 days (or <0.1 ×109/L for > 3 days), febrile neutropenia, platelets less than 25 ×109/L, and grade 3/4 non-haematologic toxicities (except nausea/vomiting). Dose level −1 of gemcitabine was 800 mg/m^2, and dose level −2 was omission of day 8 gemcitabine; carboplatin was not reduced.	Dose level −1 was a reduction to AUC 4; if additional dose reductions were required, patients were discontinued
	Cycles could be postponed up to 2 weeks due to toxicity, and longer toxicity-related delays led to treatment discontinuation. Treatment resumed after recovery from non-haematologic and hematologic toxicities (ANC ≥1.5 ×109/L and platelets ≥100 ×109/L).	
Concomitant medications	Not reported	Not reported
Duration of follow up	17 months	17 months
Baseline patient characteristics		
Age, years (range)	Median 59 (36–78)	Median 58 (21–81)
Previous treatment		
Surgery	178 (100%)	178 (100%)
Radiotherapy	4 (2%)	3 (2%)
Prior taxane use, %	125 (70.2%)	127 (71.3%)
Immunotherapy	4 (2.2%)	4 (2.2%)
Hormonal therapy	6 (3.4%)	2 (1.1%)
Platinum-free interval		
<6 months	1 (0.6%)	0
6–12 months	71 (39.9%)	71 (39.9%)
>12 months	106 (59.6%)	107 (60.1%)
Previous chemotherapy, n (%)		

One regimen	100%	100%
Primary site of disease	Not reported	
Number of sites of lesions, n (%)	Not reported	
Histologic type, n (%)		
Well differentiated	15 (8.4%)	13 (7.3%)
Moderately differentiated	51 (28.7%)	49 (27.5%)
Poorly differentiated	78 (43.8%)	88 (49.4%)
Undifferentiated	10 (5.6%)	7 (3.9%)
Unknown	24 (13.5%)	21 (11.8%)
Histologic grade:	Not reported	
Tumour size, cm	Not reported	
Disease measurability	Not reported	
FIGO stage at diagnosis		
Ia–IIa	16 (9.0%)	14 (7.9%)
IIb–IIIa	22 (12.4%)	12 (6.7%)
IIIb	16 (9.0%)	22 (12.4%)
IIIc	97 (54.5%)	107 (60.1%)
IV	27 (15.2%)	22 (12.4%)
Unspecified	0	1 (0.6%)
Performance status	ECOG score	
ND	5 (2.8%)	4 (2.2%)
0	83 (46.6%)	93 (52.2%)
1	79 (44.4%)	72 (40.4%)
2	11 (6.2%)	9 (5.1%)
Comments	None	
Abbreviations used in table: ANC, absolute neutrophil count; AUC, area under curve; ECOG, Eastern Cooperative Oncology Group; GRF, glomerular filtration rate; ND, not determined; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; QoL, quality of life; SWOG, South Western Oncology Group.		

Piccart *et al*.[25]

Item	Details
Study	Piccart *et al*.
Location	17 European centres
Trial sponsor	Debiopharm S.A., Lausanne, Switzerland
Patient enrolment	Between January 1996 and December 1997
Trial design	Multicentre, open-label trial
Line of therapy	Second and third
Inclusion criteria	• ≥18 years; • WHO performance status of 0 to 2; • Estimated life expectancy ≥12 weeks; • Histologically or cytologically confirmed metastatic ovarian carcinoma; • Progressed or stabilised after prior treatment, with relapse observed within 1 year of the last platinum-based regimen; • Received at least one and no more than two chemotherapeutic regimens with last regimen including carboplatin or cisplatin at therapeutically adequate doses. • Patients with progressive or stable disease received at least two or four consecutive cycles. • At least one bidimensionally measurable lesion by computer

	tomography scan or magnetic resonance imaging, with at least one diameter of ≥2 cm. • Baseline blood laboratory criteria: neutrophil count ≥100 x 109 platelets/L; creatine level ≤140 µmol/L; total bilirubin ≤1.25 x upper limit of normal; AST level ≤2 x upper limit of normal (≤3 in liver metastasis).	
Exclusion criteria	• Brenner or borderline tumour, low-potential (grade 0) tumours, squamous cell carcinoma, and granulosa theca cell tumours; • Prior treatment with platinum derivatives other than cisplatin or carboplatin or with paclitaxel, docetaxel, or high dose chemotherapy with hematopoietic stem cell support; • Brain or leptomeningel metastasis; • Previous or concurrent malignancies at other sites, including abdominal adenocarcinoma of unknown origin (except cone-biopsied in situ cervix carcinoma and basal or squamous cell skip carcinoma); • Symptomatic peripheral neuropathy more than or equal to grade 2 (NCIC criteria) or any other serious illness.	
Outcomes reported	Response rate, OS, PFS.	
Subgroups	Potentially platinum-sensitive versus platinum-refractory	
Stratification	Stratification by centre, performance status (0 or 1 *vs* 2), platinum-free interval (0 to 6 months *vs* 6 to 12 months), number of prior platinum-based regimens (1 *vs* 2)	
Measure of disease response or progression	Target lesions measured by CT scan or MRI every two cycles. CR, PR and disease progression as defined: • CR: disappearance of all known disease, without appearance of new lesions, lasting >4 weeks. Elevated CA125 serum level regains normal levels. • PR: decrease of >50% of the sum of the products of the largest perpendicular diameters of all measurable lesions, being confirmed by a further observation no less than 4 weeks later, without any new lesions. No change was defined for bidimensional lesions, as a decrease of <50% and an increase of <25% in the sum of the products of the largest perpendicular diameters of all measurable lesions. • Disease progression: increase ≥25% in the sum of the products of the largest perpendicular diameters of measurable lesions or the appearance of a new lesion; occurrence of positive cytology pleural effusion or ascites.	
Ethnicity	Not reported	
Disease classifications according to platinum sensitivity	Platinum sensitive: Relapse >6 months but less than12 months after their last platinum-based chemotherapy regimen. Platinum refractory: Disease progression after a minimum of two cycles of chemotherapy, no change under chemotherapy for at least four cycles, or a relapse that occurred less than 6 months after the end of prior chemotherapy.	
Other definitions	OS: day 1 of treatment to date of first observation of disease progression, treatment failure (tumour progression or change of treatment, including cross-over [which was allowed], or death). Confirmed response: verified by two independent radiologists and defined as PR or CR observed in at least two consecutive evaluations at least 4 weeks apart.	
Treatment	**Intervention: Paclitaxel**	**Comparator: Oxaliplatin**
Randomised, n	41	45
Withdrawals, n (%)	Not reported	Not reported
Treatment	Paclitaxel (175 mg/m^2) administered as a 3-hour IV infusion every 21 days	Oxaliplatin (130 mg/m^2) administered as a 3-hour IV infusion every 21 days
Treatment duration	Median number of cycle: 6 (range 1–8)	Median number of cycles: 4 (range 1–8)
Treatment discontinuation	Continued until time of disease progression, unacceptable toxicity, or patient refusal. Doses could not fall below established minimum doses per cycle (90 mg/m^2).	Continued until time of disease progression, unacceptable toxicity, or patient refusal. Doses could not fall below established minimum doses per cycle (75 mg/m^2).

Concomitant medications	Premedication with oral dexamethasone 20 mg 12 and 6 hours before paclitaxel infusion, diphenhydramine 50 mg IV and cimetidine 300 mg or ranitidine 50mg IV 30 minutes before paclitaxel.	Premedication of antiemetic with serotonin antagonist ($5HT_3$) with a single dose of corticosteroid (e.g., dexamethasone 20 mg).
Duration of follow up	Not reported	Not reported
Baseline patient characteristics		
Age, years (range)	Median 62 (37-81)	Median 59 (28-71)
Previous treatment: Regimens containing:		
Cisplatin	16 (39%)	19 (42%)
Median dose, mg	442	440
Range, mg	223–456	223–478
Carboplatin	21 (51%)	21 (47%)
Median dose, mg	1,970	1,888
Range, mg	652–3,600	1,402–3568
Both cisplatin and carboplatin	4 (10%)	5 (11%)
Treatment-free interval, months		
0–6	31 (76%)	32 (71%)
6–12	10 (24%)	13 (29%)
Previous chemotherapy, n (%)		
One regimen	30 (73%)	29 (64%)
Two regimens	11 (27%)	16 (36%)
Sites involved (not primary)		
Pelvi-perioneum	30 (73%)	25 (56%)
Lymph nodes	15 (37%)	13 (29%)
Lung	2 (5%)	2 (4%)
Liver	7 (17%)	15 (33%)
Other	7 (17%)	7 (16%)
Number of sites of lesions		
0	0	1 (2%)
1	22 (54%)	30 (67%)
2	17 (41%)	11 (25%)
3	2 (5%)	2 (4%)
>3	0	1 (2%)
Histologic type, n (%)		
Serous	17 (41%)	33 (73%)
Other	24 (59%)	12 (27%)
Histologic grade	Not reported	
Tumour size, cm	Not reported	
Disease measurability	Not reported	
FIGO stage at diagnosis		
I	5 (12%)	7 (16%)
II	2 (5%)	1 (2%)
III	26 (63%)	29 (64%)
IV	8 (20%)	8 (18%)
Performance status	WHO score	
0–1	35 (85%)	38 (84%)

2	6 (15%)	7 (16%)
Comments	None	
Abbreviations used in table: CR, complete response; CT, computed tomography; ORR, overall response rate; OS, overall survival; PR, partial response; QoL, quality of life; PFS, progression-free survival; WHO, World Health Organization.		

CALYPSO (Pujade-Lauraine *et al*.[29;39;40])

Item	**Details**	
Study	CALYPSO	
Location	Multicentre, multinational	
Trial sponsor	Schering Plough	
Patient enrolment	Between April 2005 and September 2007	
Trial design	Phase III, non-inferiority, multicentre, multinational trial	
Line of therapy	Second or third line	
Inclusion criteria	• ≥18 years; • Histologically confirmed diagnosis of cancer of the ovary, fallopian tube, or extra-ovarian papillary serous tumour; • Disease progression >6 months after first or second line platinum-based chemotherapy regimen; • Previous taxane therapy; • Measurable disease according to RECIST or CA125 assessable disease according to GCIG criteria or histologic proven diagnosis of relapse; • ECOG performance status of ≤2; • Life expectancy of at least 12 weeks; • Adequate bone marrow, renal and hepatic function.	
Exclusion criteria	Pre-existing neuropathy (NCI-CTCAE grade >1).	
Outcomes reported	PFS, adverse events.	
Subgroups	"Exploratory analyses" only	
Stratification	Stratified by therapy-free interval from last chemotherapy (6 to 12 *vs* >12 months), measurable disease (yes *vs* no) and centre.	
Measure of disease response or progression	Disease progression based on RECIST and GCIG criteria or histologic proven diagnosis of relapse. RECIST and GCIG modifications may have included: occurrence (clinically or imaging signs) of any new lesion; increase in measurable and/or non-measurable tumour defined by RECIST; CA125 elevation defined by GCIG criteria; health status deterioration attributable to disease; and death of any cause before progression is diagnosed. Evaluation assessments were independently reviewed.	
Ethnicity	Not reported	
Disease classifications according to platinum sensitivity	Platinum sensitive: disease recurrence more than 6 months after first or second line platinum therapy.	
Other definitions	None	
Treatment	**Intervention: PLDH plus carboplatin**	**Comparator: Paclitaxel plus carboplatin**
Randomised, n	467	509
Withdrawals, n (%)	1 (ineligible)	2 (missing data)
Treatment	PLDH (30 mg/m^2 intravenously on day 1) and carboplatin (AUC 5 on day 1) every 4 weeks	Paclitaxel (175 mg/m^2 intravenously on day 1) and carboplatin (AUC 5 intravenously on day 1) every 3 weeks
Treatment duration	Median number of cycles: 6 (1–14)	Median number of cycles: 6 (1–12)
Treatment discontinuation	Treatment continued until disease progression or unacceptable toxicity	
Concomitant medications	All patients received antiemetics, including serotonin antagonist and corticosteroid.	

	Patients assigned to carboplatin received premedication to prevent hypersensitivity reactions.	
Duration of follow up	5 years	5 years
Baseline patient characteristics		
Age, years (range)	Median 60.5 (24–82)	Median 61 (27–82)
Previous treatment		
Prior taxane use, %	396 (85%)	407 (80%)
Surgery for this relapse	87	100
Treatment-free interval, months		
Median	15.2	15.0
6-12	161/466 (35%)	183/507 (36%)
>12	305 (65%)	324 (64%)
Prior chemotherapy		
One regimen	408/466 (88%)	419/507 (83%)
Two regimens	58 (12%)	88 (17%)
Primary site		
Ovarian	416 (89.2)	452 (89.2%)
Fallopian	18 (3.9%)	19 (3.7%)
Peritoneal	32 (6.9%)	36 (7.1%)
Number of sites of lesions		
1	217 (46.6%)	243 (47.9%)
>1	249 (53.4%)	264 (52.0%)
Histologic type		
Serous	334 (71.4%)	366 (72.2%)
Endometroid	38 (8.2%)	35 (6.9%)
Clear cell	14 (3%)	13 (2.6%)
Mixed epithelial	8 (1.7%)	17 (3.3%)
Mucinous	9 (1.9%)	8 (1.6%)
Other	37 (7.9%)	42 (8.3%)
Unspecified	26 (5.6%)	26 (5.1%)
Histologic grade		
1	29 (6.2%)	23 (4.5%)
2	100 (21.5%)	128 (25.2%)
3	257 (55.1%)	270 (53.3%)
Unknown	80 (17.2%)	89 (17.0%)
Tumour size, cm		
<5	377 (80.9%)	417 (82.3%)
≥5	89 (19.1%)	90 (17.7%)
Measurable disease		
Yes	281 (60.3%)	321 (63.3%)
No	185 (39.7%)	186 (36.7%)
FIGO stage at diagnosis		
I/II	57 (12.3%)	66 (13.0%)
III/IV	400 (85.8%)	427 (84.2%)
Missing	9 (1.9%)	14 (2.8%)

Performance status	ECOG score	
0	286 (61.4%)	317 (62.5%)
1	158 (33.9%)	164 (32.3%)
2	13 (2.8%)	15 (3.0%)
Missing	9 (1.9%)	11 (2.2%)
Comments	Cross over: 43% PLDH and carboplatin group; 68% paclitaxel and carboplatin group	
Abbreviations used in table: AUC, area under curve; ECOG, Eastern Cooperative Oncology Group; GCIG, Gynecologic Cancer Intergroup; IV, intravenous; NCI-CTCAE, National Cancer Institute Common Toxicity Criteria for Adverse Events; PFS, progression-free survival; PLDH, pegylated liposomal doxorubicin hydrochloride; RECIST, Response Evaluation Criteria for Solid Tumors.		

Rosenberg *et al*.[28]

Item	**Details**	
Study	Rosenberg *et al*.	
Location	Sweden	
Trial sponsor	Not reported	
Patient enrolment	Between February 1995 and June 1998	
Trial design	Bi-factorial, stratified, multicentre trial, phase not reported.	
Line of therapy	Second line only	
Inclusion criteria	• One prior platinum-containing regimen of chemotherapy not containing a taxane; • Measurable disease documented clinically and/or radiologically; • Adequate physiologic function and status; • Karnofsky performance status ≥60; • Anticipated survival of ≥12 weeks	
Exclusion criteria	• History of atrial or ventricular arrhythmias or congestive heart failure, even if medically controlled, or documented myocardial infarction within 6 months or a history of second or third degree heart block; • Pre-existing motor or sensory neurotoxicity >grade 2 according to the WHO criteria.	
All outcomes reported	OS, TTP, response	
Subgroups	None	
Stratification	Platinum resistance (i.e. relapse ≤6 months *vs* >6 months after primary platinum-based therapy)	
Measure of disease response or progression	Progression and response assessed according to WHO tumour response criteria	
Ethnicity	Not reported	
Disease classifications according to platinum sensitivity	Platinum resistant/sensitive: relapse ≤6 months and >6 months after primary platinum-based therapy.	
Other definitions	OS: from the day of randomisation to the day of death or censored observation TTP: from the first day of study treatment to the day of documented progression or censored observation Response duration for patients with CR: from the day of first observation of CR to the day of documented progression or censored observation Response duration for patients with PR: from the first day of study treatment to the day of documented progression or censored observation	
Treatment	**Intervention: Paclitaxel weekly**	**Comparator: Paclitaxel 3 weekly**
Randomised, n	105	103
Withdrawals, n (%)	32 (30%)	16 (15.5%)

Treatment	Paclitaxel 67 mg/m^2 weekly	Paclitaxel 200 mg/m^2 every 3 weeks
	Patients within paclitaxel groups also randomised to oral steroids 12 and 6 hours before paclitaxel OR parenteral steroids 30 min before paclitaxel.	
Treatment duration	Median number of courses: 5.7 (1–16)	Median number of courses: 7 (1–17)
Treatment discontinuation	Protocol allowed indefinite treatment: If no haematological toxicity occurred the dose was escalated maximally by two steps. Dose reduction was performed in case of severe cytopenia. Patients who could not tolerate the lowest dose level were taken off the study treatment. No dose escalation was allowed once a dose reduction had been made. If infusion was interrupted due to a hypersensitivity reaction patients could be re-treated at the investigator's discretion. Decision on whether or not to continue treatment was made on basis of tumour assessments every 6 weeks. Patients with PD were taken off the study. Patients with SD received treatment until either progression or unacceptable toxicity occurred. Patients who achieved a CR or a PR continued study treatment for a minimum of 6 weeks and thereafter at the investigator's discretion to tumour progression/relapse or unacceptable toxicity whichever came first. Cycles were to be given as planned – not permissible to prolong treatment free interval.	
Concomitant medications	Oral dexamethasone 20 mg or its equivalent 12 and 6 hours before paclitaxel (group A1) OR dexamethasone 20 mg IV 30 min before paclitaxel (group A2). All patients received clemastine 2 mg and cimetidine 300 mg or ranitidine 50 mg 30 min before paclitaxel.	Oral dexamethasone 20 mg or its equivalent 12 and 6 hours before paclitaxel (group B1) OR dexamethasone 20 mg IV 30 min before paclitaxel (group B2). All patients received clemastine 2 mg and cimetidine 300 mg or ranitidine 50 mg 30 min before paclitaxel.
Duration of follow up	Median 27 months (range: 7–47+)	Median 27 months (range: 7–47+)
Baseline patient characteristics		
Age, years (range)	Median 59 (37–74)	Median 60 (40–76)
Previous treatment	Not reported	Not reported
Platinum-free interval Defined as platinum-resistant tumour (relapse ±6 months after primary chemotherapy)		
Yes	57	51
No	48	52
Prior chemotherapy, n (%)	One prior platinum-containing regimen of chemotherapy not containing a taxane	One prior platinum-containing regimen of chemotherapy not containing a taxane
One regimen	100%	100%
Primary site of disease	Epithelial (all patients)	
Number of sites of lesions, n (%)	Not reported	
Histologic type, n (%)	Not reported	
Histologic grade	Not reported	
Tumour size, cm		
≤2cm	7	11
2–5cm	34	26
5–10cm	30	26
≥10cm	33	40
Unknown	1	0

Measurable disease	All patients had measurable disease at baseline	
FIGO stage at diagnosis	Not reported	
Performance status	WHO criteria	
0	57	56
1	40	33
2	8	14
Comments	None	
Abbreviations used in table: CR, complete response; OS, overall survival; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria for Solid Tumors; SD, stable disease; TTP, time to progression; WHO, World Health Organization.		

Sehouli *et al*.[37]

Item	Details
Study	Sehouli *et al*.
Location	Germany: 54 German institutions
Trial sponsor	North Eastern Germany Society of Gynaecologic Oncology
Patient enrolment	Between September 2005 and February 2008
Trial design	Phase II, randomised controlled trial, active-control
Line of therapy	Second line
Inclusion criteria	• Age ≥18 years; • Recurrent platinum-resistant epithelial ovarian or primary peritoneal carcinoma after radical surgery and at least one platinum-containing chemotherapy; • Disease had to be measurable by computed tomography or magnetic resonance imaging, or evaluable by CA125 according to the GCIG criteria; • Written, informed consent, and the institutional review boards of all participating centres approved the study; • ECOG performance status of 0 to 2; • Normal values for calculated creatinine clearance or serum creatinine, bilirubin, and liver enzymes; normal bone marrow function; • Weekly laboratory monitoring included CBCs as well as liver and renal function tests. Patients were required to show leukocyte counts of at least 2 × 109/L and platelet counts of at least 100 × 109/L before continuing chemotherapy.
Exclusion criteria	• Secondary malignancy or underlying serious, uncontrolled concurrent medical or psychiatric condition; • Patients who had progressed after non-platinum salvage chemotherapy.
Outcomes reported	Response rate, PFS, and OS, toxicity, tolerability, QoL, symptom control with both regimens
Subgroups	Response rate stratified by best response, CA125 response and tumour response
Stratification	None stated
Measure of disease response or progression	CR and PR were defined according to RECIST criteria for measurable disease or GCIG criteria for serum CA125 levels.
Ethnicity	Not reported
Disease classifications according to platinum sensitivity	Platinum resistance was defined as clinical disease progression after a treatment-free interval of <6 months after a platinum-based regimen. Platinum refractory patients had stable or progressive disease while receiving platinum
Other definitions	OS was measured from random assignment to the date of death resulting from any cause or, for living patients, the date of last contact. CR was defined as complete disappearance of all measurable and assessable disease by physical examination, imaging, and normalization of CA125 as determined

	before the study began. PR was assumed in case of a 50% reduction in the sums of the product of two perpendicular diameters of the tumour. SD was considered for all patients who had less than PR, but no evidence of PD. PD was defined as an increase of least 25% in the sums of the product of the dimensions of the lesion or evidence of new tumour.	
Treatment	**Intervention: Topotecan weekly**	**Comparator: Topotecan conventional**
Randomised, n	97	97
Withdrawals, n (%)	Not reported	Not reported
Treatment	Topotecan 4.0 mg/m² once each week every 21 days	Topotecan 1.25 mg/m² daily for 5 consecutive days every 28 days
Treatment duration	Mean number of cycles (standard deviation): 3.5 (2.5)	Mean number of cycles (standard deviation): 4.8 (3.3)
Treatment discontinuation	Treatment was continued until intolerable toxicity or disease progression or until the patient refused further therapy. The protocol mandated a maximum treatment duration of 12 months after random assignment.	
Concomitant medications	All patients received 5-HT_3 antagonists intravenously for prophylaxis of nausea and emesis.	
Duration of follow up	23.4 months (range 12.7–41.4 months)	
Baseline patient characteristics		
Age, years (range)	Median 65 (41–82)	Median 61 (36–85)
Previous treatment	Not reported (all patients received prior paclitaxel)	
Platinum-free interval, months	Not reported	
Previous chemotherapy, n (%)		
One regimen	69 (71%)	66 (68%)
Two regimens	28 (29%)	31 (32%)
Primary site of disease	Not reported	
Number of sites of lesions, n (%)	Not reported	
Histologic type, n (%)		
Serous papillary adenocarcinoma	78 (80%)	73 (75%)
Mucinous carcinoma	1 (1%)	2 (2%)
Endometroid carcinoma	0 (0%)	3 (3%)
Other	15 (15%)	15 (15%)
Undifferentiated	1 (1%)	2 (2%)
Peritoneal carcinoma	0 (0%)	1 (1%)
Unknown	1 (1%)	2 (2%)
Histologic grade		
1	5 (5%)	6 (6%)
2	5 (5%)	2 (2%)
3	22 (23%)	30 (31%)
4	63 (65%)	55 (57%)
Unclear	2 (2%)	3 (3%)
Tumour size, cm	Not reported	
Measurable disease		
Yes	86 (89%)	90 (93%)

FIGO stage at diagnosis		
I	2 (2%)	0 (0%)
II	2 (2%)	2 (2%)
III	73 (75%)	76 (78%)
IV	16 (16%)	17 (18%)
Unclear	4 (4%)	2 (2%)
Performance status	ECOG score	
0	33 (34%)	34 (35%)
1	48 (49%)	50 (52%)
2	12 (12%)	11 (11%)
Unknown	4 (4%)	2 (2%)
Comments	None	
Abbreviations used in table: CR, complete response; ECOG, Eastern Cooperative Oncology Group; GCIG, Gynecologic Cancer Intergroup; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria for Solid Tumors; SD, stable disease.		

ten Bokkel Huinink *et al*.[36]

Item	Details
Study	ten Bokkel Huinink *et al*.
Location	International; countries not reported
Trial sponsor	SmithKline Beecham
Patient enrolment	Not reported
Trial design	Phase III, multi-centre, stratified open-label RCT
Line of therapy	Second line
Inclusion criteria	• Stage III/IV disease; • Histologic diagnosis of epithelial ovarian carcinoma; • Failed first-line therapy with a platinum-based chemotherapy regimen; • At least one bidimensionally measurable lesion as evidence by computed tomography or magnetic resonance imaging scan, ultrasound, or physical examination; • At least a 4 week period between prior surgery, hormonal therapy, radiotherapy, or chemotherapy and treatment in the trial; • ECOG performance status of ≤2; • Adequate bone marrow function (WBCD count ≥3500, neutrophil count ≥1500 uL, and platelet count >/+ 100,000/uL); normal liver function (bilirubin level ≤2.0 mg/dL) and normal renal function (creatinine clearance ≥1.5mg/dL or creatinine clearance >60 mL/min).
Exclusion criteria	• Patients who had received more than one previous chemotherapy regimen or who had received topotecan or paclitaxel previously
All outcomes reported	Response rate, duration of response, TTP, OS
Subgroups	Age (≥65 years *vs* <65 years), platinum sensitivity, and presence or absence of ascites
Stratification	Patients stratified by age (≥65 years *vs* <65 years), ascites (present *vs* absent) and platinum sensitivity (resistant, early, interim or late)
Measure of disease response or progression	Response and progression assessed according to WHO criteria.
Ethnicity	Not reported
Disease classifications according to platinum sensitivity	Refractory: progression during chemotherapy Disease relapse was categorised as early (within 3 months), interim (between 3 and 6

	months), or late (>6 months).	
Other definitions	CR defined as the complete disappearance of all known measurable and assessable disease on two separate measurements at least 4 weeks apart. PR defined as a 50% reduction in the sum of products of the perpendicular diameters of all measurable lesions for at least 4 weeks and with no new lesion or progression of assessable disease. Progressive disease defined as a 25% increase in a single measurable lesion, reappearance of measurable disease, clear worsening of assessable disease, or the development of new metastatic disease. Stable disease defined as any measurement not fulfilling the criteria for response or progression, and lasting more than 8 weeks. TTP measured from the time of first study drug administration to documented progressive disease or initiation of third-line therapy. Duration of response measured from the time of initial documented response to the first sign of disease progression.	
Treatment	**Intervention: Topotecan**	**Comparator: Paclitaxel**
Randomised, n	117 (112 received intervention)	118 (114 received intervention)
Withdrawals, n (%)	11/112 (10%)	4/114 (3.5%)
Treatment	Topotecan 1.5 mg/m^2 as a 30 min infusion on 5 consecutive days every 21 days	Paclitaxel 175 mg/m^2 as a 3 hour infusion every 21 days
Treatment duration	Median number of cycles: 5 (1–17)	Median number of cycles: 5 (1–12)
Treatment discontinuation	Patients were withdrawn from treatment if there was a greater than 2-week delay in treatment at the minimum dose of either medication because of toxicity. The number of cycles of both the topotecan and paclitaxel interventions were determined by the patients' response. Patients with a CR/PR continued until progression or for 6 months after the maximal response. Patients who progressed during treatment were removed from the study. Those whose best response was stable disease after 6 courses were removed or switched to the other treatment.	
Concomitant medications	Premedication was not given to the topotecan group unless nausea or vomiting occurred, in which case it was permitted in subsequent cycles. Prophylactic recombinant G-CSF was allowed after the first course of therapy to maintain dose intensity, on day 6 of the topotecan group, if participants had experienced any of: grade 4 neutropenia with fever or infection, grade 4 neutropenia lasting more than 7 days, or grade 3 neutropenia that required a delay in treatment. Dependent on toxicity the dose could vary from 1.0 mg/m^2/d to 2.0 mg/m^2/d.	Patients received premedication with dexamethasone, and both H_1 and H_2 receptor antagonists to prevent hypersensitivity reactions. Prophylactic recombinant G-CSF was allowed after the first course of therapy to maintain dose intensity, on day 2 of the paclitaxel group, if patients had experienced any of: grade 4 neutropenia with fever or infection, grade 4 neutropenia lasting more than 7 days, or grade 3 neutropenia that required a delay in treatment. Dependent on toxicity, the dose could vary from 135 mg/m^2 to 175 mg/m^2.
Duration of follow up	Long-term follow-up was 4 years	

Baseline patient characteristics		
Age, years (range)	Mean 59.2 (29–85)	Mean 58.3 (29–79)
Previous treatment		
Cyclophosphamide	66.0%	69.0%
Carboplatin	55.0%	61.0%
Cisplatin	54.0%	51.0%
Epirubicin	8.0%	5.3%
Doxorubicin hydrochloride	4.5%	6.1%
Doxorubicin	3.6%	3.5%
Etoposide	1.8%	0.9%
Mitoxantrone	1.8%	0.9%
Ifosfamide	1.8%	0.0%
Epirubicin hydrochloride	0.9%	1.8%
Chlorambucil	0.9%	0.9%
Prednimustine	0.9%	0.0%
Fluorouracil	0.0%	0.9%
Pirarubicin	0.0%	0.9%
Treatment-free interval	Platinum refractory: 52/112 (46.4%) Platinum sensitive: 60/112 (53.6%)	Platinum refractory: 55/114 (48.4%) Platinum sensitive: 59/114 (51.8%)
Previous chemotherapy, n (%)		
One regimen	100%	100%
Primary site of disease	Not reported	
Number of sites of lesions, n (%)	Not reported	
Histologic type, n (%)		
Malignant serous	58 (51.8)	59 (51.8%)
Malignant mucinous	6 (5.4%)	6 (5.3%)
Malignant endometrial	10 (8.9%)	15 (13.2%)
Undifferentiated carcinoma	18 (16.1%)	8 (7.0%)
Other	20 (17.9%)	26 (22.8%)
Histologic grade		
0–1	6 (5.0%)	8 (7.0%)
2	23 (20.5%)	29 (25.4%)
3	56 (50.0%)	50 (43.9%)
4	10 (8.9%)	12 (10.5%)
Not determined	17 (15.2%)	15 (13.2%)
Tumour size, cm		
<5cm	54 (48.2%)	53 (46.5%)
≥5cm	56 (50.0%)	59 (51.8%)
Not determined	2 (1.8%)	2 (1.8%)
Measurable disease	All patients had measurable disease at baseline	
FIGO stage at diagnosis	Not reported	
Performance status	ECOG	
0	41 (36.6%)	42 (36.8%)
1	51 (45.5%)	53 (46.5%)
2	20 (17.9%)	17 (14.9%)
3	0	2 (1.8%)

Comments	The methods section of the report states that hazard ratios with 95% CI were calculated. Survival curves were presented for the duration of response, time to progression, and survival, but hazard ratios were not reported. It was also not clear from the data presented whether the median times quoted were based on Kaplan–Meier estimates.
Abbreviations used in table: CR, complete response; ECOG, Eastern Cooperative Oncology Group; G-CSF, granulocyte colony stimulating factor; OS, overall survival; PR, partial response; TTP, time to progression; WBCD, white blood cell differential; WHO, World Health Organization.	

Trial 30–57 (details taken from TA91[32])

Item	Details
Study	30-57; Johnson & Johnson Pharmaceutical Research & Development
Location	Not reported
Trial sponsor	Not reported
Patient enrolment	Not reported
Trial design	Phase III, randomised, open-label, non-inferiority trial
Line of therapy	Second line
Inclusion criteria	• Participants with histologically proven epithelial ovarian carcinoma with measurable disease; • A recurrence of disease or disease progression indicative of failure of first-line platinum based chemotherapy; • Karnofsky performance status (KPS) >60%; • Age >18 years; • adequate bone marrow function: platelets >100,000 / mm3, haemoglobin >9g/dL, absolute neutrophil count (ANC) >1500 cells / mm3; • Adequate renal function: creatinine <2.5 mg/dL (<220 umol/L); • Adequate liver function: aspartate amino transferase (AST) and alanine amino transferase (ALT) <2 times upper limit or normal, alkaline phosphatase <2.0 times upper limit of normal, except if attributed to tumour, and bilirubin <upper limit of normal. • Cardiac (left ventricular) ejection fraction (LVEF) <50% determined by MUGA scan (or within normal range for assessing institution); • Disease free prior malignancies for >5 years with exception of curatively treated basal call or squamous cell carcinoma of the skin or carcinoma in situ of the cervix.
Exclusion criteria	• Participants who were pregnant or breast-feeding; • Life expectancy < 3 months; • Prior radiation therapy to more than one-third of hematopoietic sites within 30 days prior to first dose of study drug; • History of cardiac disease, with New York Heart Association Class II or greater with congestive heart failure; • Uncontrolled systemic infection; • Any investigational agent within 30 days of first dose of study drug; prior therapy with PLDH or paclitaxel; • Prior chemotherapy within 28 days of first dose of study; • Treatment with high dose therapy supported by bone marrow or peripheral stem cell transplantation at any time
Outcomes reported	Overall survival
Subgroups	Platinum-sensitive disease; platinum-refractory disease
Stratification	By platinum-sensitivity (platinum sensitive [PFI >6 months], platinum refractory [PFI <6 months]) and bulky disease (presence or absence of a tumour mass >5 cm in size)
Measure of disease response or progression	Not reported

Ethnicity	White: 210/216 (97.2%); Black: 1/216 (0.5%); Hispanic: 2/216 (0.9%); Asian: 3/216 (1.4%)	
Disease classifications according to platinum sensitivity	Participants who had initially responded to platinum-based therapy and who had a PFI of more than 6 months off treatment were classified as platinum-sensitive. Participants who progressed during treatment, or who had stable disease in response to initial platinum-based therapy, or whose disease relapsed within 6 months of cessation of therapy were classified as having platinum refractory disease.	
Other definitions	CR: complete disappearance of all measurable and evaluable disease. No new lesions and no disease related symptoms. PR: >50% decrease in the sum of the products of bio-dimensional perpendicular diameters of all measurable lesions. No progression of evaluable disease. No new lesions.	
Treatment	**Intervention: PLDH**	**Comparator: paclitaxel**
Randomised, n	108	108
Withdrawals, n (%)	Disease progression: 42/108 (38.9%) Death: 12/108 (11.1%) Adverse event: 18/108 (16.7%) Lost-to-follow up: 0 (0%) Other/unknown: 10/108 (9.3%) Completed protocol treatment: 26/108 (24.1%)	Disease progression: 30/108 (27.8%) Death: 5/108 (4.6%) Adverse event: 7/108 (6.5%) Lost-to-follow up: 1/108 (0.1%) Other/unknown: 12/108 (11.1%) Completed protocol treatment: 53/108 (49.1%)
Treatment	PLDH 50 mg/m^2 (1 hour infusion) every 28 days	Paclitaxel 175 mg/m^2 (3 hr infusion) every 21 days
Treatment duration	Mean (standard deviation): 98.7 days (77.05) Median (range): 85.0 (1–448)	Mean (standard deviation): 106.2 days (50.13) Median (range): 106.0 (1–260)
Treatment discontinuation	Not reported	Not reported
Concomitant medications	None; the prophylactic use of hematopoietic cytokines was discouraged in conjunction with the first dose of study drug. Their use was recommended in subsequent cycles under specific circumstances: in participants with prolonged neutropenia (Grade 4 neutropenia lasting >7days, or failure of ANC to recover within 22 days), or the occurrence of febrile neutropenia in a prior cycle of treatment. Pyridoxine (B6) was recommended for the treatment of hand-foot syndrome symptoms.	All paclitaxel treated participants were to be premedicated with corticosteroids, antihistamines, and H_2 antagonists prior to paclitaxel administration. The prophylactic use of hematopoietic cytokines was discouraged in conjunction with the first dose of study drug. Their use was recommended in subsequent cycles under specific circumstances: in participants with prolonged neutropenia (Grade 4 neutropenia lasting >7days, or failure of ANC to recover within 22 days), or the occurrence of febrile neutropenia in a prior cycle of treatment. Pyridoxine (B6) was recommended for the treatment of hand-foot syndrome symptoms.
Duration of follow up	Not reported	
Baseline patient characteristics		
Age, years (range)	Mean 58.4 (27–80)	Mean 59.5 (20–78)
Previous treatment	Platinum-based first line monotherapy regimen Prior anthracycline therapy: 10/108 (9.3%)	Platinum-based first line monotherapy regimen Prior anthracycline therapy: 15/108 (13.9%)
Duration of platinum-free interval	Mean (standard deviation): 9.0 months (9.98) Median (range): 6.6 months (1.0–69.4)	Mean (standard deviation): 11.1 months (17.34) Median (range): 6.7 months (range 0.9–109.1)
Prior chemotherapy, n (%) One regimen	108/108 (100%)	108/108 (100%)

Primary site of disease	Not reported	Not reported
Number of sites of lesions, n (%)	Not reported	Not reported
Histologic type, n (%)		
Serious papillary	29/105 (26.9%)	24/102 (22.2%)
Mucinous	0 (0%)	1/102 (0.9%)
Unspecified adenocarcinoma	12/105 (11.1%)	18/102 (16.7%)
Not specified	67/105 (62%)	65/102 (60.2%)
Histologic grade		
Moderately differentiated	1/108 (0.9%)	6.108 (5.6%)
Poorly differentiated	12/108 (11.1%)	13/108 (12.0%)
Unspecified differentiated	28/108 (25.9%)	24/108 (22.2%)
Not specified	67/108 (62%)	65/108 (60.2%)
Tumour size, cm	Not reported	
Measurable disease	Not reported	
FIGO stage at diagnosis		
I	10/108 (9.3%)	10/108 (9.3%)
II	11/108 (10.2%)	8/108 (7.4%)
III	64/108 (59.3%)	77/108 (71.3%)
IV	22/108 (20.4%)	13/108 (12.0%)
Performance status	Karnofsky Performance Status at Study Entry	
0	<80: 11/108 (10.2%)	<80: 12/108 (11.1%)
1	>80: 95/108 (88%)	>80: 90/108 (83.3%)
Comments	None	
Abbreviations used in table: AST, aspartate amino transferase; ALT, alanine amino transferase; KPS, Karnofsky performance status; LVEF, left ventricular ejection fraction; PLDH, pegylated liposomal doxorubicin hydrochloride.		

Omura *et al*.[38]

Item	Details
Study	Omura *et al*.
Location	USA (intergroup/multicentre: number of institutions not reported)
Trial sponsor	Study supported by National Cancer Institute grants of the Gynecologic Oncology Group Administrative Office (grant no. CA 27469), the Gynecologic Oncology Group Statistical Office (grant no. CA 37517), the Southwest Oncology Group, the Eastern Cooperative Oncology Group, and the North Central Cancer Treatment Group.
Patient enrolment	Between August 1992 and February 1995
Trial design	Phase III, randomised controlled trial with active control. Treatment regimen sequentially assigned from permuted blocks. Masking unclear.
Line of therapy	Second line
Inclusion criteria	• Histologically confirmed epithelial ovarian cancer treated with no more than one prior platinum-based regimen and no prior taxane; • Performance status of 0, 1, or 2; • Adequate marrow, renal, and hepatic function.
Exclusion criteria	• Borderline carcinoma (grade 0) or neoplasm termed probably malignant; • Prior paclitaxel or irradiation or more than one prior chemotherapy regimen; • Septicaemia, other active infection, acute hepatitis, or severe gastrointestinal bleeding or other serious medical conditions likely to limit the patient's ability to tolerate treatment;

	• History of congestive heart failure or unstable angina or a myocardial infarction within the past 6 months or a history of cardiac arrhythmia requiring antiarrhythmic medication; • Circumstances preventing study completion or follow-up; • Unclassified cases of ovarian cancer; • Past or concomitant malignancy other than skin (excluding melanoma); • Known hypersensitivity to *Escherichia coli*–derived drug preparations.	
Outcomes reported	PFS, OS, tumour response in patients with measurable disease (pleural effusion or elevated CA125 were not regarded as measurable disease), toxicity	
Subgroups	None prespecified	
Stratification	Clinically measurable disease, platinum-sensitivity, cooperative group (see Trial sponsor)	
Measurement of disease response or progression	CR: disappearance of all gross evidence of disease for at least 4 weeks PR: 50% or greater reduction in the product of perpendicular measurements of each lesion for at least 4 weeks.	
Ethnicity	Paclitaxel 250 mg/m^2 (N = 166 evaluated)	Paclitaxel 175 mg/m^2 (N = 164 evaluated)
Black	7 (4%)	4 (2%)
Hispanic	6 (4%)	5 (3%)
White	146 (88%)	149 (91%)
Other/NS	7 (4%)	6 (4%)
Disease classifications according to platinum sensitivity	Platinum-resistant: progression during first-line platinum treatment or within 6 months of completing therapy, a best response of stable disease after six courses of platinum, or stable disease with rising CA125 while on platinum Platinum-sensitive: Initial response to platinum therapy lasting at least 6 months, followed by progression or recurrence.	
Other definitions	PFS: date of first progression or death from any cause. OS: death or last contact if the date of death was unknown.	
Treatment	**Intervention: Paclitaxel 250 mg/m^2 (plus filgrastim 5 or 10 µg/kg)**	**Comparator: Paclitaxel 175 mg/m^2**
Randomised, n	188	184
Withdrawals, n (%)	Seven women randomized to this group were not assessed for response because of death, toxicity, or withdrawal. They were classified as not responding for an intent-to-treat analysis among eligible patients	Three women randomized to this group were not assessed for response because of death, toxicity, or withdrawal. They were classified as not responding for an intent-to-treat analysis among eligible patients.
	Reasons for ineligibility in the two treatment groups included inappropriate disease site (N = 34), improper prior treatment (N = 7), inadequately documented histology (N = 3), second primary cancer (N = 3), inadequate documentation of recurrence (N = 2), borderline tumour histology (N = 1), and wrong disease stage (N = 1).	
Treatment	Paclitaxel 250 mg/m^2 by 24-hour intravenous infusion every 3 weeks (patients in this group also randomized to filgrastim 5 or 10 mcg/kg/day subcutaneously)	Paclitaxel 175 mg/m^2 by 24-hour intravenous infusion every 3 weeks
Treatment duration	≥6 cycles (55% of patients)	≥6 cycles (58% of patients)
Treatment discontinuation	Patients who did not exhibit clinical progression or excessive toxicity after 6 cycles of therapy could continue treatment indefinitely. Paclitaxel dose could be reduced for some grade 3 or greater toxicities. Over the initial 6 cycles, approximately 70% of patients received their planned	Patients who did not exhibit clinical progression or excessive toxicity after 6 cycles of therapy could continue treatment indefinitely. Paclitaxel dose could be reduced for some grade 3 or greater toxicities. Over the initial 6 cycles, approximately 76% of patients received their planned ideal

	ideal dose.	dose.
Concomitant medications	Filgrastim 5 or 10 mcg/kg/day subcutaneously	Patients experiencing neutropenic fever were permitted to receive filgrastim during subsequent therapy cycles
Duration of follow up	Not reported	
Baseline patient characteristics (eligible patients)		
Age, years (range)	Median 62 (range 24–80)	Median 60 (range 23–88)
Previous treatment	Not reported (no more than one prior platinum-based regimen and no prior taxane)	Not reported (no more than one prior platinum-based regimen and no prior taxane)
Duration of platinum-free interval	Not reported. Platinum resistant: 132 (79%) Platinum sensitive: 34 (21%)	Not reported. Platinum resistant: 125 (76%) Platinum sensitive: 39 (24%)
Prior chemotherapy, n (%) One regimen	 166 (100%)	 164 (100%)
Primary site of disease	Histologically confirmed epithelial ovarian cancer	
Number of sites of lesions, n (%)	Not reported	
Histologic type, n (%) Serous Endometrioid Mucinous Clear cell Other	 100 (60%) 22 (13%) 7 (4%) 11 (7%) 26 (16%)	 105 (63%) 17 (10%) 0 (0%) 8 (5%) 34 (21%)
Histologic grade	Not reported	
Tumour size, cm	Not reported	
Measurable disease	134 (81%)	131 (80%)
FIGO stage at diagnosis	Not reported	
Performance status 0 1 2	GOG Performance status at study entry 88 (53%) 63 (38%) 15 (9%)	 89 (54%) 65 (40%) 10 (6%)
Comments	At initiation, the study included a paclitaxel 135 mg/m^2 treatment arm. Accrual to this low-dose arm decreased when paclitaxel became commercially available and enrolment ceased in October 1993. Patients treated with paclitaxel 250 mg/m^2 were randomly assigned to receive filgrastim (5 or 10 mcg/kg/d subcutaneously) to assess its effect on the incidence of febrile neutropenia.	
Abbreviations used in table: GOG Gynecologic Oncology Group		

Appendix 3. Table of excluded studies with rationale

Paper excluded	Full reference details	Reason for exclusion
Aghajanian 2011	Aghajanian C, Blank SV, Goff BA, Judson PL, Teneriello MG, Husain A, *et al*. OCEANS: a randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. *Int J Gynecol Cancer* 2011; **21**:S11.	Comparator (bevacizumab plus gemcitabine plus carboplatin not approved by NICE)
Aghajanian 2012(a)	Aghajanian C, Blank SV, Goff BA, Judson PL, Nycum LR, Sovak MA. An updated safety analysis of OCEANS, a randomized, double-blind, phase III trial of gemcitabine (G) and carboplatin (C) with bevacizumab (BV) or placebo (PL) followed by BV or PL to disease progression (PD) in patients with platinum-sensitive (Plat-S) recurrent	Comparator (bevacizumab plus gemcitabine plus carboplatin not approved by

	ovarian cancer [abstract]. *J Clin Oncol*: ASCO annual meeting proceedings 2012; **30**.	NICE)
Aghajanian 2012(b)	Aghajanian C, Blank SV, Goff BA. An updated safety analysis of OCEANS, a randomized, double-blind, phase III trial of gemcitabine (G) and carboplatin (C) with bevacizumab (BV) or placebo (PL) followed by BV or PL to disease progression (PD) in patients with platinum-sensitive (PS) recurrent ovarian cancer [abstract]. *J Clin Oncol*: ASCO annual meeting proceedings 2012; **30**.	Comparator (bevacizumab plus gemcitabine plus carboplatin not approved by NICE)
Aghajanian 2012(c)	Aghajanian C, Makhija S, Rutherford T, Sharma S, Nycum L, Sovak M, *et al*. Independent radiologic review of OCEANS, a phase III trial of carboplatin, gemcitabine, and bevacizumab or placebo for the treatment of platinum-sensitive, recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. *Gynecol Oncol* 2012; **125**:S30-1.	Comparator (bevacizumab plus gemcitabine plus carboplatin not approved by NICE)
Aghajanian 2012(d)	Aghajanian C, Blank SV, Goff BA, Judson PL, Teneriello MG, Husain A, *et al*. OCEANS: a randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. *J Clin Oncol* 2012; **30**:2039-45.	Comparator (bevacizumab plus gemcitabine plus carboplatin not approved by NICE)
Alberts 2007	Alberts DS, Liu PY, Wilczynski S, Clouser M, Lopez A, Lange M, *et al*. Phase III randomized trial of pegylated liposomal doxorubicin plus carboplatin versus carboplatin in platinum-sensitive patients with recurrent epithelial ovarian or peritoneal carcinoma after failure of initial platinum-based chemotherapy: Southwest Oncology Group Protocol S0200 [abstract]. *J Clin Oncol*: ASCO annual meeting proceedings 2007; **25**(1).	Conference abstract of an already identified full publication
Alexandre 2012	Alexandre J, Brown C, Coeffic D, Raban N, Pfisterer J, Maenpaa J, *et al*. CA-125 can be part of the tumour evaluation criteria in ovarian cancer trials: experience of the GCIG CALYPSO trial. *British J Cancer* 2012; **106**:633-7.	Not RCT
Alvarez 2009	Alvarez RD, Mannel R, Garcia AA, Gallion HH, Lucci J III, Kilgore LC, *et al*. Fixed-dose rate gemcitabine plus carboplatin in relapsed, platinum-sensitive ovarian cancer patients: results of a three-arm Phase I study. *Gynecol Oncol* 2009; **115**:389-95.	Not RCT
Andersson 2000	Andersson H, Boman K, Ridderheim M, Rosenberg P, Sorbe B, Puistola U, *et al*. An updated analysis of a randomized study of single agent paclitaxel (P) given weekly vs. every 3 weeks to patients (PTS) with ovarian cancer (OV) treated with prior platinum therapy [abstract]. Proceedings of the American Society of Clinical Oncology 2000; **19**:380a.	Conference abstract of an already identified full publication
Armstrong 2006	Armstrong DK, Bundy B, Wenzel L, Huang HQ, Baergen R, Lele S, *et al*. Intraperitoneal cisplatin and paclitaxel in ovarian cancer. *N Eng J Med* 2006; **354**: 34-43.	First-line therapy

Bamias 2012	Bamias A, Timotheadou E, Aravantinos G. Randomized, phase III study of carboplatin plus paclitaxel for 8 cycles (CP8) versus carboplatin x 8 cycles plus paclitaxel x 4 cycles (C8P4) in advanced ovarian, fallopian, or primary peritoneal carcinoma [abstract]. *J Clin Oncol*: ASCO annual meeting proceedings 2012; **30**.	First-line therapy
Basu 2011	Basu C. Second line chemotherapy in platinum potentially resistant recurrent epithelial ovarian cancer: Experience from Eastern India. *Int J Gynecol Cancer* 2011; **21**:99.	Author contacted with a request for additional information; Insufficient information to include
Bidzinski 2009	Bidzinski M, Poveda A, Vermorken J, Kaye S, Makhson A, Jagiello-Gruszfeld A, *et al*. Influence of an independent review on PFS and response assessments in a phase III clinical trial in relapsed ovarian cancer. *Eur J Cancer* 2009; **7** Suppl:468.	Not RCT
Bokkel Huinink 1996	Bokkel Huinink W, Gore M, Spaczynski M, Carmichael J, Davison N, Hudson I, et al. Topotecan, a new active drug, vs paclitaxel in advanced epithelial ovarian carcinoma: International Topotecan Study Group Trial [abstract]. Proceedings of the European Society of Medical Oncology 1996.	Conference abstract of an already identified full publication
Bolis 2004	Bolis G, Scarfone G, Polverino G, Raspagliesi F, Tateo S, Richiardi G, *et al*. Paclitaxel 175 or 225 mg per meters squared with carboplatin in advanced ovarian cancer: a randomized trial. *J Clin Oncol* 2004; **22**: 686-90.	First-line therapy
Boman 2010	Boman K, Colombo N, Runnebaum IB, Vergote I, Gore M, Oaknin A, et al. Tolerability of trabectedin (TR) plus pegylated liposomal doxorubicin (PLD) in platinum sensitive (p-s) vs. platinum resistant (P-R) patients (PTS) with relapsed ovarian cancer. *Ann Oncol* 2010; **21**:viii306.	Not RCT
Coleman 2007	Coleman RL, Gordon A, Barter J, Sun S, Rackoff W, Herzog TJ. Early changes in CA125 after treatment with pegylated liposomal doxorubicin or topotecan do not always reflect best response in recurrent ovarian cancer patients. *Oncologist* 2007; **12**:72-8.	Not RCT
Colombo 2011	Colombo N. Efficacy of trabectedin in platinum-sensitive-relapsed ovarian cancer: new data from the randomized OVA-301 study. *Int J Gynecol Cancer* 2011; **21**:S12-6.	Not RCT
de Jongh 2002	de Jongh FE, de Wit R, Verweij J, Sparreboom A, van den Bent MJ, Stoter G, *et al*. Dose-dense cisplatin/paclitaxel. a well-tolerated and highly effective chemotherapeutic regimen in patients with advanced ovarian cancer. *Eur J of cancer* 2002; **38**:2005-13.	First-line therapy
Diebolder 2010	Diebolder H, Runnebaum I, Poveda A, Monk BJ, Zintl P, Lehmann-Willenbrock E, *et al*. Extending platinum-free interval (PFI) in partially platinum-sensitive (PPS) patients (pts) with recurrent ovarian cancer (ROC) treated with trabectedin (Yondelis) plus pegylated liposomal doxorubicin (Caelyx [PLD]) combination versus PLD alone: results from a PPS cohort of the OVA-301 phase III study. *Arch of Gynecol & Obstet* 2010; **282**:S50.	Conference abstract of an already identified full publication
Eisenhauer 1997	Eisenhauer E, Hoskins P, Beare S, Roy M, Drouin P, Stuart G, *et al*. Randomized phase II study of two schedules of topotecan in previously treated epithelial ovarian cancer [abstract]. Proceedings of the American Society of Clinical Oncology 1997; 16:349a.	Not in TA91
Eisenhauer 1997	Eisenhauer EA, ten Bokkel Huinink WW, Swenerton KD, Gianni L, Myles J, van der Burg ME, *et al*. European-Canadian randomized trial of paclitaxel in relapsed ovarian cancer: high-dose versus low-dose and long versus short infusion. *J Clin Oncol* 1994; **12**:2654-66.	Not in TA91
Gladieff 2009	Gladieff L, Lortholary A, Largillier R, Weber B, Alexandre J, Durando X, *et al*. Weekly paclitaxel (wP) as single agent or in combination with weekly topotecan (wT) or carboplatin (C) in patients with resistant ovarian cancer (ROC): the phase II CARTAXHY randomized trial	Conference abstract of an already identified full publication

	from GINECO [abstract]. *J Clin Oncol* 2009; **27**:291.	
Gladieff 2009	Gladieff L, Lortholary A, Largillier R, Weber B, Alexandre J, Durando X, *et al*. Weekly paclitaxel (wP) as single agent or in combination with weekly topotecan (wT) or carboplatin (C) in patients with resistant ovarian cancer (ROC): the phase II CARTAXHY randomized trial from GINECO [abstract]. 45th Annual Meeting of the American Society of Clinical Oncology; Orlando, Florida, USA; 29 May–2 June 2009	Conference abstract of an already identified full publication
Gonzalez-Martin 2003	Gonzalez Martin AA, Calvo E, Bover I, Rubio MJ, Arcusa A, Casado A, *et al*. Randomised phase II study of carboplatin (C) versus paclitaxel-carboplatin (PC) in platinum-sensitive (PS) recurrent advanced ovarian carcinoma (AOC) with assessment of quality of life (QoL): a GEICO study (Spanish Group for Investigation on Ovarian Carcinoma) [abstract]. Proceedings of the American Society of Clinical Oncology 2003; **22**:451.	Conference abstract of an already identified full publication
Gordon 1998	Gordon A, Carmichael J, Malfetano J, Gore M, Spaczynski M, Clarke D, *et al*. Final analysis of a phase iii, randomized study of topotecan (T) vs. paclitaxel (P) in advanced epithelial ovarian carcinoma (Oc): International Topotecan Study Group. Proceedings of the annual meeting of the American Society of Clinical Oncology 1998.	Conference abstract of an already identified full publication
Gordon 2003	Gordon A, Teitelbaum A. Overall survival advantage for pegylated liposomal doxorubicin compared to topotecan in recurrent epithelial ovarian cancer [abstract]. *Eur J Cancer* 2003; **1**:S51.	Unobtainable
Gordon 2006	Gordon A, Sun S, Rackoff W. Incidence of adverse events in women (</=65 or >65 years) with recurrent ovarian cancer receiving pegylated liposomal doxorubicin or topotecan [abstract]. *Gynecol Oncol* 2006; **101**:S59-60.	Conference abstract of an already identified full publication
Gordon 2002	Gordon AN, Fleagle JT, Guthrie D, Parkin DE, Gore M, Lacave AJ, Mutch D. Interim analysis of a phase III randomized trial of Doxil/Caelyx (D) versus topotecan (T) in the treatment of patients with relapsed ovarian cancer [abstract]. Proceedings of the American Society of Clinical Oncology 2000; **19**:380a.	Conference abstract of an already identified full publication
Gore 1998	Gore M, Rustin G, Calvert H, Bezwoda W, Carmichael J, Oza A, *et al*. A multicentre, randomised, phase III study of topotecan (T) administered intravenously or orally for advanced epithelial ovarian carcinoma. Proceedings of the annual meeting of the American Society of Clinical Oncology 1998.	Conference abstract of an already identified full publication
Greimel 2006	Greimel ER, Bjelic-Radisic V, Pfisterer J, Hilpert F, Daghofer F, du Bois A. Randomized study of the Arbeitsgemeinschaft Gynaekologische Onkologie Ovarian Cancer Study Group comparing quality of life in patients with ovarian cancer treated with cisplatin/paclitaxel versus carboplatin/paclitaxel. *J Clin Oncol* 2006; **24**:579-86.	First-line therapy
Herzog 2011	Herzog TJ, Sill MW, Walker JL, O'Malley D, Shahin M, Degeest K, *et al*. A phase II study of two topotecan regimens evaluated in recurrent platinum-sensitive ovarian, fallopian tube or primary peritoneal cancer: a Gynecologic Oncology Group study (GOG 146Q). *Gynecol Oncol* 2011; **120**:454-8.	Not RCT
Hoskins 1998	Hoskins, P., Eisenhauer, E., Beare, S., Roy, M., Drouin, P., Stuart, G., Bryson, P., Grimshaw, R., Capstick, V., and Zee, B. Randomized phase II study of two schedules of topotecan in previously treated patients with ovarian cancer: a National Cancer Institute of Canada Clinical Trials Group study J CLIN ONCOL 1998; 16: 2233-2237.	Not in TA91
Isonishi 2008	Isonishi S, Yasuda M, Takahashi F, Katsumata N, Kimura E, Aoki D, *et al*. Randomized phase III trial of conventional paclitaxel and carboplatin (c-TC) versus dose dense weekly paclitaxel nad carboplatin (dd-TC) in women with advanced epithelial ovarian, fallopian tube or primary peritoneal cancer: Japanese Gynecologic Oncology [abstract]. *J Clin Oncol*: ASCO annual meeting proceedings 2008; **26**:29.	Unobtainable

Isonishi 2008	Isonishi S, Yasuda M, Takahashi F, Katsumata N, Kimura E, Aoki D, *et al*. Randomized phase III trial of conventional paclitaxel and carboplatin (c-TC) versus dose dense weekly paclitaxel nad carboplatin (dd-TC) in women with advanced epithelial ovarian, fallopian tube or primary peritoneal cancer: Japanese Gynecologic Oncology [abstract]. Journal of Clinical Oncology: ASCO Annual Meeting Proceedings 2008; 26: 29444th Annual Meeting of the American Society of Clinical Oncology, Chicago, IL, 30 May – 3 June, 2008	Unobtainable
Katsumata 2009	Katsumata N, Yasuda M, Takahashi F, Isonishi S, Jobo T, Aoki D, *et al*. Dose-dense paclitaxel once a week in combination with carboplatin every 3 weeks for advanced ovarian cancer: a phase 3, open-label, randomised controlled trial. *Lancet* 2009; **374**:1331-8.	First-line therapy
Katsumata 2012	Katsumata N, Yasuda M, Isonishi S. Long-term follow-up of a randomized trial comparing conventional paclitaxel and carboplatin with dose-dense weekly paclitaxel and carboplatin in women with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer: JGOG 3016 trial [abstract]. *J Clin Oncol*: ASCO annual meeting proceedings 2012; **30**.	First-line therapy
Krasner 2009	Krasner CN, Poveda A, Herzog T, Vermorken J, Monk B, Zintl P, *et al*. Health-related quality of life/patient-reported outcomes in relapsed ovarian cancer: results from a randomized phase III study of trabectedin with pegylated doxorubicin (PLD) versus PLD alone [abstract]. *J Clin Oncol*: ASCO annual meeting proceedings 2009; **27**.	Conference abstract of an already identified full publication
Ledermann 2003(a)	Ledermann A. Randomised trial of paclitaxel in combination with platinum chemotherapy versus platinum-based chemotherapy in the treatment of relapsed ovarian cancer (ICON4/OVAR 2.2). Br J Cancer 2003; **88**:S9CT2.	Not RCT
Ledermann 2003(b)	Ledermann JA. Randomized trial of paclitaxel in combination with platinum chemotherapy versus platinum/based chemotherapy in the treatment of relapsed ovarian cancer (ICON4 / OVAR 2.2) [abstract]. Proceedings of the American Society of Clinical Oncology 2003; **44**.	Not RCT
Lehmann-Willenbrock 2010	Lehmann-Willenbrock E, Runnebaum I, Nieto A, Poveda A, Monk BJ, De La Riba MI, *et al*. Extending platinum-free interval (PFI) in partially platinum-sensitive (PPS) patients (pts) with recurrent ovarian cancer (ROC) treated with trabectedin (Yondelis) plus pegylated liposomal doxorubicin (Caelyx[PLD]) combination versus PLD alone: results from a PPS cohort of the OVA-301 phase III study. *Onkologie* 2010; **33**:190.	Conference abstract of an already identified full publication
Luck 2010	Luck HJ, Jackisch C, Schmalfeldt B, Stahle A, Burges A, Kurzeder C, *et al*. Ovar 2.9: a phase III study comparing PLD-doxorubicine-carboplatin (CD) with carboplatin-paclitaxel (CP) in recurrent platin-sensible ovarian cancer. A GCIG study. *Arch Gynecol Obstet* 2010; **282**:S129-30.	Conference abstract of an already identified full publication
Mahner 2011	Mahner S, Meier W, du Bois A. Carboplatin and pegylated liposomal doxorubicin versus carboplatin and paclitaxel in very platinum-sensitive ovarian cancer patients: result from a subset analysis of the CALYPSO phase III GCIG trial [abstract]. *J Clin Oncol*: ASCO annual meeting proceedings 2011; **29**.	Conference abstract of an already identified full publication
Markman 2007	Markman M. Re: 'Randomized phase III trial of three versus six cycles of adjuvant carboplatin and paclitaxel in early stage epithelial ovarian carcinoma: a Gynecologic Oncology Group study [letter]. *Gynecol Oncol* 2007; **105**:279-80.	Not RCT
Marth 2011	Marth C, Alexandre J, Hanker LC. Pegylated liposomal doxorubicin and carboplatin (C-PLD) versus paclitaxel and carboplatin (C-P) in platinum-sensitive ovarian cancer (OC) patients (pts): treatment at recurrence and overall survival (OS) final analysis from CALYPSO Phase III GCIG trial [abstract]. *J Clin Oncol*: ASCO annual meeting proceedings 2011; **29**.	Conference abstract of an already identified full publication

Meden 2000	Meden H. Cisplatin/Paclitaxel vs Carboplatin/Paclitaxel in ovarian cancer FIGO IIB-IV: update of an AGO (Arbeitsgemeinschaft Gynaenkologischer Onkologie) Study Group trial (OVAR-3) [abstract]. *J Cancer Res Clin Oncol* 2000; **126** Suppl 1:R55.	First-line therapy
Meier 1999	Meier W, du Bois A, Olbricht S, Nitz U, Jackisch C, Richter B, *et al*. Cisplatin/paclitaxel vs carboplatin/paclitaxel in ovarian cancer: results of a prospective randomized phase III study. *Int J Gynecol Cancer* 1999; **9**:48A146.	First-line therapy
Monk 2011	Monk BJ, Herzog TJ, Kaye SB. Final survival results of the randomized phase III study of trabectedin with pegylated liposomal doxorubicin (PLD) versus PLD in recurrent ovarian cancer [abstract]. *Clin J Oncol*: ASCO annual meeting proceedings 2011; **29**.	Conference abstract of an already identified full publication
Muggia 1997	Muggia FM, Braly PS, Brady MF, Sutton G, Copeland LJ, Lentz SL, *et al*. Phase III of cisplatin or paclitaxel, versus their combination in suboptimal stage III and IV epithelial ovarian cancer: Gynecologic Oncology Group study #132 [abstract]. Proceedings of the American Society of Clinical Oncology 1997; **16**: 352a.	First-line therapy
Muggia 2000	Muggia FM, Braly PS, Brady MF, Sutton G, Niemann TH, Lentz, SL, *et al*. Phase III randomized study of cisplatin versus paclitaxel versus cisplatin and paclitaxel in patients with suboptimal stage III or IV ovarian cancer: a Gynecologic Oncology Group study. *J Clin Oncol* 2000; **18**:106-15.	First-line therapy
Pfisterer 2004(a)	Pfisterer J, Plante M, Vergote I, du Bois A, Wagner U, Hirte H, *et al*. Gemcitabine/carboplatin vs carboplatin in platinum sensitive recurrent ovarian cancer. Results of a Gynecologic Cancer Intergroup randomized phase III trial of the AGO OVAR, the NCIC CTG and the EORTC GCG [abstract]. *J Clin Oncol* 2004; **22** Suppl 14S.	Conference abstract of an already identified full publication
Pfisterer 2004(b)	Pfisterer J, Plante M, Vergote I, du Bois A, Wagner U, Hirte H, *et al*. Gemcitabine/carboplatin (GC) vs. carboplatin (C) in platinum sensitive recurrent ovarian cancer (OVCA). Results of a Gynaecologic Cancer Intergroup randomized phase III trial of the AGO OVAR, the NCIC CTG and the EORTC GCG [abstract]. Annual meeting proceedings of the American Society of Clinical Oncology 2004; **449**.	Conference abstract of an already identified full publication
Piccart 1998(a)	Piccart-Gebhart M, Green J, Lacave A, Benedetti-Panici P, Reed N, Vergote I, *et al*. A randomized phase II study of taxol or oxaliplatin in platinum-pretreated epithelial ovarian cancer patients [abstract]. Proceedings of the American Society of Clinical Oncology 1998; **17**:349a.	Conference abstract of an already identified full publication
Piccart 1998(b)	Piccart-Gebhart M, Green J, Lacave A, Benedetti-Panici P, Reed, N, Vergote I, *et al*. A randomized phase II study of taxol or oxaliplatin in platinum-pretreated epithelial ovarian cancer patients. Proceedings of the Annual Meeting of the American Society of Clinical Oncology 1998; **17**.	Conference abstract of an already identified full publication
Poveda 2010(a)	Poveda A, Tjulandin S, Kong B, Roy M, Chan S, Filipczyk-Cisarz E, *et al*. Extending platinum-free interval (PFI) in partially platinum-sensitive (PPS) patients (pts) with recurrent ovarian cancer (ROC) treated with trabectedin (Tr) plus pegylated liposomal doxorubicin (Tr+PLD) versus PLD alone: results from a PPS cohort of a phase III study. J Clin Oncol 2010; **28**.	Conference abstract of an already identified full publication
Poveda 2010(b)	Poveda A, Tjulandin S, Kong B, Roy M, Chan S. Extending platinum-free interval (PFI) in partially platinum-sensitive (PPS) patients (pts) with recurrent ovarian cancer (ROC) treated with trabectedin (Tr) plus pegylated liposomal doxorubicin (Tr+PLD) versus PLD alone: results from a PPS cohort of a phase III study [abstract]. *J Clin Oncol*: ASCO annual meeting proceedings 2010; **28**.	Conference abstract of an already identified full publication
Pujade-Lauraine 2009	Pujade-Lauraine E, Mahner S, Kaern J, Gebski V, Heywood M, Vasey P, *et al*. A randomized phase III study of carboplatin and pegylated liposomal doxorubicin versus carboplatin and paclitaxel in relapsed platinum-sensitive ovarian cancer (OC): CALYPSO study of the Gynecologic Cancer Intergroup (GCIG) [abstract]. *J Clin Oncol*:	Conference abstract of an already identified full publication

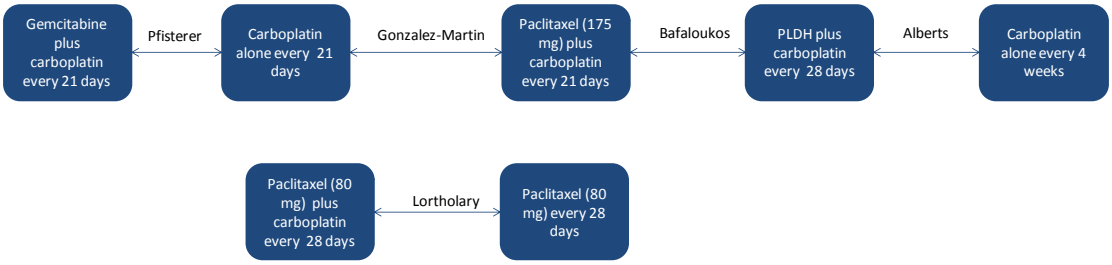
	ASCO annual meeting proceedings 2009; **27**.	
Rosenberg 1999	Rosenberg P, Andersson H, Boman K, Ridderheim M, Sorbe B, Puistola U, et al. A randomized multicenter study of single agent paclitaxel (TAXOL©) given weekly versus every three weeks to patients (PTS) with ovarian cancer (OC) previously treated with platinum therapy [abstract]. Proceedings of the American Society of Clinical Oncology 1999; **18**:368a.	Conference abstract of an already identified full publication
Ross 2001	Ross G, Lane S, Dane G. Long term survival in a phase III randomised study of topotecan (T) vs. paclitaxel (P) in advanced epithelial ovarian carcinoma [abstract]. *Eur J Cancer* 2001; **37** Suppl 6: S326.	Unobtainable
Runnebaum 2011	Runnebaum I, Sehouli J, Gebauer G, Lehmann-Willenbrock E, Schutte J, Zieger W, *et al*. Trabectedin + PLD significantly prolongs survival in platinum sensitive + partially platinum sensitive relapsed ovarian cancer (ROC) patients in comparison to PLD alone. *Onkologie* 2011; **34**:222.	Conference abstract of an already identified full publication
Runnebaum 2010	Runnebaum IB, Poveda A, Hagberg H, Lebedinsky C, Zintl P, Hossfeld M, *et al*. Extending platinum-free interval (PFI) in partially platinum-sensitive (PPS) patients (pts) with recurrent ovarian cancer (ROC) treated with trabectedin (Tr) plus pegylated liposomal doxorubicin (Tr + PLD) versus PLD alone: results from a PPS cohort of a phase III study. *Arch Gynecol Obstet* 2010; **282**:S116O	Conference abstract of an already identified full publication
Scarfone 2001	Scarfone G, Parazzini F, Sciatta C, Rabaiotti E, Richiardi G, Tateo S, *et al*. A multicenter randomized trial comparing two different doses of TAXOL (T) plus a fixed dose of carboplatin (C) in advanced ovarian cancer (AOC) [abstract]. Proceedings of the American Society of Clinical Oncology 2001; **20**(1):205a.	First-line therapy
Scarfone 2006	Scarfone G, Presti M, Scarabelli C, Polverino GP, Polonio N, Bertoglio S. Pegylated liposomal doxorubicin alone or in combination with platinum compounds in recurrent ovarian cancer after first line chemotherapy containing paclitaxel and carboplatin [abstract]. *Int J Gynecol Cancer* 2006; 16: **668**.	Abstract only; insufficient information
Sehouli 2007	Sehouli J, Oskay-Oezcelik G, Stengel D, du Bois A, Markmann S, Loibl S, *et al*. Topotecan weekly versus routine 5-day schedule in patients with platinum-resistant ovarian cancer (TOWER): a randomized, two-stage phase II study of the North-Eastern German Society of Gynaecological Oncology (NOGGO) [abstract]. *J Clin Oncol:* ASCO annual meeting proceedings 2007; **25**(1).	Conference abstract of an already identified full publication
Sehouli 2009(a)	Sehouli J, Oskay-Oezcelik G, Stengel D, Harter D, Kurzeder C, Belau A, *et al*. Topotecan weekly versus routine 5-day schedule in patients with platinum-resistant ovarian cancer (TOWER): a randomized, multicenter trial of the North-Eastern German Society of Gynecological Oncology (NOGGO) [abstract]. *J Clin Oncol* 2009; **27**:290.	Conference abstract of an already identified full publication
Sehouli 2009(b)	Sehouli J, Oskay-Oezcelik G, Stengel D, Harter P, Kurzeder C, Belau A, *et al*. Topotecan weekly versus routine 5-day schedule in patients with platinum-resistent ovarian cancer (TOWER): a randomized multicenter trial of the North-Eastern German Society of Gynecological Oncology (NOGGO) [abstract].Journal of Clinical Oncology: ASCO Annual Meeting Proceedings 2009; 27: Abstract45th Annual Meeting of the American Society of Clinical Oncology; Orlando, Florida, USA; 29 May-2 June 2009	Conference abstract of an already identified full publication
Spriggs 2004	Spriggs DR, Brady M, Rubin S, Hanley M, Copeland LJ, Clarke-Pearson D, *et al*. A phase III randomized trial of cisplatin and paclitaxel administered by either 24 hour or 96 hour infusion in patients with selected stage III or stage IV epithelail ovarian cancer (GOG162) [abstract]. Proceedings of the American Society of Clinical Oncology 2004; 23: **449**.	First-line therapy

Spriggs 2007	Spriggs DR, Brady MF, Vaccarello L, Clarke-Pearson DL, Burger RA, Mannel R, *et al*. Phase III randomized trial of intravenous cisplatin plus a 24- or 96-hour infusion of paclitaxel in epithelial ovarian cancer: a Gynecologic Oncology Group study. *J Clin Oncol* 2007; **25**:4466-71.	First-line therapy
Swenerton 1993	Swenerton K, Eisenhauer E, Bokkel Huinink W, Myles J, Mangioni C, Burg M, *et al*. Taxol in relapsed ovarian cancer: high vs. low dose and short vs. long infusion: a European-Canadian study coordinated by the NCI Canada Clinical Trials Group [abstract]. Proceedings of the American Society of Clinical Oncology 1993; **12**:256.	Unobtainable
ten Bokkel Huinink 1993	ten Bokkel Huinink WW, Eisenhauer E, Swenerton K. Preliminary evaluation of a multicenter, randomized comparative study of TAXOL (paclitaxel) dose and infusion length in platinum-treated ovarian cancer. Canadian-European Taxol Cooperative Trial Group. *Cancer Treat Rev* 1993; **19**:79-86.	Not in TA91
vall-Lundqvist 2008	vall-Lundqvist E, Wimberger P, Gladieff L, Gebski V, Huober JB, Floquet A, *et al*. Pegylated liposomal doxorubicin (PLD)-carboplatin (C) (C-D) in relapsing sensitive ovarian cancer (OC): a 500-patient interim safety analysis of the CALYPSO GCIG Intergroup phase III study [abstract]. *J Clin Oncol*: ASCO annual meeting proceedings 2008; **26**.	Conference abstract of an already identified full publication
Vasey 2009	Vasey P, Largillier R, Gropp M, Gebski V, Sandvei R, Elit L, *et al*. A GCIG randomized phase III study of carboplatin (C) & pegylated liposomal doxorubicin (PLD) (C-D) vs. carboplatin (C) & paclitaxel (P) (C-P): CALYPSO results in partially platinum-sensitive ovarian cancer (OC) patients. *Eur J Cancer* 2009; **7** Suppl 1:11.	Conference abstract of an already identified full publication
Vergote 2004	Vergote I, Plante M, Richter B, Emmerich J, Hirte H, Costa S, *et al*. Improved progression free survival (PFS) and quality of life (QOL) in a randomized study comparing gemcitabine/carboplatinum (GC) vs. carboplatin (C) in platinum sensitive ovarian cancer (OVCA) [abstract]. *Int J Gynecol Cancer* 2004; **14** Suppl 1:45-6.	Abstract only; insufficient information to include
Vergote 2007	Vergote I, Finkler N, Campo J, Lohr A, Hunter J, Matei D, et al. Single agent, canfosfamide (C, TLK286) vs. pegylated liposomal doxorubicin or topotecan in 3rd-line treatment of platinum refractory or resistant ovarian cancer: phase III study results [abstract]. *J Clin Oncol*: ASCO annual meeting proceedings 2007; **25**(1).	Incorrect comparator; results for PLDH and topotecan not reported separately
Vergote 2009	Vergote I, Finkler N, del Campo J, Lohr A, Hunter J, Matei D, *et al*. Study Group Phase 3 randomised study of canfosfamide (Telcyta, TLK286) versus pegylated liposomal doxorubicin or topotecan as third-line therapy in patients with platinum-refractory or -resistant ovarian cancer. *Eur J Cancer* 2009; **45**: 2324-32.	Incorrect comparator; results for PLDH and topotecan not reported separately
Vermorken 2001	Vermorken J, Gore M, Perren T, Vergote I, Colombo N, Harper P, *et al*. Multicenter randomized phase II study of oxaliplatin (OXA) or topotecan (TOPO) in platinum-pretreated epithelial ovarian cancer (EOC) patients (pts) [abstract]. Proceedings of the American Society of Clinical Oncology 2001; **20**(1):212a.	Abstract only; insufficient information to include

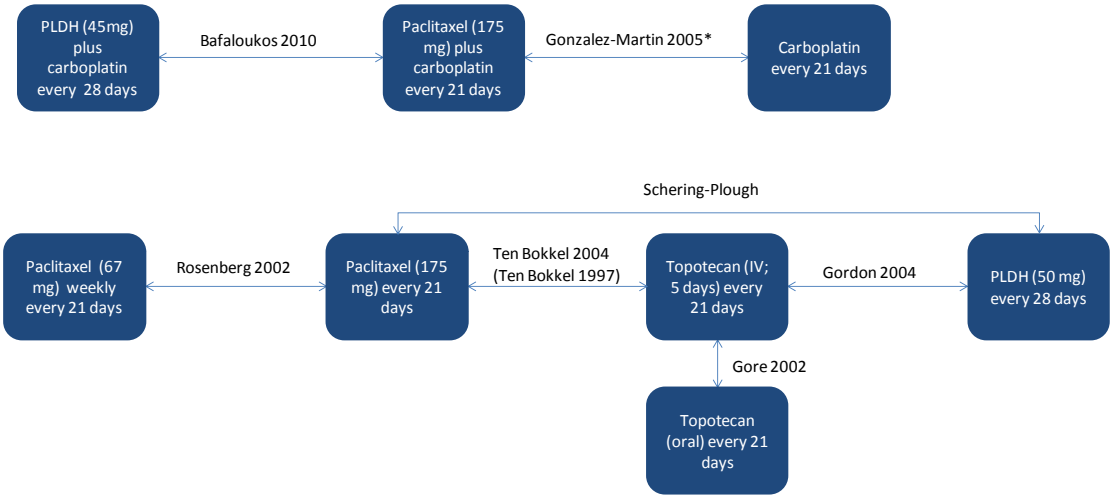
Appendix 4. Networks for the adverse effects network meta-analysis

All potential links are displayed in the networks. In some cases, zero events may have precluded analysis.

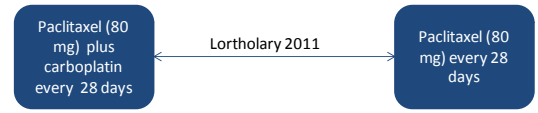
Allergic reaction

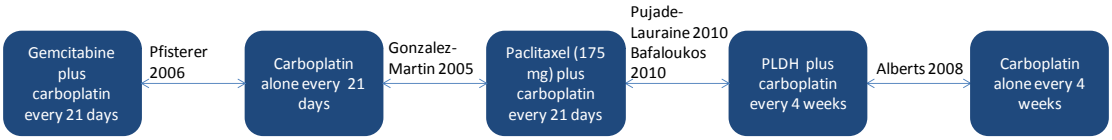


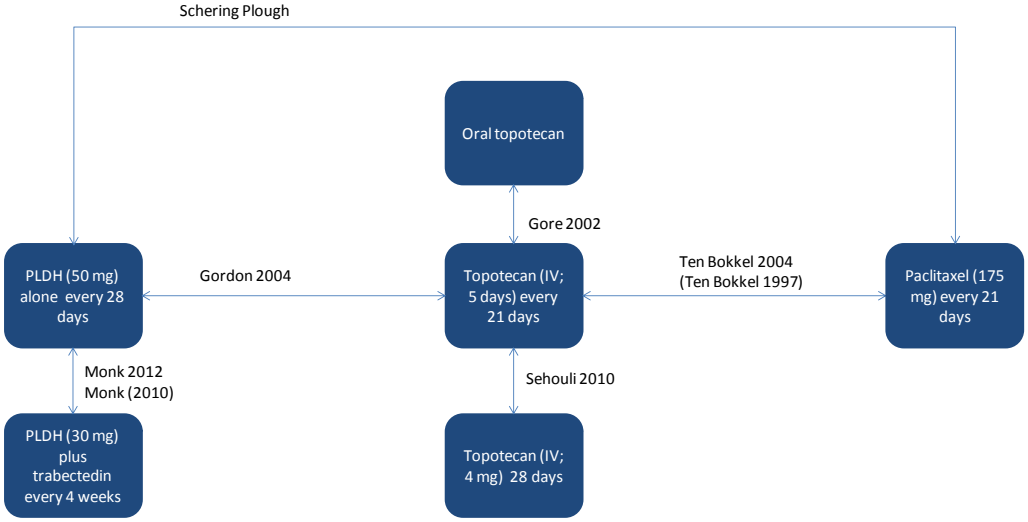
Alopecia



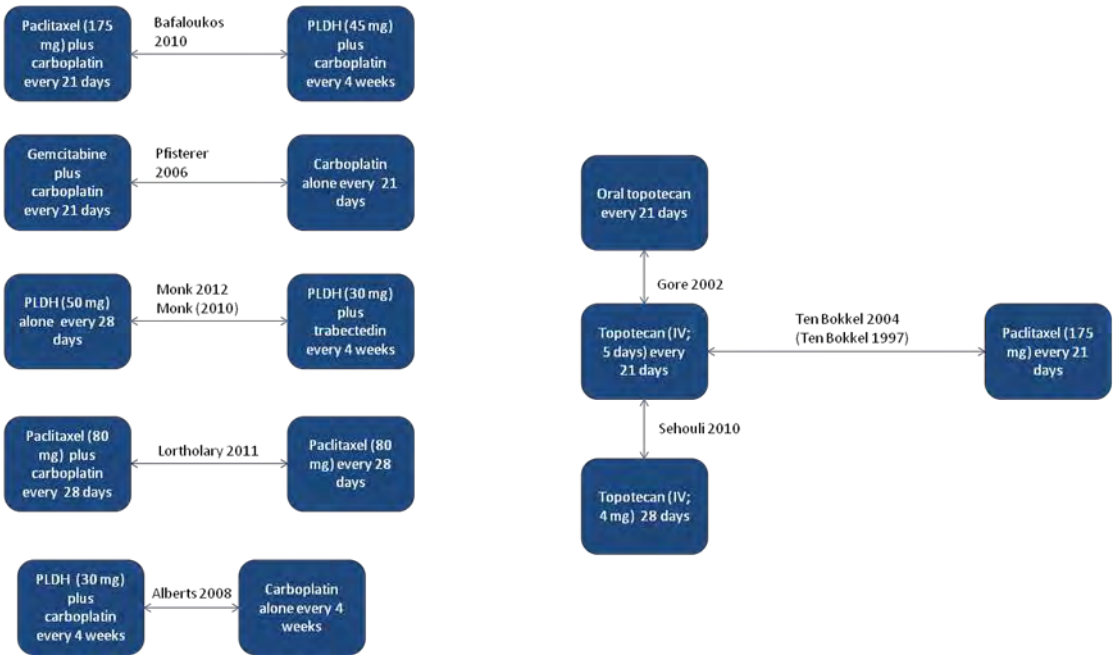
Anaemia



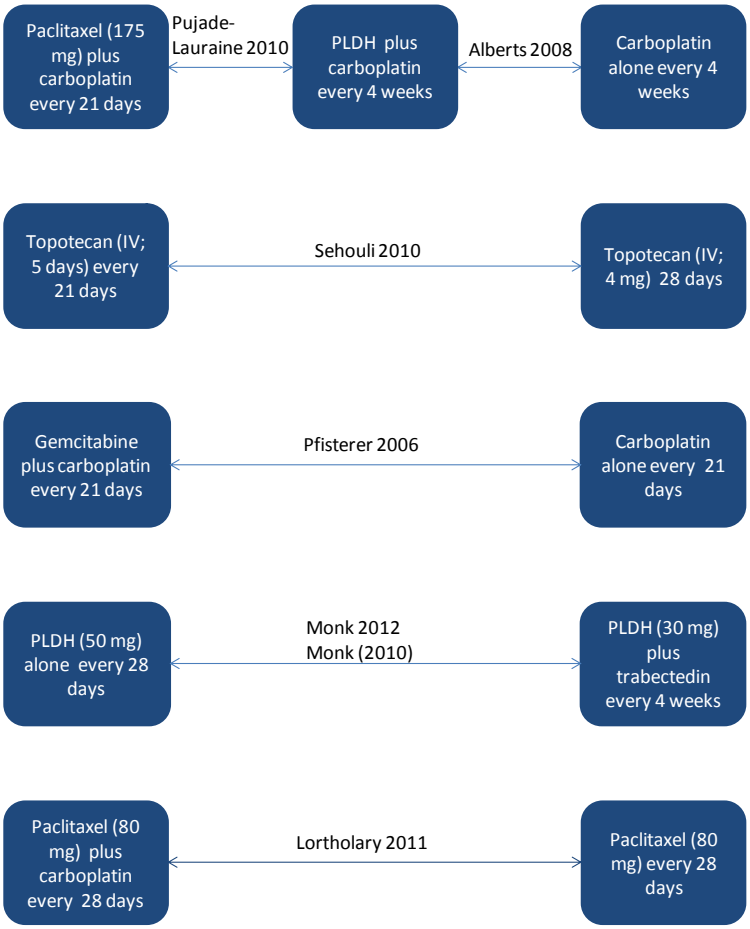




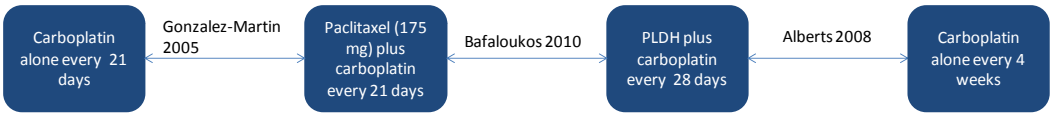
Fatigue

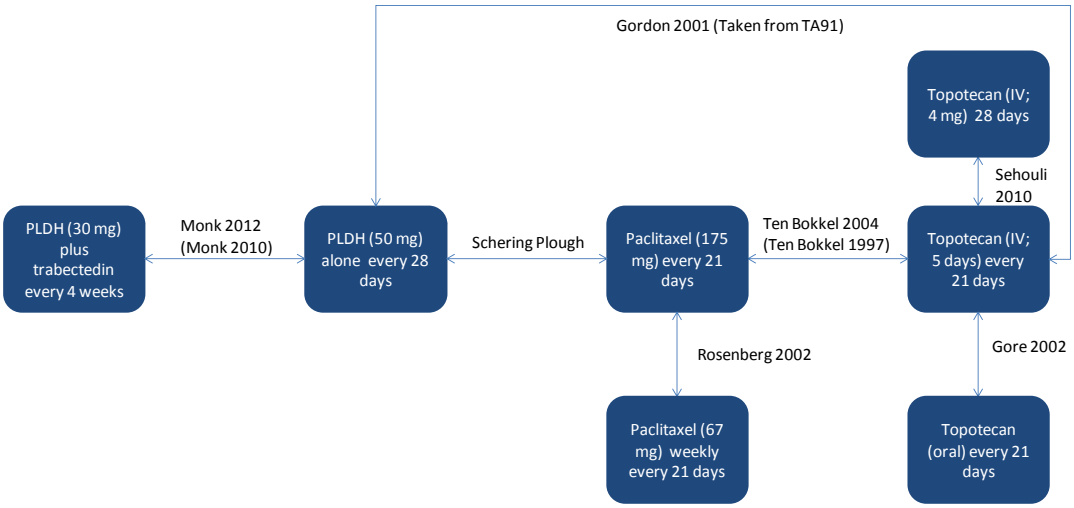


Febrile neutropenia



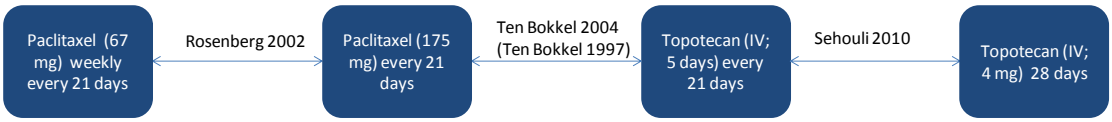
Nausea and vomiting

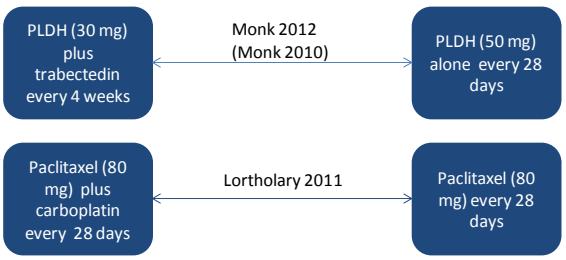

Carboplatin alone every 21 days
Gonzalez-Martin 2005
Paclitaxel (175 mg) plus carboplatin every 21 days
Bafaloukos 2010
PLDH plus carboplatin every 28 days
Alberts 2008
Carboplatin alone every 4 weeks


Gordon 2001 (Taken from TA91)
Topotecan (IV; 4 mg) 28 days
Sehouli 2010
PLDH (30 mg) plus trabectedin every 4 weeks
Monk 2012 (Monk 2010)
PLDH (50 mg) alone every 28 days
Schering Plough
Paclitaxel (175 mg) every 21 days
Ten Bokkel 2004 (Ten Bokkel 1997)
Topotecan (IV; 5 days) every 21 days
Rosenberg 2002
Gore 2002
Paclitaxel (67 mg) weekly every 21 days
Topotecan (oral) every 21 days

Neuropathy


Gemcitabine plus carboplatin every 21 days
Pfisterer 2006
Carboplatin alone every 21 days
Gonzalez-Martin 2005
Paclitaxel (175 mg) plus carboplatin every 21 days
Bafaloukos 2010
PLDH plus carboplatin every 4 weeks


Paclitaxel (67 mg) weekly every 21 days
Rosenberg 2002
Paclitaxel (175 mg) every 21 days
Ten Bokkel 2004 (Ten Bokkel 1997)
Topotecan (IV; 5 days) every 21 days
Sehouli 2010
Topotecan (IV; 4 mg) 28 days


PLDH (30 mg) plus trabectedin every 4 weeks
Monk 2012 (Monk 2010)
PLDH (50 mg) alone every 28 days
Paclitaxel (80 mg) plus carboplatin every 28 days
Lortholary 2011
Paclitaxel (80 mg) every 28 days

Appendix 5: Literature Search Strategies for TAG economic evaluation

Economic evaluation searches

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to present

#	Terms	Hits (4th December 2012)	Hits (23rd May 2013)
1	ovarian neoplasms/	57969	58587
2	exp ovarian neoplasms/	60059	60739
3	(ovar$ adj4 (cancer$ or tumo?r$ or malignan$)).ti.	27883	28450
4	(ovar$ adj4 (cancer$ or tumo?r$ or malignan$)).ab.	41322	42450
5	(ovar$ adj4 (oncolog$ or carcinoma$)).ab.	12353	12521
6	or/1-5	74774	75993
7	Topotecan/	1704	1725
8	topotecan.mp.	2446	2482
9	hycamtin.mp.	70	69
10	or/7-9	2447	2483
11	exp Doxorubicin/	40241	41211
12	doxil.mp.	281	290
13	(doxorubicin hydrochloride or doxorubicin hcl).mp.	562	585
14	liposomal doxorubicin.mp.	1287	1354
15	(caelyx or adriamycin or rubex).mp.	13911	14054
16	liposome encapsulated doxorubicin.mp.	88	88
17	(PLDH or pegylated liposomal doxorubicin hydrochloride).mp	143	163
18	or/11-17	44840	45884
19	paclitaxel/	17785	18248
20	paclitaxel.mp.	22571	23229
21	taxol.mp. or abraxane.mp	6031	6155
22	or/19-21	24178	24878
23	carboplatin/	8360	8580
24	(carboplatin or paraplatin).mp.	11703	12003
25	or/23-24	11703	12003
26	cisplatin/	37783	38561
27	cisplatin.mp.	50320	51546
28	or/26-27	50320	51546
29	10 or 18 or 22 or 25 or 28	112024	114904
30	Limit 29 to yr=2004-2012 (2013)	46970	49826
31	gemcitabine.mp.	9065	9504
32	gemzar.mp	212	216
33	or/31-32	9078	9520
34	Trabectedin.mp	388	396
35	ecteinascidin 743.mp.	131	131
36	ET-743.mp.	171	174
37	yondelis.mp	96	93
38	or/34-37	432	442
39	bevacizumab.mp	7354	7994
40	avastin.mp	927	947
41	or/39-40	7430	8069
42	etoposide.mp	19804	20237
43	Eposin.mp	0	0
44	or/42-43	19804	20237
45	(best supportive care).mp	974	1003
46	33 or 38 or 41 or 44 or 45	36770	38290
47	30 or 46	76853	80860
48	economics/	26664	26636
49	exp costs/ and cost analysis/	40385	40679
50	exp economics, hospital/	18425	18679

51	economics, medical/	8511	8501
52	economics, pharmaceutical/	2387	2442
53	(economic$ or pharmaeconomic$ or pharmacoeconomic$ or pharmaco-economic$).tw.	138434	144495
54	(cost or costs or costly or costing or costed).tw.	294675	306620
55	value for money.tw.	857	869
56	cost utility.mp.	2172	2212
57	cost effectiveness/	56140	56826
58	cost benefit/	56140	56826
59	cost consequence.mp.	107	108
60	cost minimi*ation.mp.	781	803
61	economic evaluation.mp.	4598	4683
62	Or/48-61	465315	482157
63	6 and 47 and 62	74	71
64	limit 63 to ed=20121201-20130523	N/A	**2**

Embase 1974 to present

#	Terms	Hits (4th December 2012)	Hits (23rd May 2013)
1	exp Ovary Cancer/	65122	67668
2	(ovar$ adj4 (cancer$ or tumo?r$ or malignan$)).ti.	34811	35910
3	(ovar$ adj4 (cancer$ or tumo?r$ or malignan$)).ab.	51886	53822
4	(ovar$ adj4 (oncolog$ or carcinoma$)).ab.	15047	15442
5	or/1-4	90905	94505
6	Topotecan/	7884	8187
7	topotecan.mp.	8124	8437
8	hycamtin.mp.	581	591
9	or/6-8	8124	8437
10	exp Doxorubicin/	125207	129170
11	doxil.mp.	1521	1619
12	(doxorubicin hydrochloride or doxorubicin hcl).mp.	645	674
13	liposomal doxorubicin.mp.	1867	1983
14	(caelyx or adriamycin or rubex).mp.	24081	24468
15	liposome encapsulated doxorubicin.mp.	107	112
16	(PLDH or pegylated liposomal doxorubicin hydrochloride).mp.	220	247
17	or/10-16	127421	131439
18	paclitaxel/	57308	60283
19	paclitaxel.mp.	59414	62489
20	(taxol or abraxane).mp.	11748	12030
21	or/18-20	60485	63583
22	carboplatin/	38672	40505
23	(carboplatin or paraplatin).mp.	39961	41870
24	or/22-23	39961	41870
25	cisplatin/	112665	116858
26	cisplatin.mp.	117604	121966
27	or/25-26	117604	121966
28	9 or 17 or 21 or 24 or 27	255147	264864
29	limit 28 to yr=2004-2012 (2013)	130702	140463
30	gemcitabine.mp.	28137	29972
31	gemzar.mp.	1706	1751
32	or/30-31	28148	29985
33	Trabectedin.mp.	1198	1267
34	ecteinascidin 743.mp.	178	181
35	ET-743.mp.	477	490
36	yondelis.mp.	329	344
37	or/33-36	1224	1293
38	bevacizumab.mp.	24620	27022
39	avastin.mp.	6598	6921
40	or/38-39	24651	27054
41	etoposide.mp.	62570	64348
42	Eposin.mp.	20	20

43	or/41-42	62576	64354
44	best supportive care.mp.	1624	1786
45	32 or 37 or 40 or 43 or 44	107900	113504
46	29 or 45	200564	213305
47	economics/	207721	209851
48	exp costs/ and cost analysis/	16393	16842
49	exp economics, hospital/	567261	584236
50	economics, medical/	32131	32624
51	economics, pharmaceutical/	5762	5828
52	(economic$ or pharmaeconomic$ or pharmacoeconomic$ or pharmaco-economic$).tw.	176979	184758
53	(cost or costs or costly or costing or costed).tw.	378322	395583
54	value for money.tw.	1152	1213
55	cost utility.mp.	5779	6082
56	cost effectiveness/	84693	88469
57	cost benefit/	62729	64078
58	cost consequence.mp.	166	173
59	cost minimi*ation.mp.	2723	2824
60	economic evaluation.mp.	11827	12399
61	or/47-60	981563	1014510
62	4 and 46 and 61	633	712
65	limit 62 to em=201247-201321	N/A	77

HTA database (HTA)

Date of search	4th December 2012	21st May 2013
Search terms (and fields searched)	Ovarian neoplasm (all fields) Ovarian cancer (all fields) Ovary cancer (all fields)	Ovarian neoplasm (all fields) Ovarian cancer (all fields) Ovary cancer (all fields) Limit December 4th 2012 to 21st May 2013
Number of hits	65	5

NHS Economic Evaluations Database (NHS EED)

Date of search	4th December 2012	21st May 2013
Search terms (and fields searched)	Ovarian neoplasm (all fields) Ovarian cancer (all fields) Ovary cancer (all fields)	Ovarian neoplasm (all fields) Ovarian cancer (all fields) Ovary cancer (all fields) Limit December 4th 2012 to 21st May 2013
Number of hits	70	7

HRQoL searches

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to present

#	Terms	Hits (4th December 2012)	Hits (23rd May 2013)
1	exp Ovarian Neoplasms/	60059	60739
2	(ovar$ adj4 (cancer$ or tumo?r$ or malignan$ or oncolog$ or carcinoma$ or neoplas$ or mass$ or growth$ or cyst$)).mp.	81853	83124
3	(adenexa$ adj4 mass$).mp.	7	7
4	or/1-3	83643	84962
5	animal/ not (animal/ and human/)	3720388	3757872
6	4 not 5	78554	79809
7	exp Life Tables/	12317	12163
8	exp "Quality of Life"/	104747	108376
9	Health Status/	54169	55687
10	exp Health Status Indicators/	177713	182827
11	(utilit$ approach$ or health gain or hui or hui2 or hui 2 or hui3 or hui 3).ti,ab.	1287	1344
12	(health measurement$ scale$ or health measurement$ questionnaire$).ti,ab.	39	39
13	(standard gamble$ or categor$ scal$ or linear scal$ or linear analog$ or visual scal$ or magnitude estmat$).ti,ab.	3223	3312
14	(time trade off$ or rosser$ classif$ or rosser$ matrix or rosser$ distress$ or hrqol).ti,ab.	6670	7134
15	(index of wellbeing or quality of wellbeing or qwb).ti,ab.	165	166
16	(rating scale$ or multiattribute$ health ind$ or multi attribute$ health ind$).ti,ab.	31065	32283
17	(health utilit$ index or health utilit$ indices).ti,ab.	582	620
18	(multiattribute$ theor$ or multi attribute$ theor$ or multiattribute$ analys$ or multi attribute$ analys$).ti,ab.	9	9
19	(health utilit$ scale$ or classification of illness state$ or 15d or 15 d or 15 dimension).ti,ab.	3303	3393
20	(health state$ utilit$ or 12d or 12 d or 12 dimension).ti,ab.	2279	2350
21	well year$.ti,ab.	22	21
22	(multiattribute$ utilit$ or multi attribute$ utilit$).ti,ab.	173	179
23	health utilit$ scale$.ti,ab.	8	9
24	(qol or 5d or 5-d or 5 dimension or quality of life or eq-5d or eq5d or eq 5d or euroqol).ti,ab.	139143	145531
25	(qualy or qaly or qualys or qalys or quality adjusted life year$).ti,ab.	6089	6240
26	life year$ gain$.ti,ab.	1573	1613
27	willingness to pay.ti,ab.	1978	2039
28	(hye or hyes or health$ year$ equivalent$).ti,ab.	62	62
29	(person trade off$ or person tradeoff$ or time tradeoff$ or time trade off$).ti,ab.	915	942
30	theory utilit$.ti,ab.	7	7
31	life table$.ti,ab.	7420	7166
32	health state$.ti,ab.	3326	3467
33	(sf36 or sf 36).ti,ab.	11840	12389
34	(short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).ti,ab.	5504	5736
35	(6d or 6-d or 6 dimension).ti,ab.	5207	5553
36	or/7-35	430827	444856
37	6 and 36	1518	1539
38	letter.pt.	785671	794959
39	editorial.pt.	322998	330055
40	comment.pt.	527227	538874
41	or/38-40	1223799	1246592

42	37 not 41	1474	1496
43	limit 42 to yr=2004-2012 (2013)	841	865
44	limit 43 to ed=20121201-20130523	N/A	54

Embase 1974 to current

#	Terms	Hits (4th December 2012)	Hits (23rd May 2013)
1	exp Ovarian Cancer/	90833	93629
2	(ovar$ adj4 (cancer$ or tumo?r$ or malignan$ or oncolog$ or carcinoma$ or neoplas$ or mass$ or growth$ or cyst$)).mp.	123449	127280
3	(adenexa$ adj4 mass$).mp.	13	13
4	or/1-3	126934	130811
5	animal/ not (animal/ and human/)	1354956	1367021
6	4 not 5	122457	126280
7	exp Life Tables/	3392	3446
8	exp "Quality of Life"/	221902	234293
9	Health Status/	75649	78135
10	exp Health Status Indicators/	141853	1113
11	(utilit$ approach$ or health gain or hui or hui2 or hui 2 or hui3 or hui 3).ti,ab.	1625	1702
12	(health measurement$ scale$ or health measurement$ questionnaire$).ti,ab.	50	53
13	(standard gamble$ or categor$ scal$ or linear scal$ or linear analog$ or visual scal$ or magnitude estmat$).ti,ab.	3738	3847
14	(time trade off$ or rosser$ classif$ or rosser$ matrix or rosser$ distress$ or hrqol).ti,ab.	9305	9977
15	(index of wellbeing or quality of wellbeing or qwb).ti,ab.	188	194
16	(rating scale$ or multiattribute$ health ind$ or multi attribute$ health ind$).ti,ab.	41599	43458
17	(health utilit$ index or health utilit$ indices).ti,ab.	713	739
18	(multiattribute$ theor$ or multi attribute$ theor$ or multiattribute$ analys$ or multi attribute$ analys$).ti,ab.	14	14
19	(health utilit$ scale$ or classification of illness state$ or 15d or 15 d or 15 dimension).ti,ab.	3968	4109
20	(health state$ utilit$ or 12d or 12 d or 12 dimension).ti,ab.	2682	2785
21	well year$.ti,ab.	24	24
22	(multiattribute$ utilit$ or multi attribute$ utilit$).ti,ab.	232	234
23	health utilit$ scale$.ti,ab.	10	11
24	(qol or 5d or 5-d or 5 dimension or quality of life or eq-5d or eq5d or eq 5d or euroqol).ti,ab.	192239	202999
25	(qualy or qaly or qualys or qalys or quality adjusted life year$).ti,ab.	8724	9257
26	life year$ gain$.ti,ab.	2118	2202
27	willingness to pay.ti,ab.	2720	2874
28	(hye or hyes or health$ year$ equivalent$).ti,ab.	83	90
29	(person trade off$ or person tradeoff$ or time tradeoff$ or time trade off$).ti,ab.	1115	1145
30	theory utilit$.ti,ab.	8	8
31	life table$.ti,ab.	7641	7769
32	health state$.ti,ab.	4797	4995
33	(sf36 or sf 36).ti,ab.	16506	17526
34	(short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).ti,ab.	6610	7022
35	(6d or 6-d or 6 dimension).ti,ab.	5644	5831
36	or/7-35	525702	420454
37	6 and 36	3356	3221
38	letter.pt.	806544	823694
39	editorial.pt.	421004	431762
40	comment.pt.	0	0
41	or/38-40	1227548	1255456
42	37 not 41	3155	3026
43	limit 42 to yr=2004-2012 (2013)	2216	2179
44	limit 43 to em=201247-201321	N/A	184

HTA database (HTA)

Date of search	5th December 2012	23rd May 2013
Search terms (and fields searched)	Ovarian neoplasm (all fields) or Ovarian cancer (all fields) or Ovary cancer (all fields) or **and** quality of life (all fields) or qol (all fields) or qaly (all fields) or	Ovarian neoplasm (all fields) or Ovarian cancer (all fields) or Ovary cancer (all fields) or **and** quality of life (all fields) or qol (all fields) or qaly (all fields) or
Date restriction	2004 to 2012	December 4th 2012 to 21st May 2013
Number of hits	3	0

NHS Economic Evaluations Database (NHS EED)

Date of search	5th December 2012	23rd May 2013
Search terms (and fields searched)	Ovarian neoplasm (all fields) or Ovarian cancer (all fields) or Ovary cancer (all fields) or **and** quality of life (all fields) or qol (all fields) or qaly (all fields) or	Ovarian neoplasm (all fields) or Ovarian cancer (all fields) or Ovary cancer (all fields) or **and** quality of life (all fields) or qol (all fields) or qaly (all fields) or
Date restriction	2004 to 2012	December 4th 2012 to 21st May 2013
Number of hits	30	1

Appendix 6: Excluded studies for TAG economic evaluation

Summary of reasons for excluding economic evaluation studies

Reference	Primary reason for exclusion
December 2012 search	
L. J. P. Havrilesky. Cost-effectiveness of combination versus sequential docetaxel and carboplatin for the treatment of platinum-sensitive, recurrent ovarian cancer. Cancer 118 (2):386-391, 2012.	Duplicate paper
T. Dranitsaris Kim. The lifecycle value of oncology medicines. Value in Health Conference (var.pagings):A224, 2012. Volume 15 issue 4 June 2012 Page A224	Review paper
M. Koczorek. Angiogenesis inhibition: Bevacizumab in ovarian carcinoma is approved. Arzneimitteltherapie 30 (10):320-321, 2012.	Not an economic evaluation
NHSC. Farletuzumab for ovarian cancer: relapsed, platinum-sensitive â€“ in combination with carboplatin and a taxane. Anonymous. Anonymous. 2012.	Not an economic evaluation
C. T. B. Pike. Healthcare costs and workloss burden of patients with chemotherapy-associated peripheral neuropathy in breast, ovarian, head and neck, and nonsmall cell lung cancer. Chemotherapy Research and Practice 2012 , 2012. Article Number:913848, 9138.	Not an economic evaluation
C. Basu. Second line chemotherapy in epithelial ovarian cancer: Experience from a cancer institute of Eastern India. International Journal of Gynecological Cancer Conference (var.pagings):98, 2011. 21(11) May 2011	Not an economic evaluation
C. Basu. Second line chemotherapy in platinum potentially resistant recurrent epithelial ovarian cancer: Experience from Eastern India. International Journal of Gynecological Cancer Conference (var.pagings):99, 2011.	Not an economic evaluation
Comite d'Avaluacio de Medicaments d'Utilitzacio Hospitalaria (CAMUH). [Trabectedin (Yondelis) for the treatment of ovarian cancer]. Anonymous. Anonymous. 2011.	Review paper
M. L. Hensley. Big costs for little gain in ovarian cancer. Journal of Clinical Oncology 29 (10):1230-1232, 2011.	Review paper
K. Manahan Wood. The cost effectiveness of bevacizimab in the primary treatment of ovarian cancer. International Journal of Gynecological Cancer Conference (var.pagings):S674, 2011. Volume 21 Suppl 3 12 S674	Not an economic evaluation
NHSC. Paclitaxel (Paclical) for epithelial ovarian cancer, fallopian tube cancer or peritoneal cancer â€“ second or third line. Anonymous. Anonymous. 2011.	Not an economic evaluation
F. Beijnen Kazazi-Hyseni. Bevacizumab. Oncologist 15 (8):819-825, 2010.	Not an economic evaluation
J. Benard. Enhance the cancer cell in platinum, at all costs. Bulletin du Cancer 97 (9):1029, 2010.	Not an economic evaluation
S. Faure. Cytotoxic antineoplastics. Actualites Pharmaceutiques (497):51-54, 2010.	Not an economic evaluation
L. G. S. Gordon. Medical costs and outcomes for Australian women with ovarian cancer: A patient-level analysis over 2.5 years. International Journal of Gynecological Cancer 20 (5):757-765, 2010.	Not an economic evaluation
K. Hintringer. Trabectedin (Yondelis) for second-line recurrent platinum-sensitive ovarian cancer. Anonymous. Anonymous. 2010.	Not an economic evaluation
P. Jungmayr. The 29th German Cancer Congress - Trabectedin: Approval for soft tissue and ovary carcinoma. Deutsche Apotheker Zeitung 150 (10):49-50, 2010.	Not an economic evaluation
G. Mkele. Rational selection of cancer chemotherapy. SA Pharmaceutical Journal 77 (5):32-34, 2010.	Not an economic evaluation

Anonymous. Gemcitabine: new indication. Relapsed ovarian cancer: simply more toxic. Increases haematologic toxicity but not overall survival. Prescrire international 18 (102):156, 2009.	Not an economic evaluation
M. Murphy and J. Cunningham. Intraperitoneal chemotherapy for ovarian cancer patients: a review of the clinical and cost-effectiveness. Anonymous. Anonymous. 2009.	Review paper
National Horizon Scanning Centre (. Bevacizumab (Avastin) for advanced metastatic ovarian cancer. Anonymous. Anonymous. 2009.	Not an economic evaluation
Anonymous. Avastin (bevacizumab) for the treatment of ovarian cancer. Anonymous. Anonymous. 2008.	Not an economic evaluation
T. Petit. Gynecological cancers. Oncologie 10 (7-8):463-465, 2008.	Not an economic evaluation
M. Marosi Preusser. Topotecan (Hycamtin). Gynakologische Praxis 32 (2):337-340, 2008.	Not an economic evaluation
M. Marosi Preusser. Topotecan (Hycamtin). Internistische Praxis 48 (2):401-404, 2008.	Not an economic evaluation
T. D. D. Szucs. Balancing costs and benefits in cancer therapy and prevention. Annals of Oncology 19 (SUPPL. 7):vii313-vii319, 2008.	Not an economic evaluation
J. Weiss. Which treatment is cost-effective in recurrent ovarian cancer? Geburtshilfe und Frauenheilkunde 68 (5):466-467, 2008.	Review paper
M. Fedders Hartmann. Markov-modeling for the administration of platinum analogues and paclitaxel as first-line chemotherapy as well as topotecan and liposomal doxorubicin as second-line chemotherapy with epithelial ovarian carcinoma. Journal of Cancer Research and Clinical Oncology 133 (9):619-625, 2007.	Duplicate paper
A. Purins, L. Mundy, and J. E. Hiller. Ovarian cancer symptom index. Anonymous. Anonymous. 2007.	Did not include interventions or comparators of interest
Anonymous. Off-label uses of bevacizumab: renal cell carcinoma and other miscellaneous non-colorectal cancer indications. Technology Evaluation Center Assessment Program Executive summary. 21 (9):1-4, 2006.	Not an economic evaluation
Anonymous. Trading places. Lancet Oncology 7 (4):275, 2006.	Not an economic evaluation
S. M. Campos. Phase II study of CT-2103 in patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal carcinoma. Women's Oncology Review 5 (2):105-107, 2005.	Not an economic evaluation
W. J. Gradishar. Albumin-bound nanoparticle paclitaxel. Clinical Advances in Hematology and Oncology 3 (5):348-349, 2005.	Not an economic evaluation
T. J. Herzog. The challenge of paying for our targeted future. Women's Oncology Review 5 (1):1, 2005.	Not an economic evaluation
G. Lidouren. Anticancers. Actualites Pharmaceutiques (443):58-63, 2005.	Not retrievable
P. Possinger Schmid. Gemcitabin (Gemzar). Chirurgische Praxis 64 (2):351-358, 2005.	Not an economic evaluation
P. Possinger Schmid. Gemcitabin (Gemzar). Gynakologische Praxis 29 (2):351-358, 2005.	Not an economic evaluation
P. Possinger Schmid. Gemcitabine (Gemzar). Tagliche Praxis 46 (2):415-422, 2005.	Not retrievable
P. Muller-Bohn Jungmayr. Tumor disease: Prevention, treatment, health economics. Deutsche Apotheker Zeitung 144 (6):56-69, 2004.	Not retrievable
M. Prasad, L. Ben-Porat, B. Hoppe, C. Aghajanian, P. Sabbatini, D. S. Chi, M. L. Hensley, Monica Prasad, Leah Ben-Porat, Brad Hoppe, Carol Aghajanian, Paul Sabbatini, Dennis S. Chi, and Martee L. Hensley. Costs of treatment and outcomes associated with second-line therapy and greater for relapsed ovarian cancer.	Did not include interventions or comparators of interest

Gynecologic Oncology 93 (1):223-228, 2004.	
Anonymous. Trabectedin: ET 743, Ecteinascidin 743, Yondelis. Drugs in R and D 4 (1):75-81, 2003.	Not an economic evaluation
J. Hernandez Exposito. New Chemotherapy Treatments in Advanced Cancer Patients: An Easily Applicable Evaluation of Clinical Efficacy and Cost-effectiveness. Acta Oncologica 42 (8):895-902, 2003.	Not an economic evaluation
NHSC. Gemcitabine for recurrent ovarian cancer - horizon scanning review. Birmingham: National Horizon Scanning Centre (NHSC), 2003.	Paper not retrievable; archived
National Institute for Clinical Excellence. Guidance on the use of pegylated liposomal doxorubicin hydrochloride (PLDH) for the treatment of advanced ovarian cancer. Anonymous. Anonymous. 2002.	Paper not retrievable; archived
Anonymous. Clinical and pharmacoeconomic aspects both play an important role in the treatment of ovarian cancer. Drugs and Therapy Perspectives 17 (12):12-15, 2001.	Review paper
Anonymous. Taxanes (ovarian cancer): update. Health Technology Assessment, 2001.	Paper not retrievable; archived
National Institute for Clinical Excellence. Guidance on the use of topotecan for the treatment of advanced ovarian cancer. Anonymous. Anonymous. 2001.	Paper not retrievable; replaced
Anonymous. Is top-level care for ovarian cancer patients more cost-effective than regular care? The Netherlands Organisation for Health Research and Development (ZonMw), 2000.	Not an economic evaluation
National Horizon Scanning Centre. Trabectedin (Yondelis) for ovarian cancer - relapsed, second line: horizon scanning technology briefing. Birmingham: National Horizon Scanning Centre (NHSC), 2000.	Paper not retrievable; archived
National Institute for Clinical Excellence. Guidance on the use of taxanes for ovarian cancer. Anonymous. Anonymous. 2000.	Paper not retrievable; replaced
E. M. Greenspan. New chemoimmunotherapy: Courtesy of a more flexible Food and Drug Administration. Cancer Investigation 17 (5):371-373, 1999.	Review paper
NHS Centre for Reviews and Dissemination. Management of gynaecological cancers. Anonymous. Anonymous. 1999.	Review paper
J. W. Orr, P. Orr, and D. H. Kern. Cost-effective treatment of women with advanced ovarian cancer by cytoreductive surgery and chemotherapy directed by an in vitro assay for drug resistance. Cancer Journal from Scientific American 5(3):174-178, 1999.	Not an economic evaluation
T. J. Stinson, E. Calhoun, T. Yang, J. R. Lurain, C. L. Bennett, T. J. Stinson, E. Calhoun, T. Yang, J. R. Lurain, and C. L. Bennett. Cost analysis of second-line therapies for platinum-refractory ovarian cancer: reimbursement dilemmas for Medicare patients. Cancer Investigation 17 (8):559-565, 1999.	Not an economic evaluation
J. F. Bishop, K. arounas-Kirchman, J. F. Bishop, and K. arounas-Kirchman. The pharmacoeconomics of cancer therapies. [Review] [33 refs]. Seminars in Oncology 24 (6 Suppl 19):S19, 1997.	Review paper
L. Best. Paclitaxel as a first line chemotherapy agent in the treatment of ovarian cancer. Southampton: Wessex Institute for Health Research and Development (WIHRD), 1996.	Paper not retrievable; archived
T. Lynch. Topotecan today. Journal of Clinical Oncology 14 (12):3053-3055, 1996.	Not an economic evaluation
K. Bertelsen and A. Kruhoffer. What have we achieved in ovarian cancer: a comparison of survivals and resources in two different periods. International Journal of Gynecological Cancer 5(2):148-155, 1995.	Did not include interventions or comparators of interest
A. M. L. Chica Marchal. Pharmacoeconomic study of intravenous antineoplastic therapy in a centralized cytostatics unit. Farmacia Clinica 12 (3):202-209, 1995.	Not an economic evaluation

Summary of reasons for excluding health-related quality of life papers reviewed in full

Study	Reason for exclusion
December 2012 search	
M. R. Andersen, E. Sweet, K. A. Lowe, L. J. Standish, C. W. Drescher, B. A. Goff, M. Robyn Andersen, Erin Sweet, Kimberly A. Lowe, Leanna J. Standish, Charles W. Drescher, and Barbara A. Goff. Involvement in decision-making about treatment and ovarian cancer survivor quality of life. Gynecologic Oncology 124 (3):465-470, 2012.	Generic non-preference based QoL
Cui S.Ba. B ultrasound-guided hyperthermic intraperitoneal perfusion chemotherapy for the treatment of malignant ascites. Oncology Reports 28 (4):1325-1331, 2012.	Review paper
S. Dhillon. Bevacizumab combination therapy: For the first-line treatment of advanced epithelial ovarian, fallopian tube or primary peritoneal cancer. Drugs 72 (7):917-930, 2012.	Review paper
S. Farghaly. Long term survival of female patients with peritoneal carcinomatosis utilizing robot assisted laparoscopic ultra radical cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC). International Journal of Gynecology and Obstetrics Conference (var.pagings):October, 2012.	No QoL data
J. E. Frampton and James E. Frampton. Catumaxomab: in malignant ascites. Drugs 72 (10):1399-1410, 2012.	Review paper
Gilbertson-White S.Aouizerat. Determination of cutpoints for low and high number of symptoms in patients with advanced cancer. Journal of Palliative Medicine 15 (9):1027-1036, 2012.	Condition specific QoL
F. Hilpert, P. Wimberger, Bois A. du, J. Pfisterer, P. Harter, Felix Hilpert, Pauline Wimberger, Andreas du Bois, Jacobus Pfisterer, and Philipp Harter. Treatment of elderly ovarian cancer patients in the context of controlled clinical trials: a joint analysis of the AGO Germany experience. Onkologie 35 (3):76-81, 2012.	Condition specific QoL
A. A. Izzo. Limited value of traditional Chinese medicine in improving quality of life in cancer patients. Focus on Alternative and Complementary Therapies 17 (4):228-229, 2012.	Generic non-preference based QoL
N. Jayatilleke, N. Pashayan, J. W. Powles, N. Jayatilleke, N. Pashayan, and J. W. Powles. Burden of disease due to cancer in England and Wales. Journal of Public Health 34 (2):287-295, 2012.	Generic non-preference based QoL
K. Lindemann, R. D. Christensen, I. Vergote, G. Stuart, M. A. Izquierdo, J. Kaern, H. Havsteen, E. Eisenhauer, M. Ridderheim, A. B. Lopez, H. Hirte, E. avall-Lundquvist, E. Vrdoljak, J. Green, G. B. Kristensen, K. Lindemann, R. D. Christensen, I. Vergote, G. Stuart, M. A. Izquierdo, J. Kaern, H. Havsteen, E. Eisenhauer, M. Ridderheim, A. B. Lopez, H. Hirte, E. avall-Lundquvist, E. Vrdoljak, J. Green, and G. B. Kristensen. First-line treatment of advanced ovarian cancer with paclitaxel/carboplatin with or without epirubicin (TEC versus TC)--a gynecologic cancer intergroup study of the NSGO, EORTC GCG and NCIC CTG. Annals of Oncology 23 (10):2613-2619, 2012.	Condition specific QoL
A. Madeddu MacCio. A randomized phase III clinical trial of a combined treatment for cachexia in patients with gynecological cancers: Evaluating the impact on metabolic and inflammatory profiles and quality of life. Gynecologic Oncology 124 (3):417-425, 2012.	Condition specific QoL
C. Street Nagel. Clinical course of ovarian cancer after two salvage regimens. Gynecologic Oncology Conference (var.pagings):S27-S28, 2012.	No QoL data
D. A. A. Perwitasari. Impact of chemotherapy-induced nausea and vomiting on quality of life in Indonesian patients with gynecologic cancer. International Journal of Gynecological Cancer 22 (1):139-145, 2012.	Generic non-preference based QoL
A. Pilger, R. Richter, C. Fotopoulou, C. Beteta, C. Klapp, J. Sehouli, Adak Pilger, Rolf Richter, Christina Fotopoulou, Carmen Beteta, Christine Klapp, and Jalid Sehouli. Quality of life and sexuality of patients after treatment for gynaecological malignancies: results of a prospective study in 55 patients. Anticancer Research 32 (11):5045-5049, 2012.	Generic non-preference based QoL
R. Richter, G. Oskay-Oezcelik, R. Chekerov, A. Pilger, H. J. Hindenburg, H. Sommer, O. Camara, E. Keil, J. Einenkel, J. Sehouli, Rolf Richter, Guelten Oskay-Oezcelik, Radoslav Chekerov, Adak Pilger, Hans Joachim Hindenburg, Harald Sommer, Oumar Camara, Elke Keil, Jens Einenkel, and Jalid Sehouli. Health-related quality of life during sequential chemotherapy with carboplatin followed by weekly paclitaxel in advanced ovarian cancer: a multicenter phase ii study of the North Eastern German Society of Gynecological Oncology. Anticancer Research 32 (9):3969-3976, 2012.	Condition specific QoL

K. M. Robinson, K. B. Christensen, B. Ottesen, A. Krasnik, Kirstine M. Robinson, Karl Bang Christensen, Bent Ottesen, and Allan Krasnik. Diagnostic delay, quality of life and patient satisfaction among women diagnosed with endometrial or ovarian cancer: a nationwide Danish study. Quality of Life Research 21 (9):1519-1525, 2012.	Condition specific QoL
A. A. B. Secord. A multicenter, randomized, phase 2 clinical trial to evaluate the efficacy and safety of combination docetaxel and carboplatin and sequential therapy with docetaxel then carboplatin in patients with recurrent platinum-sensitive ovarian cancer. Cancer 118 (13):3283-3293, 2012.	Condition specific QoL
B. Sorbe, M. Graflund, L. Nygren, G. Horvath, M. Swahn, K. Boman, R. Bangshoj, M. Lood, H. Malmstrom, Bengt Sorbe, Marianne Graflund, Lisa Nygren, Gyorgy Horvath, Marie Swahn, Karin Boman, Rene Bangshoj, Margareta Lood, and Henric Malmstrom. A phase II study of docetaxel weekly in combination with carboplatin every three weeks as first line chemotherapy in stage IIB-IV epithelial ovarian cancer: neurological toxicity and quality-of-life evaluation. International Journal of Oncology 40 (3):773-781, 2012.	Condition specific QoL
D. W. P. Sommeijer. Quality of life and coping in ovarian cancer: The last year of life. Asia-Pacific Journal of Clinical Oncology Conference (var.pagings):November, 2012.	No QoL data
C. Stavraka, A. Ford, S. Ghaem-Maghami, T. Crook, R. Agarwal, H. Gabra, S. Blagden, Chara Stavraka, Amy Ford, Sadaf Ghaem-Maghami, Tim Crook, Roshan Agarwal, Hani Gabra, and Sarah Blagden. A study of symptoms described by ovarian cancer survivors. Gynecologic Oncology 125 (1):59-64, 2012.	Condition specific QoL
Patidar S.Telepak. A "snapshot" of photovoice as a psychosocial intervention for individuals affected by ovarian cancer. Psycho-Oncology Conference (var.pagings):February, 2012.	Condition specific QoL
C. Basu. Second line chemotherapy in epithelial ovarian cancer: Experience from a cancer institute of Eastern India. International Journal of Gynecological Cancer Conference (var.pagings):98, 2011.	No QoL data
C. Basu. Second line chemotherapy in platinum potentially resistant recurrent epithelial ovarian cancer: Experience from Eastern India. International Journal of Gynecological Cancer Conference (var.pagings):99, 2011.	No QoL data
V. L. Beesley, M. A. Price, P. N. Butow, A. C. Green, C. M. Olsen, Australian Ovarian Cancer Study Group, Australian Ovarian Cancer Study - Quality of Life Study Investigators, P. M. Webb, Vanessa L. Beesley, Melanie A. Price, Phyllis N. Butow, Adele C. Green, Catherine M. Olsen, Australian Ovarian Cancer Study Group, Australian Ovarian Cancer Study - Quality of Life Study Investigators, and Penelope M. Webb. Physical activity in women with ovarian cancer and its association with decreased distress and improved quality of life. Psycho-Oncology 20 (11):1161-1169, 2011.	Condition specific QoL
C. M. Donnelly, J. M. Blaney, A. Lowe-Strong, J. P. Rankin, A. Campbell, E. Crum-Gardner, J. H. Gracey, C. M. Donnelly, J. M. Blaney, A. Lowe-Strong, J. P. Rankin, A. Campbell, E. Crum-Gardner, and J. H. Gracey. A randomised controlled trial testing the feasibility and efficacy of a physical activity behavioural change intervention in managing fatigue with gynaecological cancer survivors. Gynecologic Oncology 122 (3):618-624, 2011.	Condition specific QoL
L. A. J. Faul. Relationship of exercise to quality of life in cancer patients beginning chemotherapy. Journal of Pain and Symptom Management 41 (5):859-869, 2011.	Generic non-preference based QoL
T. K. K. Gorasia. Phase II study of intraperitoneal chemotherapy in inoperable epithelial ovarian and primary peritoneal cancers. International Journal of Gynecological Cancer Conference (var.pagings):115, 2011.	No QoL data
G. C. Guimaraes, G. Baiocchi, F. O. Ferreira, L. Y. Kumagai, C. C. Fallopa, S. Aguiar, B. M. Rossi, F. A. Soares, A. Lopes, Gustavo Cardoso Guimaraes, Glauco Baiocchi, Fabio Oliveira Ferreira, Lillian Yuri Kumagai, Carlos Chaves Fallopa, Samuel Aguiar, Benedito Mauro Rossi, Fernando Augusto Soares, and Ademar Lopes. Palliative pelvic exenteration for patients with gynecological malignancies. Archives of Gynecology & Obstetrics 283 (5):1107-1112, 2011.	No QoL data
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Uwe Wagner, Elisabeth avall-Lundqvist, Val Gebski, Mark Heywood, Paul A. Vasey, Birgit Volgger, Ignace Vergote, Sandro Pignata, Annamaria Ferrero, Jalid Sehouli, Alain Lortholary, Gunnar Kristensen, Christian Jackisch, Florence Joly, Chris Brown, Nathalie Le Fur, and Andreas du Bois. Pegylated liposomal Doxorubicin and Carboplatin compared with Paclitaxel and Carboplatin for patients with platinum-sensitive ovarian cancer in late relapse. Journal of Clinical Oncology 28 (20):3323-3329, 2010.	
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A. A. P. Wright. Associations between age and quality of life in advanced ovarian cancer. Journal of Clinical Oncology Conference (var.pagings), 2010.	Condition specific QoL
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V. Champion, S. D. Williams, A. Miller, K. M. Reuille, K. Wagler-Ziner, P. O. Monahan, Q. Zhao, D. Gershenson, D. Cella, Gynecologic Oncology Group., Victoria Champion, Stephen D. Williams, Anna Miller, Kristina M. Reuille, Kim Wagler-Ziner, Patrick O. Monahan, Qianqian Zhao, David Gershenson, David Cella, and Gynecologic Oncology Group. Quality of life in long-term survivors of ovarian germ cell tumors: a Gynecologic Oncology Group study. Gynecologic Oncology 105 (3):687-694, 2007.	Generic non-preference based QoL
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M. M. Zhang, J. K. Chan, A. Husain, H. Y. Guo, N. N. Teng, Mallory M. Zhang, John K. Chan, Amreen Husain, Hong Yan Guo, and Nelson N. H. Teng. Safety and efficacy of lenalidomide (Revlimid) in recurrent ovarian and primary peritoneal carcinoma. Gynecologic Oncology 105 (1):194-198, 2007.	Condition specific QoL
L. B. Wenzel, H. Q. Huang, D. K. Armstrong, J. L. Walker, D. Cella, Gynecologic Oncology Group., Lari B. Wenzel, Helen Q. Huang, Deborah K. Armstrong, Joan L. Walker, David Cella, and Gynecologic Oncology Group. Health-related quality of life during and after intraperitoneal versus intravenous chemotherapy for optimally debulked ovarian cancer: a Gynecologic Oncology Group Study. Journal of Clinical Oncology 25 (4):437-443, 2007.	Condition specific QoL
C. Stevinson, W. Faught, H. Steed, K. Tonkin, A. B. Ladha, J. K. Vallance, V. Capstick, A. Schepansky, K. S. Courneya, Clare Stevinson, Wylam Faught, Helen Steed, Katia Tonkin, Aliya B. Ladha, Jeffrey K. Vallance, Valerie Capstick, Alexandra Schepansky, and Kerry S. Courneya. Associations between physical activity and quality of life in ovarian cancer survivors. Gynecologic Oncology 106 (1):244-250, 2007.	Condition specific QoL
D. K. Armstrong, B. Bundy, L. Wenzel, H. Q. Huang, R. Baergen, S. Lele, L. J. Copeland, J. L. Walker, R. A. Burger, Gynecologic Oncology Group., Deborah K. Armstrong, Brian Bundy, Lari Wenzel, Helen Q. Huang, Rebecca Baergen, Shashikant Lele, Larry J. Copeland, Joan L. Walker, Robert A. Burger, and Gynecologic Oncology Group. Intraperitoneal cisplatin and paclitaxel in ovarian cancer. New England Journal of Medicine 354 (1):34-43, 2006.	Condition specific QoL
H. Hirte, I. B. Vergote, J. R. Jeffrey, R. N. Grimshaw, S. Coppieters, B. Schwartz, D. Tu, A. Sadura, M. Brundage, L. Seymour, H. Hirte, I. B. Vergote, J. R. Jeffrey, R. N. Grimshaw, S. Coppieters, B. Schwartz, D. Tu, A. Sadura, M. Brundage, and L. Seymour. A phase III randomized trial of BAY 12-9566 (tanomastat) as maintenance therapy in patients with advanced ovarian cancer responsive to primary surgery and paclitaxel/platinum containing chemotherapy: a National Cancer Institute of Canada Clinical Trials Group Study. Gynecologic Oncology 102 (2):300-308, 2006.	Condition specific QoL
S. M. Apte, S. Vadhan-Raj, L. Cohen, R. L. Bassett, I. O. Gordon, C. F. Levenback, P. T. Ramirez, S. T. Gallardo, R. S. Patenia, M. E. Garcia, R. B. Iyer, R. S. Freedman, Sachin M. Apte, Saroj Vadhan-Raj, Lorenzo Cohen, Roland L. Bassett, Ilyssa O. Gordon, Charles F. Levenback, Pedro T. Ramirez, Stacie T. Gallardo, Rebecca S. Patenia, Michael E. Garcia, Revathy B. Iyer, and Ralph S. Freedman. Cytokines, GM-CSF and IFNgamma administered by priming and post-chemotherapy cycling in recurrent ovarian cancer patients receiving carboplatin. Journal of Translational Medicine 4:16, 2006.	Condition specific QoL
J. S. de Moor, C. A. de Moor, K. Basen-Engquist, A. Kudelka, M. W. Bevers, L. Cohen, Janet S. de Moor, Carl A. de Moor, Karen Basen-Engquist, Andrzej Kudelka, Michael W. Bevers, and Lorenzo Cohen. Optimism, distress, health-related quality of life, and change in cancer antigen 125 among patients with ovarian cancer undergoing chemotherapy. Psychosomatic Medicine 68 (4):555-562, 2006.	Condition specific QoL
C. Livartowski Buron. Considering simultaneously quality of life and quantity of life in oncology. Oncologie 8 (5):483-488, 2006.	No QoL data
Griffin S.Bojke. Incorporating direct and indirect evidence using Bayesian methods: An applied case study in ovarian cancer. Value in Health 9 (2):123-131, 2006.	No QoL data
M. Markman. Intraperitoneal chemotherapy as primary treatment of advanced ovarian cancer. Community Oncology 3 (6):352-353, 2006.	No QoL data
J. K. Wolf, D. C. Bodurka, C. Verschraegen, C. C. Sun, D. Branham, A. D. Jenkins, N. Atkinson, D. M. Gershenson, Judith K. Wolf, Diane C. Bodurka, Claire Verschraegen, Charlotte C. Sun, Donna Branham, Alfred D. Jenkins, Neely Atkinson, and David M. Gershenson. A phase II trial of oral capecitabine in patients with platinum--and taxane--refractory ovarian, fallopian tube, or peritoneal cancer. Gynecologic Oncology 102 (3):468-474, 2006.	Condition specific QoL
Gruenigen Von, V, H. E. Frasure, E. L. Jenison, M. P. Hopkins, K. M. Gil, Vivian E. von Gruenigen, Heidi E. Frasure, Eric L. Jenison, Michael P. Hopkins, and Karen M. Gil. Longitudinal assessment of quality of life and lifestyle in newly diagnosed ovarian cancer patients: the roles of surgery and chemotherapy. Gynecologic Oncology 103 (1):120-126, 2006.	Condition specific QoL

P. M. Wilkinson, M. Antonopoulos, M. Lahousen, M. Lind, P. Kosmidis, I. N. T. EPO, P. M. Wilkinson, M. Antonopoulos, M. Lahousen, M. Lind, P. Kosmidis, and I. N. T. EPO. Epoetin alfa in platinum-treated ovarian cancer patients: results of a multinational, multicentre, randomised trial. British Journal of Cancer 94 (7):947-954, 2006.	Condition specific QoL
J. Pfisterer, M. Plante, I. Vergote, Bois A. du, H. Hirte, A. J. Lacave, U. Wagner, A. Stahle, G. Stuart, R. Kimmig, S. Olbricht, T. Le, J. Emerich, W. Kuhn, J. Bentley, C. Jackisch, H. J. Luck, J. Rochon, A. H. Zimmermann, E. Eisenhauer, O. V. A. R. AGO, C. T. G. NCIC, G. C. G. EORTC, Jacobus Pfisterer, Marie Plante, Ignace Vergote, Andreas du Bois, Hal Hirte, Angel J. Lacave, Uwe Wagner, Anne Stahle, Gavin Stuart, Rainer Kimmig, Sigrid Olbricht, Tien Le, Janusz Emerich, Walther Kuhn, James Bentley, Christian Jackisch, Hans Joachim Luck, Justine Rochon, Annamaria Hayden Zimmermann, Elizabeth Eisenhauer, O. V. A. R. AGO, C. T. G. NCIC, and G. C. G. EORTC. Gemcitabine plus carboplatin compared with carboplatin in patients with platinum-sensitive recurrent ovarian cancer: an intergroup trial of the AGO-OVAR, the NCIC CTG, and the EORTC GCG. Journal of Clinical Oncology 24 (29):4699-4707, 2006.	Condition specific QoL
V. Wasta. Intraperitoneal chemotherapy improves survival in ovarian cancer patients when combined with intravenous chemotherapy. Cancer Biology and Therapy 5 (2):130-131, 2006.	Review paper
Y.-P. Yan Zhu. Effect of polysaccharide-peptide plus chemotherapy on the immune function and quality of life in patients with ovarian or endometrial cancer. Chinese Journal of Clinical Rehabilitation 10 (47):212-214, 2006.	Condition specific QoL
F. Y. De Vos, A. M. Bos, M. Schaapveld, C. A. de Swart, Graaf H. de, A. G. van der Zee, H. M. Boezen, E. G. de Vries, P. H. Willemse, F. Y. F. L. De Vos, A. M. E. Bos, M. Schaapveld, C. A. M. de Swart, H. de Graaf, A. G. J. van der Zee, H. M. Boezen, E. G. E. de Vries, and P. H. B. Willemse. A randomized phase II study of paclitaxel with carboplatin +/- amifostine as first line treatment in advanced ovarian carcinoma. Gynecologic Oncology 97 (1):60-67, 2005.	Condition specific QoL
H. Fushiki, H. Yoshimoto, T. Ikoma, S. Ota, Hiroshi Fushiki, Hideo Yoshimoto, Tomomi Ikoma, and Satoru Ota. [A trial of biweekly paclitaxel administration in consideration of QOL for advanced or recurrent gynecologic cancer]. [Japanese]. Gan to Kagaku Ryoho [Japanese Journal of Cancer & Chemotherapy] 32 (5):691-693, 2005.	Not retrievable
E. S. Costanzo, S. K. Lutgendorf, A. K. Sood, B. Anderson, J. Sorosky, D. M. Lubaroff, Erin S. Costanzo, Susan K. Lutgendorf, Anil K. Sood, Barrie Anderson, Joel Sorosky, and David M. Lubaroff. Psychosocial factors and interleukin-6 among women with advanced ovarian cancer. Cancer 104 (2):305-313, 2005.	Condition specific QoL
Secord A. Alvarez, E. L. Jones, C. A. Hahn, W. P. Petros, D. Yu, L. J. Havrilesky, J. T. Soper, A. Berchuck, I. Spasojevic, D. L. Clarke-Pearson, L. R. Prosnitz, M. W. Dewhirst, A. varez Secord, E. L. Jones, C. A. Hahn, W. P. Petros, D. Yu, L. J. Havrilesky, J. T. Soper, A. Berchuck, I. Spasojevic, D. L. Clarke-Pearson, L. R. Prosnitz, and M. W. Dewhirst. Phase I/II trial of intravenous Doxil and whole abdomen hyperthermia in patients with refractory ovarian cancer. International Journal of Hyperthermia 21 (4):333-347, 2005.	Condition specific QoL
K. J. Dedes, M. Bramkamp, T. D. Szucs, Konstantin J. Dedes, Matthias Bramkamp, and Thomas D. Szucs. Paclitaxel: cost-effectiveness in ovarian cancer. Expert review of pharmacoeconomics & outcomes research 5 (3):235-243, 2005.	Review paper
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C. Stauch Oberhoff. Prevention and therapy of anemia in tumor patients with Epoetin beta (NeoRecormon). Tumor Diagnostik und Therapie 26 (4):166-171, 2005.	Condition specific QoL
F. Denniston Baker. Adult cancer survivors: How are they faring? Cancer 104 (11 SUPPL.):2565-2576, 2005.	Condition specific QoL
B. Miller. Spiritual journey during and after cancer treatment. Gynecologic Oncology 99 (3 SUPPL.):S129-S130, 2005.	Condition specific QoL
C. C. Sun, D. C. Bodurka, C. B. Weaver, R. Rasu, J. K. Wolf, M. W. Bevers, J. A. Smith, J. T. Wharton, E. B. Rubenstein, Charlotte C. Sun, Diane C. Bodurka, Candice B. Weaver, Rafia Rasu, Judith K. Wolf, Michael W. Bevers, Judith A. Smith, J. Taylor Wharton, and Edward B. Rubenstein. Rankings and symptom assessments of side effects from chemotherapy: insights from experienced patients with ovarian cancer. Supportive Care in Cancer 13 (4):219-227, 2005.	Generic non-preference based QoL

L. Wenzel, H. Q. Huang, B. J. Monk, P. G. Rose, D. Cella, Lari Wenzel, Helen Q. Huang, Bradley J. Monk, Peter G. Rose, and David Cella. Quality-of-life comparisons in a randomized trial of interval secondary cytoreduction in advanced ovarian carcinoma: a Gynecologic Oncology Group study. Journal of Clinical Oncology 23 (24):5605-5612, 2005.	Condition specific QoL
S. D. K. Passik. A pilot examination of the impact of cancer patients' fatigue on their spousal caregivers. Palliative & supportive care 3 (4):273-279, 2005.	No QoL data
C. A. T. Presant. Effects of weekly paclitaxel or paclitaxel plus carboplatin on functionality and symptoms of geriatric patients with cancer as measured by a brief geriatric oncology module: A pilot experience. Cancer 103 (12):2623-2628, 2005.	Generic non-preference based QoL
A. A. J. Secord. Phase I/II trial of intravenous Doxil and whole abdomen hyperthermia in patients with refractory ovarian cancer. International Journal of Hyperthermia 21 (4):333-347, 2005.	No QoL data
Pujade-Lauraine E.Du Bois. Epirubicin/paclitaxel/carboplatin (TEC) vs paclitaxel/carboplatin (TC) in first-line treatment of ovarian cancer FIGO stages IIB-IV. Results of a randomized AGO-GINECO GCIG Intergroup phase III trial. International Journal of Gynecological Cancer 15 (6 SUPPL. 3):222-223, 2005.	No QoL data
R. Advani, P. Peethambaram, B. L. Lum, G. A. Fisher, L. Hartmann, H. J. Long, J. Halsey, J. T. Holmlund, A. Dorr, B. I. Sikic, Ranjana Advani, Prema Peethambaram, Bert L. Lum, George A. Fisher, Lynn Hartmann, Harry J. Long, Joanne Halsey, Jon T. Holmlund, Andrew Dorr, and Branimir I. Sikic. A Phase II trial of aprinocarsen, an antisense oligonucleotide inhibitor of protein kinase C alpha, administered as a 21-day infusion to patients with advanced ovarian carcinoma. Cancer 100 (2):321-326, 2004.	Condition specific QoL
L. Butler, M. Bacon, M. Carey, B. Zee, D. Tu, A. Bezjak, Lorna Butler, Monica Bacon, Mark Carey, Benny Zee, Dongsheng Tu, and Andrea Bezjak. Determining the relationship between toxicity and quality of life in an ovarian cancer chemotherapy clinical trial. Journal of Clinical Oncology 22 (12):2461-2468, 2004.	Condition specific QoL
J. S. Berek, P. T. Taylor, A. Gordon, M. J. Cunningham, N. Finkler, J. Orr, Jr., S. Rivkin, B. C. Schultes, T. L. Whiteside, C. F. Nicodemus, Jonathan S. Berek, Peyton T. Taylor, Alan Gordon, Mary J. Cunningham, Neil Finkler, James Jr Orr, Saul Rivkin, Birgit C. Schultes, Theresa L. Whiteside, and Christopher F. Nicodemus. Randomized, placebo-controlled study of oregovomab for consolidation of clinical remission in patients with advanced ovarian cancer. Journal of Clinical Oncology 22 (17):3507-3516, 2004.	Condition specific QoL
S. Limat, M. C. Woronoff-Lemsi, C. Menat, A. Madroszyk-Flandin, and Y. Merrouche. From randomised clinical trials to clinical practice: a pragmatic cost-effectiveness analysis of paclitaxel in first-line therapy for advanced ovarian cancer. PharmacoEconomics 22(10):633-641, 2004.	Generic non-preference based QoL
B. K. Piao, Y. X. Wang, G. R. Xie, U. Mansmann, H. Matthes, J. Beuth, H. S. Lin, B. K. Piao, Y. X. Wang, G. R. Xie, U. Mansmann, H. Matthes, J. Beuth, and H. S. Lin. Impact of complementary mistletoe extract treatment on quality of life in breast, ovarian and non-small cell lung cancer patients. A prospective randomized controlled clinical trial. Anticancer Research 24 (1):303-309, 2004.	Condition specific QoL
V. I. Solov'ev, E. N. Semkina, V. I. Solov'ev, and E. N. Semkina. [Impact of special treatment methods on life quality and lifespan of patients with widespread forms of ovarian cancer]. [Russian]. Antibiotiki i Khimioterapiia 49 (2):14-18, 2004.	Condition specific QoL
P. A. Vasey, G. C. Jayson, A. Gordon, H. Gabra, R. Coleman, R. Atkinson, D. Parkin, J. Paul, A. Hay, S. B. Kaye, Scottish Gynaecological Cancer Trials Group., Paul A. Vasey, Gordon C. Jayson, Alan Gordon, Hani Gabra, Rob Coleman, Ronnie Atkinson, David Parkin, James Paul, Andrea Hay, Stan B. Kaye, and Scottish Gynaecological Cancer Trials Group. Phase III randomized trial of docetaxel-carboplatin versus paclitaxel-carboplatin as first-line chemotherapy for ovarian carcinoma. Journal of the National Cancer Institute 96 (22):1682-1691, 2004.	Condition specific QoL
M. L. Rothenberg, P. Y. Liu, S. Wilczynski, W. A. Nahhas, G. L. Winakur, C. S. Jiang, C. M. Moinpour, B. Lyons, G. R. Weiss, J. H. Essell, H. O. Smith, M. Markman, D. S. Alberts, Mace L. Rothenberg, P. Y. Liu, Sharon Wilczynski, William A. Nahhas, Gaye L. Winakur, Caroline S. Jiang, Carol M. Moinpour, Ben Lyons, Geoffrey R. Weiss, James H. Essell, Harriet O. Smith, Maurie Markman, and David S. Alberts. Phase II trial of vinorelbine for relapsed ovarian cancer: a Southwest Oncology Group study. Gynecologic Oncology 95 (3):506-512, 2004.	Generic non-preference based QoL
W. Lane ten Bokkel Huinink. Long-term survival in a phase III, randomised study of topotecan versus paclitaxel in advanced epithelial ovarian carcinoma. Annals of Oncology 15 (1):100-103, 2004.	Condition specific QoL

May 2013 search	
P.-L. Hilpert Eric. AURELIA: A randomized phase III trial evaluating bevacizumab (BEV) plus chemotherapy (CT) for platinum (PT)-resistant recurrent ovarian cancer (OC). *J Clin Oncol.* Conference (var.pagings), 2012.	No QoL data
Uppal S.Hernandez. Prolonged postoperative venous thrombo-embolism prophylaxis is cost-effective in advanced ovarian cancer patients. *Gynecol.Oncol.* 127 (3):631-637, 2012.	No QoL data
N. Sidhu Kiss. Quality of life and patient preferences in platinum sensitive ovarian cancer. *Value in Health* Conference (var.pagings):A429, 2012.	No QoL data
D. Nankivell Stark. Standard chemotherapy with or without bevacizumab in advanced ovarian cancer: Quality-of-life outcomes from the International Collaboration on Ovarian Neoplasms (ICON7) phase 3 randomised trial. *The Lancet Oncology* 14 (3):236-243, 2013.	Condition specific QoL
Abbreviations used in table: HRQoL, health-related quality of life; QoL, quality of life	

Summary of reasons for excluding costing studies

Reference	Primary reason for exclusion
December 2012 search	
A. Geisler Walter. Annual cost of bevacizumab in the adjuvant treatment of ovarian cancer to the U.S. Medicare system. Gynecologic Oncology Conference (var.pagings):March, 2012.	US study
I. Cajaraville Oyaguez. Budget impact of trabectedin and pegylated liposomal doxorubicin (PLD) for the treatment of partially platinum-sensitive ovarian cancer. Pharmacoeconomics - Spanish Research Articles 9 (3):83-94, 2012.	Spanish study
C. T. B. Pike. Healthcare costs and workloss burden of patients with chemotherapy-associated peripheral neuropathy in breast, ovarian, head and neck, and nonsmall cell lung cancer. Chemotherapy Research and Practice 2012 , 2012. Article Number:913848, 9138.	US study
V. R. M. Jacobs. Financial quality control of in-patient chemotherapy in Germany: Are additional payments cost-covering for pharmaco-oncological expenses? Breast Care 6 (2):120-125, 2011.	German study
M. Frederick Barnes. Evaluating the true cost of a major phase III GOG clinical trial: A cause for concern. Gynecologic Oncology Conference (var.pagings):S13, 2010.	US study
L. G. S. Gordon. Medical costs and outcomes for Australian women with ovarian cancer: A patient-level analysis over 2.5 years. International Journal of Gynecological Cancer 20 (5):757-765, 2010.	Australian study
L. J. K. Havrilesky. Impact of a chemoresponse assay on treatment costs for recurrent ovarian cancer. American Journal of Obstetrics and Gynecology 203 (2):160, 2010.	US study
A. Gao Parthan. Health care resource utilization (HRU) in advanced ovarian cancer-findings from linked seer-medicare data. Value in Health Conference (var.pagings):A31, 2010.	US study
A. Gao Parthan. Health care resource use (HRU) with nonplatinum chemotherapy for previously treated advanced ovarian cancer (aOC): Findings from SEER-Medicare data. Journal of Clinical Oncology Conference (var.pagings), 2010.	US study
A. L. N. Cooper. Long-term survival and cost of treatment in patients with stage IIIC epithelial ovarian cancer. Current Women's Health Reviews 5 (1):44-50, 2009.	US study
L. J. K. Havrilesky. Cost analysis of ovarian cancer chemotherapy based on the use of a chemoresponse assay. Gynecologic Oncology Conference (var.pagings):S22, 2009.	US study
H. Nagai Nomura. Compared medical costs of treating ovarian cancer patients with weekly paclitaxel, carboplatin (TC) chemotherapy. Gan to kagaku ryoho Cancer & chemotherapy. 34 (7):1091-1094, 2007.	Japanese study

M. Prasad, L. Ben-Porat, B. Hoppe, C. Aghajanian, P. Sabbatini, D. S. Chi, M. L. Hensley, Monica Prasad, Leah Ben-Porat, Brad Hoppe, Carol Aghajanian, Paul Sabbatini, Dennis S. Chi, and Martee L. Hensley. Costs of treatment and outcomes associated with second-line therapy and greater for relapsed ovarian cancer. Gynecologic Oncology 93 (1):223-228, 2004.	US study
W. K. N. Evans. Cancer care Ontario's new drug funding program: Controlled introduction of expensive anticancer drugs. Chronic Diseases in Canada 23 (4):152-156, 2002.	Canadian study
C. L. Bennett, T. J. Stinson, T. Yang, J. R. Lurain, C. L. Bennett, T. J. Stinson, T. Yang, and J. R. Lurain. The effect of reimbursement policies on the management of Medicare patients with refractory ovarian cancer. Seminars in Oncology 26 (1 Suppl 1):40-45, 1999.	US study
T. J. Stinson, E. Calhoun, T. Yang, J. R. Lurain, C. L. Bennett, T. J. Stinson, E. Calhoun, T. Yang, J. R. Lurain, and C. L. Bennett. Cost analysis of second-line therapies for platinum-refractory ovarian cancer: reimbursement dilemmas for Medicare patients. Cancer Investigation 17 (8):559-565, 1999.	US study
R. P. B. Rozek. The costs to the U.S. health care system of extending marketing exclusivity for Taxol. Journal of Research in Pharmaceutical Economics 9 (4):21-41, 1998.	US study
A. M. L. Chica Marchal. Pharmacoeconomic study of intravenous antineoplastic therapy in a centralized cytostatics unit. Farmacia Clinica 12 (3):202-209, 1995.	Spanish study

Appendix 7: Data abstraction for TAG economic evaluation

Identified economic evaluations in people with recurrent ovarian cancer

Author, year, country	Overview	Patient population	Intervention / comparator	Costs and source	Outcomes and source	ICER	Uncertainty
NICE; 2013; UK[15]	Manufacturer submission, ERG comments and appraisal committee conclusions for NICE TA285, Cost utility analysis from the perspective of the UK NHS Manufacturer developed a semi-Markov economic model with three health states (PFS, PD, death) based upon NICE TA91	Recurrent platinum sensitive ovarian cancer	Bevacizumab plus carboplatin and gemcitabine versus carboplatin and gemcitabine	Costs captured included costs relating to treatment, costs of managing stable disease, cost of further therapies, cost of adverse events, cost of palliative care. Costs discounted at 3.5%.	OCEANS provided PFS and OS data on which survival distributions were fitted to extrapolate beyond the trial duration. Quality of life data were taken from TA222. Outcomes discounted at 3.5%.	Incremental cost per additional QALY Bevacizumab in addition to gemcitabine and carboplatin versus gemcitabine and carboplatin was estimated by the manufacturer to be £149,050 (deterministic) in the base case	Model uncertainty was tested in one way sensitivity analysis and via monte carlo simulations. The Appraisal Committee considered that the uncertainty in estimates of OS in particular meant that the true ICER was likely to be much higher than £149,050.

Montalar et al; 2012; Spain[97]	Cost-utility analysis Semi-Markov model with lifetime time horizon. Model based upon TA91.	Recurrent platinum sensitive ovarian cancer	Trabectedin plus PLDH versus PLDH monotherapy	Costs discounted at 3% Costs captured included drug costs, medical management costs, adverse event management cost	Outcomes discounted at 3%. PFS and OS taken from OVA-301. Utility taken from EQ-5D data collected as part of OVA-301. .	Incremental cost per QALY Addition of trabectedin versus PLDH alone resulted in an estimated ICER of Euros (2011) 45,592	Addressed through deterministic sensitivity analysis and probabilistic sensitivity analysis
Havrilesky et al; 2012; US[101]	Cost-utility analysis Markov model with 24 month time horizon. Health states include probability of completed treatment (no disease); progressed disease; and active treatment with or without neurotoxicity	Recurrent, platinum-sensitive ovarian cancer	Docetaxel and carboplatin combination; docetaxel and carboplatin sequentially	2010 cost year Costs included: costs associated with adverse events with a significant difference in incidence between treatment arms; treatment cost; infusion treatment charges; costs of standard pre-treatment medications. Costs were estimated using national 2010 Medicare reimbursement data	PFS was taken from the published literature and modelled for 24 months at which time >95% patients had experienced recurrence or had died in each arm Rates of grade 2 and above adverse events with a significant difference was documented between treatment arms and modelled. Quality of life was obtained as FACTG and converted to a utility using Dobrez *et al.*[123] 2007. QoL estimates were not estimated for health states.	Incremental cost per additional QALY Combination versus sequential: $25,239	Model uncertainty was tested in one way sensitivity analysis and via monte carlo simulations. At a threshold of $50,000 the combination was estimated to be cost-effective in 72% of simulations

Chan; 2011; US[100]	Cost-effectiveness analysis In trial analysis	Recurrent ovarian cancer	Gemcitabine and carboplatin; gemcitabine, carboplatin and bevacizumab	Details of costs included and source of data was not reported	PFS was taken from the OCEANS clinical trial Data on bowel perforation was also taken from OCEANS	Incremental cost per life year saved for the addition of bevacizumab to gemcitabine and carboplatin combination therapy was $253,968	A series of threshold analyses were carried out on the cost of bevacizumab, PFS and rate of bowel perforation
Gore; 2011; UK[96]	Cost-utility analysis from the perspective of the UK NHS. Decision analytic model	Patients with relapsed platinum sensitive ovarian cancer	Trabectedin and PLDH; PLDH	Costs were discounted at a rate of 3.5% Drug, administration, medical management and adverse event costs were based on BNF prices and UK HRG codes	Outcomes were discounted at a rate of 3.5% Effectiveness data for PFS and OS was based on the phase III randomised trial OVA301 in 672 patients with relapsed ovarian cancer; parametric survival distributions were fitted to the data from the platinum sensitive subgroup to calculate mean PFS and OS for each treatment. QoL was measured by EQ-5D data collected in the OVA-301 trial	Incremental cost per additional QALY Trabectedin plus PLDH versus PLDH: (deterministic) and £39,505 (probabilistic)	Uncertainty was explored through univariate and probabilistic sensitivity analyses
Lee et al; 2011; Korea[107]	Cost-utility analysis Markov model with four health states: responsive; progressive; clinical remission; death. The model time horizon was 10 years, with 9 week cycle length	Korean women with platinum sensitive ovarian cancer at second line	PLDH and carboplatin; paclitaxel and carboplatin	Both direct and indirect costs were included in the model: drug acquisition costs; test costs; monitoring costs; best supportive care costs; out of pocket costs; transportation related expenses	Median time to progression and OS was either estimated from a literature review and meta-analysis or from an expert panel Utilities were obtained from existing literature (reference not reported)	Incremental cost per quality adjusted life year PLDH and carboplatin versus paclitaxel and carboplatin: 19,712,349 Korean Won (equivalent to $US 18,093)	Uncertainty was explored though deterministic and probabilistic sensitivity analyses. In deterministic analyses the model was robust to all changes except median time to progression. In the probabilistic analysis the probability of cost effectiveness for PLDH and carboplatin combination was 50.6% at a willingness to pay threshold of

							22,000,000 Korean Won (US$20,202), the Korean GDP per capita
Lesnock; 2011; US[102]	Cost utility analysis Decision model with three health states PFS, recurrence, and death	Women with relapsed ovarian cancer	Carboplatin and paclitaxel; carboplatin and paclitaxel followed by paclitaxel; carboplatin and paclitaxel followed by carboplatin, paclitaxel and bevacizumab	2009 cost year Costs captured included reimbursement costs of medication and administration, major complications and surveillance. With the exception of bevacizumab cost, all costs were estimated based on hospital costs, Medicare reimbursement rates, the Agency for Healthcare Research and Quality database, the American Medical Association database, the CMS Physician Payment database or Red Book medication costs. Bevacizumab cost was included at the cost to the authors' home institution	OS, PFS, complications of treatment all taken from the published data Quality of life adjustments were estimated using a panel of three gynaecological oncology experts	Incremental cost per additional QALY Carboplatin, paclitaxel and paclitaxel following initial treatment versus carboplatin and paclitaxel: $13,402 Carboplatin, paclitaxel and bevacizumab was dominated	Uncertainty was explored in two way sensitivity analysis and threshold analyses. Sensitivity analyses demonstrated that model conclusions were robust to variation across parameters
Lesnock; 2011b; US[103]	Cost utility analysis	Women with relapsed ovarian cancer	Carboplatin and paclitaxel; carboplatin and paclitaxel followed by paclitaxel; carboplatin and paclitaxel followed by carboplatin, paclitaxel and bevacizumab	Reimbursement costs of chemotherapy, administration, complications and surveillance. Key data based upon Medicare reimbursement rates, and the Agency for Healthcare Research and Quality Database	OS, PFS, complications of treatment all taken from the published data QoL adjustments were estimated using a panel of three gynaecological oncology experts	Incremental cost per additional QALY Carboplatin, paclitaxel and paclitaxel following initial treatment versus carboplatin and paclitaxel: $12,888 Carboplatin, paclitaxel and bevacizumab dominated when compared with carboplatin, paclitaxel and paclitaxel following initial treatment	Sensitivity analyses were performed to account for uncertainty and demonstrated that results were robust to PFS variation
NICE;	Manufacturer	Women with	Trabectedin	Costs captured included	Outcomes were discounted	Incremental cost per	Uncertainty was

2011; UK[79]	submission, ERG comments and appraisal committee conclusions for NICE TA222, Cost utility analysis from the perspective of the UK NHS Manufacturer developed a semi-Markov economic model with three health states (PFS, PD, death) based upon NICE TA91	relapsed platinum sensitive ovarian cancer	and PLDH; topotecan; paclitaxel; PLDH	costs relating to treatment, costs of managing stable disease, cost of progressive disease cost of adverse events	at 3.5% Manufacturer used PFS from OVA-301 and a meta-analysis and presented results for: the entire platinum sensitive population, the partially platinum-sensitive population; the fully platinum sensitive population. Interim analyses of OS were taken from OVA-301 AE rates were taken from OVA-301 Utilities were derived from the OVA-301 trial which collected EQ-5D	QALY gained PLDH versus paclitaxel: £15,234 Topotecan was dominated by PLDH Trabectedin plus PLDH compared with PLDH alone: £70,076 Alternative results using differing assessments of efficacy through the OVA-301 trial were also presented	explored by the manufacturer using one-way and probabilistic sensitivity analysis. Results showed that key drivers of cost effectiveness were OS, average number of treatment cycles, drug costs and utility weights. The probability of trabectedin plus PLDH being cost effective compared with PLDH was approximately 23% at a threshold of £30,000
Papaioannou; 2011; UK[95]	ERG assessment and additional analysis associated with a cost-utility analysis submitted by a manufacturer from the perspective of the UK NHS. Manufacturer developed a semi-Markov model with three health states: stable disease,	Women with relapsed platinum sensitive ovarian cancer	Trabectedin and PLDH; paclitaxel; topotecan; PLDH	NR	Evidence on mean time to progression and death provided by the manufacturer for NICE TA222 was derived from a phase III RCT (OVA-301). The manufacturer extrapolated estimates of survival using the exponential function. The ERG did not agree that this was appropriate and used alternative distributions to represent the data Utilities were taken from OVA-301	Incremental cost per QALY gained ERG estimates: Trabectedin and PLDH versus PLDH: £46,503 to £54,607 in the partially platinum sensitive population Manufacturer estimates: in the entire population trabectedin and PLDH versus PLDH: £94,832 In the partially platinum sensitive population, trabectedin and PLDH versus PLDH: £43,996 In the fully platinum	Uncertainty was explored in univariate sensitive analyses for the main analysis and probabilistic sensitivity analysis

	progressive disease, death. Model derived from NICE TA91					sensitive population trabectedin and PLDH versus PLDH: £31,092	
Papaioannou; 2010; UK[147]	ERG report for NICE TA222: cost utility analysis from the perspective of the UK NHS. ERG review and amends to the manufacturer submission in which the manufacturer developed a semi-Markov economic model with three health states (PFS, PD, death) based upon NICE TA91	Women with relapsed platinum sensitive ovarian cancer	Trabectedin and PLDH; topotecan; paclitaxel; PLDH	Cost captured included drug and administration costs from the BNF and national reference costs; management costs from assumptions around management requirement and reference costs for costs; costs associated with adverse events	Outcomes were discounted at 3.5% Manufacturer estimated efficacy using OVA-301 trial and a meta-analysis with extrapolation using an exponential function. The ERG did not believe that an exponential distribution was appropriate to extrapolate survival. HRQoL was taken from patients within the OVA-301 trial and the values across treatment arms were used. Data by platinum sensitivity was not used by the manufacturer, and the ERG deemed this to be appropriate because the estimated values were counterintuitive.	Incremental cost per QALY gained The ERG reviewed the comparison of PLDH in combination with trabectedin versus PLDH monotherapy. The ERG considered that the oncologist assessment of progression was most appropriate and noted that the manufacturer's ICER with this was £39,262.	The ERG changed a number of parameters and believed that the most plausible ICER for trabectedin in combination with PLDH versus PLDH in women with partially platinum sensitive disease to be within the range of £46,503 to £54,607

Case; 2007; US[104]	Trial-based cost effectiveness analysis Perspective of third party payer	Hypothetical cohort of 10,000 platinum-sensitive patients with advanced, recurrent, epithelial ovarian cancer	BSC; second-line monotherapy; Second-line combination therapy; third-line chemotherapy after disease progression on second-line chemotherapy; fourth-line chemotherapy after disease progression on third line chemotherapy	2004 cost year Drug costs and costs associated with chemotherapy administration were included in the economic evaluation. Costs were estimated by adjusting local charges using a cost-to-charge ratio of 60% The University of Alabama was used for all laboratory and procedure cost estimates. Pharmacy costs were calculated using average wholesale drug costs	PFS was used to estimate OS (average PFS plus time in hospice care) PFS data was estimated from the literature with the exception of BSC, where PFS was estimated based upon clinical experience	Incremental cost per life year saved: Second-line monotherapy vs. BSC: $24,228 Second-line combination (vs. second-line monotherapy): $46,068 Third-line previous combination (vs. second-line combination): $66,012 Fourth-line previous combination (vs. third-line chemotherapy): $162,552 Third and fourth-line previous monotherapy strategies were dominated	One-way sensitivity analysis was carried out on survival and total costs. No rationale was provided for the selected ranges
Havrilesky et al; 2007; US[105]	Cost-effectiveness analysis with some adjustment for QoL in a sensitivity analysis A Markov model with 42-month time horizon was developed from the payer perspective	Patients with ovarian cancer recurring more than 6 months following completion of first-line platinum based therapy	Carboplatin; gemcitabine and carboplatin; paclitaxel and carboplatin	2006 cost year Costs were not discounted Costs of chemotherapy were calculated for a hypothetical 58 year old woman. Costs of AEs were applied to treatment of AEs whose rates differed significantly between treatment groups. All costs were inflated to 2006 dollars using the medical component of the CPI	Survival data was taken from published sources Data on toxicity was taken from published sources. AEs were included if direct medical costs would be incurred and whose rates differed significantly between arms in the published trials	Incremental cost per progression free life year Paclitaxel and carboplatin versus carboplatin: $15,564 Gemcitabine and carboplatin versus paclitaxel and carboplatin: $278,388	PFS was varied using the 95% CIs; one way sensitivity analysis was undertaken on AE rates and cost of thrombocytopenia; costs of chemotherapy were varied; QoL was included for neurotoxicity
Griffin et al; 2006;	A publication reporting on	Second line ovarian	PLDH; topotecan;	NR	A systematic review identified RCTs reporting	Incremental cost per QALY gained	NR

UK[98]	the meta analysis carried out, and the model developed by the assessment group for TA91. Cost-utility analysis from the UK NHS perspective with three health states: stable disease; progressive disease; death	cancer	paclitaxel		PFS and OS. Data were combined via a mixed treatment comparison meta-analysis	Topotecan: dominated by paclitaxel; PLDH versus paclitaxel £16,714	
Main et al; 2006; UK[99]	Cost-utility analysis from the perspective of the UK NHS. Model with three health states: stable disease, progressive disease, death	Advanced second line ovarian cancer	PLDH; topotecan; paclitaxel	2003/4 cost year. Costs were not discounted as they were assumed to be incurred in year 1 The costs captured were: drug acquisition cost; costs of monitoring; costs of administration; costs of managing adverse events Costs were sourced from the literature (adverse events), BNF (drug costs), and via data from manufacturer's submissions for NICE TA91	Outcomes were discounted at 1.5% Efficacy was estimated from data obtained from a literature search and manufacturers. Data was meta-analysed using mixed treatment comparison techniques Data was available by subgroup (platinum sensitive vs. platinum refractory and whole population) such that two separate analyses were carried out Utility values were obtained through a systematic review for stable disease, however no value for progressed disease were obtained. A proxy was therefore used in breast cancer	Incremental cost per QALY ERG estimates (analysis 1): PLDH versus paclitaxel: £7,033 in the overall patient population; £5,777 in the platinum-sensitive population; and £9,555 in the platinum-refractory/resistant population ERG estimates (analysis 2): Cyclophosphamide, doxorubicin and cisplatin versus platinum monotherapy: £16,421 in the platinum-sensitive population; paclitaxel–platinum	Uncertainty was explored through deterministic and probabilistic sensitivity analyses. In sensitivity analysis subgroup specific treatment estimates were applied; results remained similar. Cost assumptions were also varied and results remain similar. An additional trial was also included; this reduced the effectiveness of PLDH

						combination therapy compared with cyclophosphamide, doxorubicin and cisplatin: £20,950 for the platinum-sensitive population	
Rocconi et al; 2006; US[106]	Cost effectiveness analysis from the perspective of a third party payer Decision analytic model	A hypothetical cohort of 4,000 platinum resistant patients with recurrent ovarian cancer	BSC; second line chemotherapy (monotherapy); second line chemotherapy (combination); third line chemotherapy after disease progression on second line monotherapy; third line chemotherapy after disease progression on second line combination	2004 cost year Direct costs were calculated for each strategy. Costs were estimated by adjusting local charges using a cost to charge ratio of 60%. Laboratory and procedure estimates were taken from the University of Alabama at Birmingham. Pharmacy costs were calculated using average wholesale drug costs. AE costs were not included. Cost of BSC was $135.50 per day	Clinical estimates were obtained from a review of published literature and included both phase II and phase III trials	Incremental cost per life year saved Second line monotherapy versus BSC: $64,104 Second line combination versus second line monotherapy: $302,316 Third line previous combination versus second line combination: $303,984	Uncertainty was tested in sensitivity analysis (one way)
NICE; 2005; UK[10]	Manufacturer submissions for NICE TA91: GSK, Schering-Plough: cost minimisation analysis BMS: cost effectiveness analysis Assessment group: summarised in Main et al	Women with second-line or subsequent advanced ovarian cancer	GSK: topotecan; PLDH Schering-Plough: topotecan; PLDH BMS: paclitaxel and platinum; paclitaxel; topotecan; PLDH	GSK: costs taken from a published analysis with inclusion of additional costs associated with toxicity monitoring Schering-Plough: similar to published cost minimisation analysis except expert opinion was used to estimate number and types of resources used to treat all adverse events. BMS: costs included drug	BMS: three trials were used to estimate effectiveness in the model. No adjustments were made for differences in baseline characteristics. Survival was estimated up to three years.	BMS: incremental cost per life year gained from paclitaxel/platinum relative to single agent paclitaxel was £12,120	Sensitivity analyses carried out by the assessment group were discussed

	(2006)			acquisition costs and costs of administration. No costs of adverse events were included.			
Capri and Cattaneo; 2003; Italy[82]	Cost minimisation analysis from the perspective of Italy's National Health Service Trial based estimation of cost based on rationale that PLDH and topotecan efficacy data was similar	Women with second-line advanced ovarian cancer	PLDH; topotecan	2002 cost year Direct medical costs including cost of drug, medical visits, laboratory tests, adverse events and hospital stays. Dosages quantified according to Gordon 2001. A panel of experts determined the resource consumption related to AEs (5 oncologists)	Efficacy data was considered to be similar for PLDH versus topotecan based upon findings from a phase III RCT with 474 patients. The following adverse events were included: anaemia, thrombocytopenia, neutropenia, sepsis, fever, stomatitis/ pharyngitis, nausea/ vomiting, diarrhoea, palmar-plantar erythrodysesthesia	Mean total cost of treatment with PLDH per patient was 8,812 Euros versus topotecan at 15,788 Euro	Sensitivity analysis tested AE cost and found variability; however, the authors concluded that PLDH was the most efficient choice of treatment
Ojeda et al; 2003; Spain[81]	Cost minimisation analysis with trial-based estimation of cost based on rationale that PLDH and topotecan efficacy data was similar	474 patients with ovarian cancer, all of whom had failed or relapsed after first line chemotherapy with a platinum based regimen	PLDH; topotecan	2001 cost year Direct medical costs (study drug, drug administration, cost of managing adverse events) were included in the economic evaluation Cost of study drug was taken from the Spanish Catalogue of Medicinal Products 2001. Unit costs of procedures were taken from the Spanish Data Base of Sanitary Costs and the published literature. Costs were converted from pesetas to Euros at the rate of 166.386 pesetas per Euro. Estimates of resource utilisation associated with	Efficacy data was considered to be similar for PLDH versus topotecan based upon findings from a phase III RCT with 474 patients Incidence of the following adverse events were included: anaemia, thrombocytopenia, neutropenia, sepsis, fever, stomatitis/ pharyngitis, nausea/ vomiting, diarrhoea, palmar-plantar erythrodysesthesia	Total cost of PLDH was 9614.72 Euros versus topotecan where total cost was 11,824.69 Euros The estimated difference in cost in the base case was 2,209.97 Euros	Uncertainty was tested in one-way sensitivity analysis via changes in a number of key variables. Results remained favourable to PLDH

				treatments when managing adverse events was made through an expert panel			
Forbes et al; 2002; UK[94]	Cost effectiveness analysis from the perspective of the UK NHS	474 patients with ovarian cancer, all of whom had failed or relapsed after first line chemotherapy with a platinum based regimen	PLDH; topotecan	Costs were taken from Smith 2002	OS was extrapolated from median survival presented from a manufacturer submission for NICE TA45. Extrapolation was based upon an exponential distribution HRQoL was not derived from the literature, instead, a sensitivity analysis was conducted to explore what relative magnitude of HRQoL might cause the conclusions of the CEA based on life-years to alter	Incremental cost per incremental survival PLDH was dominant compared with topotecan (PLDH was cost saving and improved mean survival duration versus topotecan)	Uncertainty was explored in scenario analyses and monte carlo simulation The authors found that 80% simulations were dominant for PLDH, and 20% of monte carlo simulations resulted in estimates of lower cost and a reduction in survival for PLDH versus topotecan
Smith; 2002; USA and UK[80]	Cost minimisation analysis from the payer perspective Trial based estimation of cost based on rationale that PLDH and topotecan efficacy data was similar	474 patients with ovarian cancer, all of whom had failed or relapsed after first line chemotherapy with platinum based regimen	PLDH; topotecan	Costs included cost of study drug, cost of drug administration, and management of adverse events UK costs were presented as US$ using the conversion rate of $1.4 = £1 Cost data was taken from a clinical trial for study drug volume and BNF for estimates of drug cost; clinical trial data for quantities of resource use estimated were used to estimate cost of adverse event treatment as well as estimates from a panel of oncologists from the USA and UK; costs of blood products	N/A	Total UK cost per patient $1.4 = £1: Topotecan, $16,906 (95% CI $15,617, $18,847); PLDH $13,997 (95% CI $12,863, $15,392) Incremental cost (P-T): -$2,909 (95% CI -$779, -$3,415)	Uncertainty: in an extreme analysis to favour topotecan, 89% of the replicates showed PLDH to be cost saving

				come from the National Blood Authority, 2000 tariff; cost of inpatient stay came from a national costing database on literature from a UK Trust that studied patients in ICU; costs of an outpatient clinic visit and a chemotherapy administration come from tariffs at a UK cancer centre and were similar to costs at two other major cancer centres in England			
Abbreviations used in table: AE, adverse event; BMS, Bristol Myers Squibb; BNF, British National Formulary; BSC, best supportive care; CEA, cost-effectiveness analysis; CI, confidence interval; ERG, evidence review group; FACTG, Functional Assessment of Cancer Therapy – General; GDP, gross domestic product; GSK, GlaxoSmithKline; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio; ICU, intensive care unit; N/A, not applicable; NICE, National Institute for Health and Care Excellence; NR, not reported; OS, overall survival; PD, progressed disease; PFS, progression free survival; PLDH, pegylated liposomal doxorubicin hydrochloride; QALY, quality adjusted life year; QoL, quality of life; RCT, randomised controlled trial; UK, United Kingdom; US, United States							

Additional identified economic evaluations

Author, year, country	Overview
NICE; 2013; UK[11]	UK cost-utility analysis modelled using a semi-Markov model comparing bevacizumab plus paclitaxel and carboplatin versus paclitaxel and carboplatin. Patients were those with first line ovarian cancer.
Barnett; 2012; US[148]	US cost-effectiveness analysis modelled using a Markov model comparing bevacizumab incorporated into standard platinum/taxane chemotherapy for all with bevacizumab incorporated into treatment and maintenance for sub optimally debulked stage IV disease, and a predictive biomarker test that would identify a subset of women who derive survival advantage from the addition of bevacizumab. Patients were those with first line ovarian cancer
Chan; 2012; US[149]	US cost-effectiveness analysis comparing the addition of bevacizumab and maintenance bevacizumab to paclitaxel and carboplatin for stage IIIC and stage IV ovarian cancer after primary surgery
Dalton; 2012; US[150]	US cost-effectiveness analysis comparing dose dense weekly paclitaxel plus carboplatin versus paclitaxel plus carboplatin in patients with first line ovarian cancer
Geisler; 2012; US[151]	US cost-effectiveness analysis comparing carboplatin and paclitaxel at four alternative dosages in patients with first line, high-risk, ovarian cancer
Havrilesky; 2012; US[126]	US cost-utility analysis modelled using a Markov model comparing standard treatment; paclitaxel and carboplatin; paclitaxel drug shortage; docetaxel and carboplatin. Patients had newly diagnosed, untreated ovarian cancer.
Havrilesky; 2012; US[152]	US cost-utility analysis modelled using a Markov model comparing standard treatment; paclitaxel and carboplatin; paclitaxel drug shortage; docetaxel and carboplatin. Patients had newly diagnosed, untreated ovarian cancer. [Conference abstract].
Lechuga; 2012; Mexico[153]	Mexico cost-effectiveness analysis modelled using a Markov model with three health states (PFS, PD, death), comparing carboplatin plus paclitaxel with bevacizumab plus carboplatin plus paclitaxel, in patients with first line ovarian cancer
Neymark; 2012; Belgium[154]	Belgian within trial cost-effectiveness analysis comparing cisplatin and cyclophosphamide with cisplatin and paclitaxel in women with first line ovarian cancer stage IIB – IV
Cohn; 2011; US[155]	US cost-effectiveness analysis modelled using a decision tree, comparing paclitaxel plus carboplatin (PC) versus PC plus bevacizumab (PCB) versus PCB plus bevacizumab maintenance therapy (PCB+B) in patients with first line ovarian cancer
Dalton; 2011; US[150]	US cost-effectiveness analysis modelled using a Markov model comparing dose dense paclitaxel plus carboplatin versus standard paclitaxel plus carboplatin in women with first line advanced ovarian cancer
Fuh; 2011; US[156]	US cost-effectiveness analysis comparing paclitaxel, carboplatin and bevacizumab and maintenance bevacizumab with gemcitabine, carboplatin and bevacizumab and maintenance bevacizumab. The study investigated cost-effectiveness in the recurrent setting with first line data
Krysinski; 2011; Poland[157]	Polish retrospective cost-effectiveness analysis comparing cisplatin plus paclitaxel versus cisplatin plus cyclophosphamide in women with ovarian cancer stage III and IV
Cohn et al; 2010; US[158]	US cost-effectiveness analysis comparing paclitaxel plus carboplatin (PC) versus PC plus bevacizumab in patients with advanced first line ovarian cancer
Havrilesky; 2008; US[159]	US cost-utility analysis modelled using a decision analysis and comparing cisplatin plus paclitaxel with carboplatin plus paclitaxel in women with first line stage III optimally resected ovarian cancer
Bristow; 2007; US[160]	US cost-utility analysis comparing paclitaxel and cisplatin in patients with first line ovarian cancer with stage III disease

Fedders; 2007; Germany[161]	German cost-effectiveness analysis modelled using a Markov model comparing paclitaxel and platinum versus carboplatin in women with first line ovarian cancer, as well as topotecan and liposomal doxorubicin as second-line chemotherapy
Dranitsaris; 2004; Canada[162]	Canadian cost-benefit analysis comparing docetaxel and paclitaxel in patients with first line advanced ovarian cancer
Limat; 2004; France[163]	French retrospective cost-effectiveness analysis comparing cyclophosphamide and cisplatin with paclitaxel and cisplatin in patients with first line advanced ovarian cancer
NICE; 2003; UK[5]	Guidance on the use of first line paclitaxel in the treatment of ovarian cancer and summary of submitted manufacturer models for TA55; second line recommendations were super ceded by TA91
Bennett; 1998; US[164]	US cost-utility analysis comparing the addition of amifostine as an adjunctive supportive therapy to cyclophosphamide plus cisplatinum in patients with newly diagnosed advanced ovarian cancer
Berger; 1998; Germany, Spain, France, Italy, The Netherlands and the UK[165]	Cost-effectiveness analysis comparing cisplatin plus cyclophosphamide or paclitaxel in women with first line advanced ovarian cancer
Messori; 1998; US[166]	US cost-utility analysis comparing cisplatin based chemotherapy with or with paclitaxel at either a convention or high dose in patients with newly diagnosed ovarian cancer
Elit; 1997; Canada[167]	Canadian cost-effectiveness analysis comparing cisplatin and cyclophosphamide with cisplatin and paclitaxel in women with first line stage III/IV ovarian cancer
McGuire; 1997; US[168]	US cost-effectiveness analysis comparing paclitaxel plus cisplatin versus cyclophosphamide plus cisplatin in patients with first line advanced ovarian cancer
Abbreviations used in table: NICE, National Institute for Health and Care Excellence; PD, progressed disease; PFS, progression free survival; UK, United Kingdom; US, United States	

Identified studies including utility data

Author, year, country	Population	Health states	Instrument (valuation)	Utility results
Studies identified from the literature search				
Hess; 2013; US[121]	People with ovarian cancer enrolled within GOG-0152 or GOG-0172	No specific health states; instead mean utility at different time points, and overall, were reported	Valuation of FACT scores using two methods: • Dobrez *et al.* [123] valued the FACT questionnaire using the time trade-off method with 1,433 cancer patients who had one of 10 different cancer diagnoses and was 53% male; • Cheung *et al.* [122] mapped the FACT questionnaire to EQ-5D	GOG-0152 Mean utility / N; GOG-0172 Mean utility / N Cheung 0.81 / 1362 / 0.76 / 1323 Dobrez 0.84 / 1342 / 0.80 / 1294
TA285[75]	People with recurrent, platinum-sensitive ovarian cancer enrolled on OVA-301	Stable disease Progressed disease	EQ-5D	Mean stable disease 0.718 (se 0.01); mean progressive disease 0.649 (se 0.019)
TA284[71]	People with first-line ovarian cancer enrolled on ICON7	Stable disease Progressed disease	EQ-5D	Mean utility PFS weeks 0-2 0.6571 PFS weeks 3-5 0.7153 PFS weeks 6-8 0.7443 PFS weeks 9-11 0.7683 PFS weeks 12-14 0.7643 PFS weeks 15-20 0.7444 PFS weeks 21-26 0.7638 PFS weeks 27-32 0.7718 PFS weeks 33-38 0.7638 PFS weeks 39-44 0.7785 PFS weeks 45-50 0.7533 PFS weeks 51-53 0.7760 PFS weeks 54+ 0.8129 Progressed disease 0.7248
Montalar; 2012; Spain[97]	People with recurrent, platinum-sensitive ovarian cancer enrolled on OVA-301	Stable disease Progressed disease	EQ-5D	Stable disease: 0.72 Progressed disease: 0.65
Havrilesky; 2012; US[101]	People with recurrent, platinum-sensitive ovarian cancer who had completed the FACT questionnaire as part of a phase II RCT. Sample	No specific health states were described (e.g. progression free survival), instead the study reported utility by study	Dobrez *et al.*[123] valued the FACT questionnaire using the time trade-off method with 1,433 cancer patients who had one of	Utility at randomization was mean 0.87 for both arms, and 0.83 to 0.84 at the end of the study

	size was not reported, however, the text indicates that participants who completed the FACT questionnaire were enrolled in a phase II clinical trial with 150 participants	arm at different time points	10 different cancer diagnoses and was 53% male	
Havrilesky; 2012; US[126]	QoL data were sources from a previous study, *Leung et al.*[127]	Utility on treatment with carboplatin and paclitaxel; utility on treatment with carboplatin and docetaxel	Utilities were derived from *Leung et al.*[127]	Utility on treatment with carboplatin and paclitaxel (0.62); utility on treatment with carboplatin and docetaxel (0.51)
Krasner; 2012; UK[65]	672 patients treated with PLDH (n=335) and trabectedin plus PLDH (n=337) in a phase III clinical trial. Although not reported within the paper, the trial recruited women with recurrent ovarian cancer after failure of first-line, platinum-based chemotherapy	Health states were not described, instead quality of life was assessed at baseline, and at end of study by treatment group	EQ-5D, valuation was not described	PLDH: 0.78 (sd 0.163) at baseline (n=318), with -0.05 (sd 0.191) change from baseline (n=211) Trabectedin plus PLDH 0.78 (sd 0.171) at baseline (n=323) with -0.05 (sd 0.201) change from baseline (n=233)
Pickard; 2012; US/UK[128]	People with advanced breast, brain, colorectum, hepatobiliary system, lung and ovary cancer. N = 41 to 49 for each subgroup	The aim of the study was to compare preference based scores between the EQ-5D and FACT, by cancer type. No health states within each cancer were described	EQ-5D and FACT	No utility results for ovarian cancer were presented within the abstract
Grann; 2011; N/A[129]	QoL data were sourced from a previous study, Grann (2010)	A QoL value was reported for ovarian cancer	Grann *et al.*{Grann, 2010 923 /id valued health states using time trade-off in two groups of women: women without ovarian cancer; women with BRCA1/2 mutations	The utility estimated for ovarian cancer was 0.83 (women without ovarian cancer n=160) and 0.84 (women with BRCA1/2 mutation n=83)
Lesnock; 2011; US[103]	QoL data were sourced from a previous study, *Greving et al.*[131]	Progression free survival	Utilities were derived from *Greving et al.*[131]. Greving et al (2009) derived utilities from *Grann 1998*[134] and *Grann 1999*[135] where time trade-off was used to value health states	The utility for PFS was 0.85
TA222; 2011; UK[90]	Individual patient data within the OVA-301 trial. The OVA-301 trial included 672 patients treated with PLDH (n=335) and trabectedin plus PLDH (n=337)	Progression free survival; progressed disease	EQ-5D, valuation was not described	As there was no evidence of an interaction between experimental group and health utility, and also no evidence of a systematic difference in health utility within a health state (stable or progressive) over time, health utility was based upon the first health utility estimate for each subject in that health state. Mean stable disease 0.718 (se 0.01); mean progressive disease 0.649 (se 0.019)

Gordon; 2010; Australia[132]	85 Australian women aged 18-79 referred for chemotherapy for ovarian cancer but newly presenting or recurrent completed the SF-6D questionnaire. 60 women had recurrent disease of which 55% were platinum sensitive and 37% were platinum resistant (remainder unknown)	Mean SF-6D score by stage of disease (I/II; III; IV) and as a whole group. These groups were a mix of drug therapies, platinum status, first line/subsequent line etc.	SF-6D, valuation was not described	Stage I/II (n=13) 0.74 (sd 0.11) Stage III 0.68 (n=63) (sd 0.09) Stage IV 0.69 (n=9) (sd 0.08) Total population 0.69 (sd 0.10)
Grann; 2010; Canada[130]	160 Canadian women without a personal or family history of breast or ovarian cancer and without known high risk for either breast or ovarian cancer, and 83 women with known BRCA1/2 mutation carrier status were recruited to value health states using the time trade of method	Breast and ovarian cancer health states; gene positive health states; prophylactic surgery health states; chemo preventive health states; screening methods	Time trade-off	Mean preference rating for ovarian cancer was 0.84 for mutation carriers and 0.83 for controls
Hess; 2010; US[133]	34 US oncologists who prescribed treatment for women with ovarian cancer. 51 US women with ovarian cancer.	Six health states: • Low AEs; low treatment efficacy; poor emotional wellbeing • Low-moderate AEs; low treatment efficacy; moderate emotional wellbeing • Moderate-high AEs; moderate treatment efficacy; poor emotional wellbeing • High AEs; moderate treatment efficacy; positive emotional wellbeing • Extremely high AEs; high treatment efficacy; positive emotional wellbeing • Extremely high AEs; high treatment efficacy; poor emotional wellbeing	Standard gamble	Utility scores presented graphically. Reading values from the graph: • Health state 1: physicians 0.395; patients receiving chemotherapy: 0.58; patients under surveillance: 0.32 • Health state 2: physicians 0.44; patients receiving chemotherapy: 0.52; patients under surveillance: 0.335 • Health state 3: physicians 0.50; patients receiving chemotherapy: 0.52; patients under surveillance: 0.305 • Health state 4: physicians 0.51; patients receiving chemotherapy: 0.58; patients under surveillance: 0.38 • Health state 5: physicians 0.70; patients receiving chemotherapy: 0.61; patients under surveillance: 0.38 • Health state 6: physicians 0.64; patients receiving chemotherapy: 0.58; patients under surveillance: 0.30
Greving; 2009; the	Utilities were derived from the literature from studies *Grann*	Progression free survival; relapsed disease	Utilities were derived from the literature from studies *Grann*	Utility for progression free survival (0.85) and relapsed disease (0.65) although unclear how

Netherlands[131]	*1998[134] and Grann 1999[135]*		*1998[134] and Grann 1999[135]* Both studies used time trade-off to value health states	utilities from *Grann 1998[134] and Grann 1999[135]* related to these numbers
Havrilesky; 2009; US[136]	37 female members of the public without a personal history of ovarian cancer and 13 women with a prior diagnosis of ovarian cancer were recruited to evaluate the 25 health states; the average age of patients was 58, the average age of the volunteers was 41	25 descriptive health states	Time trade-off	Diagnosis health states • Ovarian cancer – clinical remission n=16 mean 0.83 (sd 0.25) • Recurrent ovarian cancer responding to chemotherapy grades 3/4 toxicity n=14 0.61 (sd 0.24) • Recurrent ovarian cancer responding to chemotherapy grades 1/2 toxicity n=1 0.50 (sd 0.34) • Recurrent ovarian cancer progressive grades 3/4 toxicity n=15 0.47 (sd 0.34) • Recurrent ovarian cancer progressive grades 1/2 toxicity n=16 0.40 (sd 0.33) • End stage ovarian cancer n=15 0.16 (sd 0.25) Chemotherapy related health states also included for patients and volunteers separately: Alopecia grade 2; Peripheral neuropathy grade 1-2; stomatitis grade 2; myalgia/pain grade 1-2; nausea/vomiting grade 1-2; myalgia/pain grade 3-4; neutropenia grade 4; peripheral neuropathy grade 3-4; nausea vomiting grade 3-4; fatigue grade 3-4; febrile neutropenia

Havrilesky; 2007; US[105]	QoL for neurotoxicity taken from *Sun 2002*[137]	Neurotoxicity	Utility was derived from *Sun 2002*[137] in which utilities were estimated via time trade-off	Utility score for neurotoxicity was varied from 0.28 – 1.00. In *Sun 2002*[137] the median utility weight was 0.90 to 1.00
Stein; 2007; UK[138]	66 people with advanced ovarian cancer on chemotherapy who had participated in an RCT of routine quality of life measurement, completed the EORTC QLQ-C30	No specific health states were described (e.g. progression free survival), instead six clusters of patients were described as health states and included varying proportions of performance status, disease stage, and response after treatment	Each health state was valued by the Value of Health Panel, a panel which contains members of the public recruited from the electoral registers of four UK cities. The panel included 39 panel members. Health states were valued using the standard gamble technique	The mean utility for each cluster ranged from 0.694 (cluster 6, high levels of physical, role, and social impairment, poor emotional and cognitive function, older than average age, and highest proportion of metastatic disease) to 0.977 (cluster 1, good performance status, few limitations)
Main; 2006; UK[99]	Utility for stable disease taken from *Tengs 2000*[88], a US review of QoL weights in the literature. Utility for progressed disease was taken from *Brown 1998*[89] for breast cancer	Health states were stable disease and progressed disease	Not reported in the study. Stable disease taken from *Tengs 2000*[88] from "ovarian cancer, metastatic" with 54 participants via time trade-off, which in itself was taken from *Grann 1998*[134]. In *Grann 1998*[134], the utility of 0.63 was for "metastatic disease". For progressed disease, a utility value was estimated from *Brown 1998*[89] by subtracting the utility for progressed disease from the utility for stable disease	Stable disease 0.63 Progressed disease 0.34
Calhoun; 2004; US[139]	39 ovarian cancer patients, 15 women at increased risk, 39 women at baseline risk, and 11 gynecologic oncologists completed utility assessment surveys	Fifteen specific health states reflecting varying levels of toxicity severity, patient functioning and progressive cancer disease for neurotoxicity, nephrotoxicity and ototoxicity	Modified time trade-off	Mean utility scores were presented for those with disease, those at risk, the general population and physicians. The mean utility scores for the general population (n=39) were estimated to be: Mild ototoxicity: 0.88 Mild nephrotoxicity: 0.95 Mild neurotoxicity: 0.92 Severe ototoxicity: 0.38 Severe nephrotoxicity: 0.27 Severe neurotoxicity: 0.47

Studies identified from review of reference lists				
Sun; 2002[137]	Forty patients with ovarian cancer enrolled in phase II trials of high dose chemotherapy with peripheral stem cell support were asked to participate. 34 completed two surveys. These patients were either second line (n=27) or third line (n=7). All women had prior platinum/paclitaxel therapy	Side effects associated with chemotherapy: alopecia, pancytopenia, fatigue, neuropathy, ototoxicity, dysuria, mucositis, nausea/vomiting, hepatotoxicity, "ideal" chemotherapy, "worst" chemotherapy	Time trade-off	Median values where T1 refers to survey 1, and T2 refers to survey 2: alopecia, T1 1.00, T2 1.00 pancytopenia, T1 1.00 T2 0.90 fatigue, T1 0.95 T2 0.9 neuropathy, T1 0.90 T2 1.00 ototoxicity, T1 1.00 T2 0.90 dysuria, T1 0.75 T2 0.70 mucositis, T1 0.78 T2 0.70 nausea/vomiting, T1 0.70 T2 0.50 hepatotoxicity, T1 0.75 T2 0.50 "ideal" chemotherapy, T1 and T2 1.00 "worst" chemotherapyT1 and T2 0.00
Tengs; 2000[88]	Study was a review of HRQoL weights from the literature. The weight for "ovarian cancer, metastatic" used within Main et al 2006 for TA91 was taken from *Grann 1998*[134] from 54 participants via time trade-off	Ovarian cancer, metastatic and other ovarian cancer health states that were treatment related and captured from the literature	The weight for "ovarian cancer, metastatic" used within Main *et al.*[99] for TA91 was taken from *Grann 1998*[134] from 54 participants via time trade-off	The weight for "ovarian cancer, metastatic" used within Main et al 2006 for TA91 was 0.63
Grann; 1999[135]	21 breast cancer patients, 28 women with a personal history of multiple breast biopsies or a family history of breast cancer, and 135 women without these conditions	Ovarian cancer, metastatic cancer and other cancer states, preventive measures and genetic risk	Time trade-off	Valued by reference group aged 20-32 (n=92) Ovarian cancer mean 0.84 (sd 0.22) Metastatic mean 0.73 (sd 0.27) Valued by reference group aged 33-50 (n=42) Ovarian cancer mean 0.58 (sd 0.36) metastatic cancer 0.52 (sd 0.35)
Leung; 1999[127]	25 healthy volunteers and 25 women with breast cancer	Health states by treatment: paclitaxel, docetaxel and vinorelbine; toxicity from treatment, response to treatment and no response to treatment	Time trade-off	No ovarian cancer health states reported
Brown; 1998[89]	29 US oncology nurses at two large oncology centre's provided one estimate of average utility; in addition 25-30 nurses from each of Germany, Italy, Netherlands, Spain and the UK also estimated patient preferences	All breast cancer: • At start of second line therapy • Partial/full response • Stable disease • Progressive disease • Terminal disease	Standard gamble	No ovarian cancer health states reported

		• Peripheral neuropathy and partial/full response • Peripheral neuropathy and stable disease • Severe edema and partial/full response • Severe edema and stable disease • Severe skin condition • Cardiac toxicity • Febrile neutropenia with hospitalization • Infection with no hospitalization		
Grann; 1998[134]	A sample of 54 participants (unclear whether these participants had or did not have the condition)	Well postoophotectomy; well postmastectomy and oophorectomy; breast cancer; ovarian cancer; metastatic disease	Time trade-off	Ovarian cancer mean = 0.82 (IQR 0.750-1.00); metastatic disease mean = 0.63 (IQR 0.50-0.83)
Abbreviations used in table: AE, adverse event; EORTC QLQ-C30; European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; FACT, functional assessment of cancer therapy; IQR, inter-quartile range; n, sample size; PFS, progression free survival; PLDH, pegylated liposomal doxorubicin hydrochloride; QoL, quality of life; RCT, randomised controlled trial; sd, standard deviation; se, standard error; UK, United Kingdom; US, United States				

Appendix 8: Quality assessment of cost-effectiveness evidence

Quality assessment of the PharmaMar submission versus the NICE reference case

Attribute	**Reference case**	**Does the *de novo* economic evaluation match the reference case?**
Decision problem	The scope developed by NICE	Partially; within the scope trabectedin was listed as a comparator in people with platinum-sensitive ovarian cancer, and people who are allergic to platinum-based compounds. Within the economic evaluation, the manufacturer considered trabectedin in combination with PLDH in people who are partially platinum sensitive (i.e. a subset of the full platinum-sensitive population) and people who are allergic to platinum-based compounds. The manufacturer's rationale for this was to "align with the inclusion criteria of the OVA-301 trial and the clinical unmet need for non-platinum alternatives in these populations" (MS, page 29)
Comparator(s)	Alternative therapies routinely used in the NHS	Partially; the manufacturer compared trabectedin in combination with PLDH versus PLDH monotherapy. However, within the scope, a number of additional therapies were listed as comparator treatments.[38] The manufacturer provided rationale for not including these comparators within the submission; however, the TAG considers that consideration of platinum-based therapies as comparators for the group of patients with no allergy or intolerance to platinum would have been appropriate.
Perspective costs	NHS and Personal Social Services	Yes
Perspective benefits	All health effects on individuals	Yes
Form of economic evaluation	Cost-utility analysis	Yes
Time horizon	Sufficient to capture differences in costs and outcomes	Yes, lifetime time horizon
Synthesis of evidence on outcomes	Systematic review	No; utilities were obtained from head-to-head trial data (OVA-301)
Outcome measure	Quality adjusted life years	Yes
Health states for QALY	Described using a standardised and validated instrument	Yes, EQ-5D
Benefit valuation	Time-trade off or standard gamble	Yes; EQ-5D
Source of preference data for valuation of changes in HRQoL	Representative sample of the public	Yes; EQ-5D

Discount rate	An annual rate of 3.5% on both costs and health effects	Yes
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes; however, the manufacturer requested consideration under end-of-life criteria
Sensitivity analysis	Probabilistic sensitivity analysis	Yes
Abbreviations used in table: HRQoL, health-related quality of life; MS, manufacturer's submission; NICE, National Institute for Health and Care Excellence; PLDH, pegylated liposomal doxorubicin hydrochloride; QALY, quality adjusted life year; TAG, Technology Assessment Group.		

Quality assessment of the PharmaMar submission using the Philips checklist[(108)]

Attribute	Assessment	Comment
Structure		
S1: Statement of decision problem/objective	Yes	Stated
S2: Statement of scope/perspective	Yes	Stated
S3: Rationale for structure	Yes	Stated; based upon TA91, a previous technology appraisal in recurrent ovarian cancer
S4: Structural assumptions	Yes	Stated
S5: Strategies/comparators	**?**	Partial; the manufacturer compared trabectedin in combination with PLDH versus PLDH monotherapy. However, within the scope, a number of additional therapies were listed as comparator treatments.[(38)] The manufacturer provided rationale for not including these comparators within the submission; however, the TAG considers that the exclusion of platinum-based therapies as comparators for the group of patients with no allergy or intolerance to platinum was inappropriate
S6: Model type	Yes	Stated, semi-Markov model
S7: Time horizon	Yes	Stated, lifetime
S8: Disease states/pathways	Yes	Stated, PFS and OS
S9: Cycle length	–	N/A
Data		
D1: Data identification	Yes	Stated

D2: Pre-model data analysis	**?**	Partial; pre-analysis of PFS and OS extrapolation is discussed, but it is not possible to validate the regression analysis controlling for baseline characteristics
D2a: Baseline data	**?**	Partial; with the exception of the extrapolated curves for PFS and OS all data sources are described
D2b: Treatment effects	Yes	Stated
D2d: Quality of life weights (utilities)	Yes	Stated
D3: Data incorporation	Yes	Stated
D4: Assessment of uncertainty	Yes	Deterministic and probabilistic analysis
D4a: Methodological	No	Not reported
D4b: Structural	Yes	Assessed through alternative functional forms for the extrapolated PFS and OS curves
D4c: Heterogeneity	Yes	Assessed through consideration of the partially platinum sensitive and fully platinum sensitive populations
D4d: Parameter	Yes	Assessed through deterministic and probabilistic analysis
Consistency		
C1: Internal consistency	Yes	Discussed
C2: External consistency	No	Not assessed; in particular the long tail for OS established via use of the log-logistic extrapolation is not discussed
Abbreviations used in table: OS, overall survival; PFS, progression free survival; PLDH, pegylated liposomal doxorubicin hydrochloride; TAG, Technology Assessment Group		

Quality assessment of the included economic evaluations against the NICE reference case

Attribute	**Reference case**	**Comments**								
		NICE 2013 (TA285)[15]	Montalar; 2012; Spain[97]	Chan 2011, US[100]	Havrilesky et al; 2012; US[101]	Gore; 2011; UK[96]	Lee et al; 2011; Korea[107]	Lesnock; 2011; US[102]	Lesnock; 2011b; US[103]	NICE; 2011; UK[10]
Decision problem	The scope developed by NICE	partial	partial	partial	partial	partial	partial	partial	partial	partial
Comparator(s)	Alternative therapies routinely used in the NHS	partial	partial	partial	partial	partial	partial	partial	partial	partial

Perspective costs	NHS and Personal Social Services	Yes	No	No	No	Yes	No	No	No	Yes
Perspective benefits	All health effects on individuals	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Form of economic evaluation	Cost-utility analysis	Yes	Yes	No, cost per life year saved	Yes	Yes	Yes	Yes	Yes	Yes
Time horizon	Sufficient to capture differences in costs and outcomes	Yes, ten years	Yes, lifetime	No, trial duration	No, 24 months	Yes	Yes	No, not reported	No, not reported	Yes
Synthesis of evidence on outcomes	Systematic review	No, head-to-head clinical trial	No, head-to-head clinical trial	No, head to head clinical trial	No, head to head clinical trial	No, head to head clinical trial	Yes	No, not reported	Yes	No, head to head clinical trial
Outcome measure	QALYs	Yes	Yes	No, life years saved	Yes	Yes	Yes	Yes	Yes	Yes
Health states for QALY	Described using a standardised and validated instrument	Yes, EQ-5D	Yes, EQ-5D	N/A	Yes, FACT mapped to utility	Yes, EQ-5D	No, not reported	No, not reported	No, expert opinion	Yes, EQ-5D
Benefit valuation	Time-trade off or standard gamble	Yes, TTO via EQ-5D	Yes, TTO via EQ-5D	N/A	No, not reported	Yes, TTO via EQ-5D	No, not reported	No, not reported	No, expert opinion	Yes, TTO via EQ-5D
Source of preference data for valuation of changes in HRQoL	Representative sample of the public	Yes, the public via EQ-5D	Yes, the public via EQ-5D	N/A	No, not reported	Yes, the public via EQ-5D	No, not reported	No, not reported	No, expert opinion	Yes, the public via EQ-5D
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes	No, 3% on both costs and benefits	No, not reported	No	Yes	No, not reported	No, not reported	No, not reported	Yes

Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes	Yes	N/A	Yes	Yes	Yes	Yes	Yes	Yes
Sensitivity analysis	Probabilistic sensitivity analysis	Yes	Yes	No	Yes	Yes	No	No	No	Yes
Attribute	**Reference case**	**Comments**								
		Papaioannou; 2011; UK[95]	Papaioannou; 2010; UK[147]	Case; 2007; US[104]	Havrilesky et al; 2007; US[105]	Griffin et al; 2006; UK[98]	Main et al; 2006; UK[99]	Rocconi et al; 2006; US[106]	NICE; 2005; UK[10]	Forbes et al; 2002; UK[94]
Decision problem	The scope developed by NICE	partial	partial	partial	partial	partial	partial	partial	partial	Partial
Comparator(s)	Alternative therapies routinely used in the NHS	partial	partial	partial	partial	partial	partial	partial	partial	Partial
Perspective costs	NHS and Personal Social Services	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes
Perspective benefits	All health effects on individuals	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Form of economic evaluation	Cost-utility analysis	Yes	Yes	No	No	Yes	Yes	No	Yes	No
Time horizon	Sufficient to capture differences in costs and outcomes	Yes	Yes	Yes, implicitly lifetime	No, 42 months	Yes	Yes	Yes	Yes	Yes
Synthesis of evidence on outcomes	Systematic review	No, head to head clinical trial	No, head to head clinical trial	partial; assumptions made for	partial	Yes	Yes	partial	Yes	Yes

				best supportive care						
Outcome measure	QALYs	Yes	Yes	No	No	Yes	Yes	No	Yes	No
Health states for QALY	Described using a standardised and validated instrument	Yes, EQ-5D	Yes, EQ-5D	N/A	N/A	?	?	N/A	?	N/A
Benefit valuation	Time-trade off or standard gamble	Yes, TTO via EQ-5D	Yes, TTO via EQ-5D	N/A	N/A	Yes	Yes	N/A	Yes	N/A
Source of preference data for valuation of changes in HRQoL	Representative sample of the public	Yes, the public via EQ-5D	Yes	N/A	N/A	?	?	N/A	?	N/A
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes	Yes	No	No	Yes	Yes	No	Yes	partial, discounting at 6%
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes	Yes	N/A	N/A	Yes	Yes	Yes	Yes	N/A
Sensitivity analysis	Probabilistic sensitivity analysis	Yes	Yes	No	No	No	Yes	No	Yes	Yes
Abbreviations used in table: HRQoL, health-related quality of life; N/A, not applicable; NICE, National Institute for Health and Care Excellence; QALY, quality adjusted life year; TTO, time trade-off; UK, United Kingdom; US, United States										

Quality assessment of the included economic evaluations using the Philips checklist[(108)]

Dimension of quality	**Comments**					
Study	Chan 2011, US[(100)]	Havrilesky et al; 2012;	Gore; 2011; UK[(96)]	Lee et al; 2011;	Lesnock; 2011;	Lesnock; 2011b;

			US[101]				Korea[107]		US[102]		US[103]	
Structure												
S1: Statement of decision problem/objective	✓	Stated	✓	Stated	✓	Stated	✓	Stated	✓	Stated	✓	Stated
S2: Statement of scope/perspective	X	Not stated	✓	Stated	✓	Stated	✓	Stated	X	Not stated	✓	Stated
S3: Rationale for structure	X	Not stated	X	Not stated	X	Not stated	X	Not stated	X	Not stated	X	Not stated
S4: Structural assumptions	X	Not stated; the analysis was a within trial evaluation	✓	Stated	?	Partially	✓	Stated	X	Not stated	✓	Stated
S5: Strategies/comparators	?	Did not include the full range of comparators, but considered: • g emcitabine plus carboplatin • g emcitabine, carboplatin and bevacizumab	?	Did not include the full range of comparators, but considered: • c ocetaxel and carboplatin combination • c ocetaxel and sequential carboplatin	?	Did not include the full range of comparators, but considered: • t rabectedin in combination with PLDH • LDH	?	Did not include the full range of comparators, but considered: • P LDH plus carboplatin • P aclitaxel plus carboplatin	?	Did not include the full range of comparators, but considered: • aclitaxel • evacizumab	?	Did not include the full range of comparators, but considered: • aclitaxel • evacizumab
S6: Model type	✓	Within trial economic evaluation	✓	Markov model based upon RCT	✓	Decision analytic model based upon RCT	✓	Markov model	✓	Decision analytic model based upon RCT	✓	Markov model
S7: Time horizon	X	Trial duration, <1 year; unlikely to reflect the lifetime horizon for these patients	X	24 months; unlikely to reflect the lifetime horizon for these patients	✓	Lifetime time horizon	✓	Ten-years; likely to reflect the lifetime time horizon for these patients	X	Not reported	X	Not reported
S8: Disease states/pathways	?	Partially, progression free survival and bowel perforation was captured, but overall survival was not considered	?	Partially, progression free survival and neurotoxicity was captured, but overall survival was not considered	✓	Progression free survival, overall survival	✓	Responsive, progressive, clinical remission, death	✓	Progression free survival, overall survival	✓	Progression free survival, overall survival, complications

S9: Cycle length	–	N/A	✓	21 days, equivalent to one chemotherapy cycle	–	N/A	?	9 weeks; no rationale for this duration provided	X	Not reported	X	Not reported
Data												
D1: Data identification	?	Partially	✓	Stated	?	Partially	?	Partially	?	Partially	✓	Stated
D2: Pre-model data analysis	?	Not reported	✓	Stated	?	Not reported	✓	Stated	?	Not reported	?	Not reported
D2a: Baseline data	?	Not reported	✓	Stated	?	Not reported	?	Not reported	?	Not reported	✓	Stated
D2b: Treatment effects	?	Progression free survival and bowel perforation, although not reported in sufficient detail to obtain estimates	✓	Stated	?	Relative treatment effects were reported for PFS and OS	X	Not reported	X	Not reported	✓	Stated
D2d: Quality of life weights (utilities)	X	N/A; no quality of life weights were used	✓	Condition specific weights were mapped to utilities	✓	EQ-5D data was used	X	N/A; no quality of life weights were used	?	Utilities, but with no description of how these have been obtained	?	Utilities, but limited description of methods
D3: Data incorporation	X	It is not possible to validate the incorporation of data due to a lack of reporting	✓	Stated	X	It is not possible to validate the incorporation of data due to a lack of reporting	X	It is not possible to validate the incorporation of data due to a lack of reporting	X	It is not possible to validate the incorporation of data due to a lack of reporting	✓	Stated
D4: Assessment of uncertainty	?	Some scenario analyses were carried out	?	A number of sensitivity analyses were carried out	?	A number of sensitivity analyses were carried out	?	A number of sensitivity analyses were carried out	?	A number of sensitivity analyses were carried out	?	A number of sensitivity analyses were carried out
D4a: Methodological	X	Not reported	X	Not reported	X	Not reported	X	Not reported	X	Not reported	X	Not reported
D4b: Structural	X	Not reported	X	Not reported	X	Not reported	X	Not reported	X	Not reported	X	Not reported
D4c: Heterogeneity	X	Not reported	X	Not reported	X	Not reported	X	Not reported	X	Not reported	X	Not reported
D4d: Parameter	✓	Some scenario analyses on progression free survival benefit and bowel	✓	A number of one-way sensitivity analyses were carried out, as were monte carlo	✓	Probabilistic sensitivity analysis	✓	One-way sensitivity analysis	✓	Some scenario analyses on progression free survival and overall survival	✓	A number of deterministic sensitivity analyses were carried out, as

		perforation		simulation, accounting for simultaneous uncertainty								were monte carlo simulation, accounting for simultaneous uncertainty
Consistency												
C1: Internal consistency	X	Not reported	✓	Discussed	X	Not reported	X	Not reported	X	Not reported	✓	Discussed
C2: External consistency	X	Not reported	✓	Comparison with results from previous cost-effectiveness analyses was considered	X	Not reported	X	Not reported	X	Not reported	X	Not reported

Dimension of quality	Comments											
Study	NICE; 2011; UK[10]		Papaioannou; 2011; UK[95]		Papaioannou; 2010; UK[147]		Case; 2007; US[104]		Havrilesky et al; 2007; US[105]		Griffin et al; 2006; UK[98]	
Structure												
S1: Statement of decision problem/objective	✓	Discussion of manufacturers submission	✓	Discussion of manufacturers submission	✓	Discussion of manufacturers submission	✓	Stated	✓	Stated	✓	Stated
S2: Statement of scope/perspective	✓	Stated	✓	Stated	✓	Stated	✓	Stated	✓	Stated	✓	Stated
S3: Rationale for structure	–	N/A; discussion of manufacturer's structure only	–	N/A; discussion of manufacturer's structure only	–	N/A; discussion of manufacturer's structure only	X	Not reported	X	Not reported	X	Not reported
S4: Structural assumptions	–	N/A; discussion of manufacturer's structure only	✓	Stated	✓	Stated	✓	Stated	✓	Stated	✓	Stated
S5: Strategies/comparators	?	Did not include the full range of comparators, but considered: • P LDH plus trabectedin • P LDH	?	Did not include the full range of comparators, but considered: • P LDH plus trabectedin • P LDH	?	Did not include the full range of comparators, but considered: • P LDH plus trabectedin • P LDH	?	Did not include the full range of comparators, but considered: • B est supportive care • C arboplatin • C arboplatin and paclitaxel • P LDH • C emcitabine	?	Did not include the full range of comparators, but considered: • (arboplatin • (emcitabine plus carboplatin • I aclitaxel plus carboplatin	?	Did not include the full range of comparators, but considered: • opotecan • aclitaxel • I LDH
S6: Model type	✓	Stated, semi-Markov model	✓	Stated, semi-Markov model	✓	Stated, semi-Markov model	✓	Stated, decision analytic	✓	Stated, Markov model	✓	Stated, semi-Markov model
S7: Time horizon	✓	Lifetime	✓	Lifetime	✓	Lifetime	✓	Although not explicitly stated, implicitly lifetime	X	42 months; unlikely to reflect the lifetime horizon for these patients	✓	Lifetime
S8: Disease	✓	Progression free	✓	Progression free	✓	Progression free	✓	Progression free	?	Progression free	✓	Progression free

states/pathways		survival, overall survival		survival, overall survival		survival, overall survival		survival, overall survival		survival and neurotoxicity		survival, overall survival
S9: Cycle length	–	N/A	–	N/A	–	N/A	–	N/A	✓	3 months	–	N/A
Data												
D1: Data identification	✓	Reported	✓	Reported	✓	Reported	✓	Stated	✓	Stated	✓	Stated
D2: Pre-model data analysis	✓	Reported	✓	Reported	✓	Reported	✓	Stated	✓	Stated	✓	Stated
D2a: Baseline data	✓	Reported	✓	Reported	✓	Reported	✓	Stated	✓	Stated	✓	Stated
D2b: Treatment effects	✓	Reported	✓	Reported	✓	Reported	✓	Stated	✓	Stated	✓	Stated
D2d: Quality of life weights (utilities)	✓	Reported	✓	Reported	✓	Reported	X	Quality of life not considered	X	Quality of life not considered in the main analysis	?	Not reported in detail
D3: Data incorporation	✓	Reported	✓	Reported	✓	Reported	✓	Stated	✓	Stated	✓	Stated
D4: Assessment of uncertainty	✓	Reported	✓	Reported	✓	Reported	✓	Stated	✓	Stated	?	Not reported in detail
D4a: Methodological	–	N/A	✓	Reported	✓	Reported	X	Not reported	X	Not reported	✓	Stated; related to the network meta-analysis
D4b: Structural	✓	Reported	✓	Reported	✓	Reported	X	Not reported	✓	Stated	X	Not reported
D4c: Heterogeneity	✓	Sub-groups reported	✓	Sub-groups reported	✓	Sub-groups reported	X	Not reported	✓	Stated	X	Not reported
D4d: Parameter	✓	Reported	✓	Reported	✓	Reported	✓	Stated	✓	Stated	X	Not reported
Consistency												
C1: Internal consistency	✓	Discussed	✓	Discussed	✓	Discussed	X	Not reported	X	Not reported	✓	Stated
C2: External consistency	✓	Discussed	✓	Discussed	✓	Discussed	X	Not reported	✓	Stated	X	Not reported

Dimension of quality	Comments											
Study	Main et al; 2006; UK[99]		Rocconi et al; 2006; US[106]		NICE; 2005; UK[10]		Forbes et al; 2002; UK[94]		NICE 2013 (TA285)[15]		Montalar; 2012; Spain[97]	
Structure												
S1: Statement of decision problem/objective	✓	Stated	✓	Stated	✓	Discussion of manufacturers submissions and TAG report	✓	Stated	✓	Stated	✓	Stated
S2: Statement of scope/perspective	✓	Stated	?	Partially	✓	Stated	✓	Stated	✓	Stated	✓	Stated
S3: Rationale for structure	✓	Stated	X	Not reported	–	N/A	✓	Stated	✓	Stated	✓	Stated
S4: Structural assumptions	✓	Stated	✓	Stated	–	N/A	✓	Stated	✓	Stated	✓	Stated
S5: Strategies/comparators	?	Did not include the full range of comparators, but considered: • aclitaxel • opotecan • LDH • aclitaxel in combination • latinum • AP	?	Did not include the full range of comparators, but considered: • LDH • emcitabine plus cisplatin • opotecan	?	Did not include the full range of comparators, but considered: • aclitaxel • opotecan • LDH • aclitaxel in combination • latinum • AP	?	Did not include the full range of comparators, but considered: • opotecan • LDH	?	Did not include the full range of comparators, but considered: • evacizumab plus gemcitabine and carboplatin • emcitabine and carboplatin	?	Did not include the full range of comparators, but considered: • rabectedin in combination with PLDH • LDH
S6: Model type	✓	Stated, semi-Markov	✓	Stated, decision analytic	✓	Stated, semi-Markov model	✓	Stated, cost-minimisation analysis	✓	Stated, semi-Markov model	✓	Stated, semi-Markov model
S7: Time horizon	✓	Lifetime	✓	Implicitly lifetime	✓	Lifetime	✓	Lifetime	✓	Ten years	✓	Lifetime
S8: Disease states/pathways	✓	Progression free survival, overall survival	✓	Progression free survival, overall survival	✓	Progression free survival, overall survival	✓	Overall survival	✓	Progression free survival, overall survival	✓	Progression free survival, overall survival

S9: Cycle length	–	N/A	–	N/A	–	N/A	–	N/A	✓	One week	–	N/A

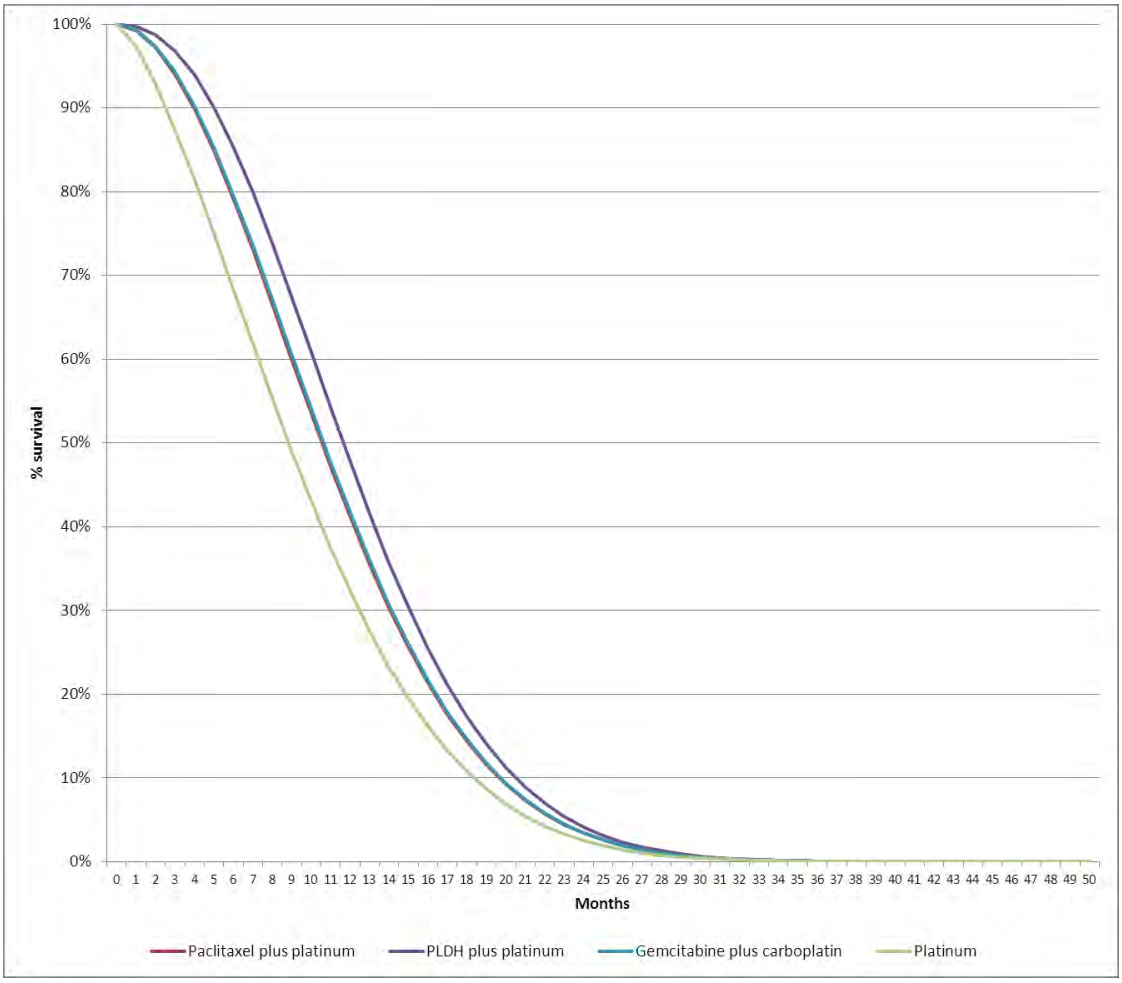
Data												
D1: Data identification	✓	Stated	✓	Stated	✓	Reported	✓	Stated	✓	Reported	✓	Stated
D2: Pre-model data analysis	✓	Stated	✓	Stated	✓	Reported	✓	Stated	✓	Reported	✓	Stated
D2a: Baseline data	✓	Stated	✓	Stated	✓	Reported	✓	Stated	✓	Reported	✓	Stated
D2b: Treatment effects	✓	Stated	✓	Stated	✓	Reported	✓	Stated	✓	Reported	✓	Stated
D2d: Quality of life weights (utilities)	✓	Stated	X	Quality of life not considered	✓	Reported	X	Quality of life not considered	✓	Reported	✓	Stated
D3: Data incorporation	✓	Stated	✓	Stated	✓	Reported	✓	Stated	✓	Reported	✓	Stated
D4: Assessment of uncertainty	✓	Stated	✓	Stated	✓	Reported	✓	Stated	✓	Reported	✓	Stated
D4a: Methodological	✓	Stated	X	Not reported	–	N/A	✓	Stated	✓	Reported	✓	Stated
D4b: Structural	X	Not reported	X	Not reported	–	N/A	✓	Stated	✓	Reported	✓	Stated
D4c: Heterogeneity	✓	Stated; sub-groups	X	Not reported	✓	Sub-groups reported	X	Not reported	✓	Reported	X	Not reported
D4d: Parameter	✓	Stated	✓	Stated	✓	Reported	✓	Stated	✓	Reported	✓	Stated
Consistency												
C1: Internal consistency	✓	Discussed	X	Not reported	✓	Discussed	✓	Discussed	✓	Discussed	✓	Discussed
C2: External consistency	✓	Discussed	✓	Discussed	✓	Discussed	✓	Discussed	✓	Discussed	X	Not reported

Abbreviations used in table: AG, assessment group; CAP, cyclophosphamide, adriamycin, platinum; N/A, not applicable; NICE, National Institute for Health and Care Excellence; OS, overall survival; PFS, progression free survival; PLDH, pegylated liposomal doxorubicin hydrochloride; RCT, randomised controlled trial; UK, United Kingdom; US, United States

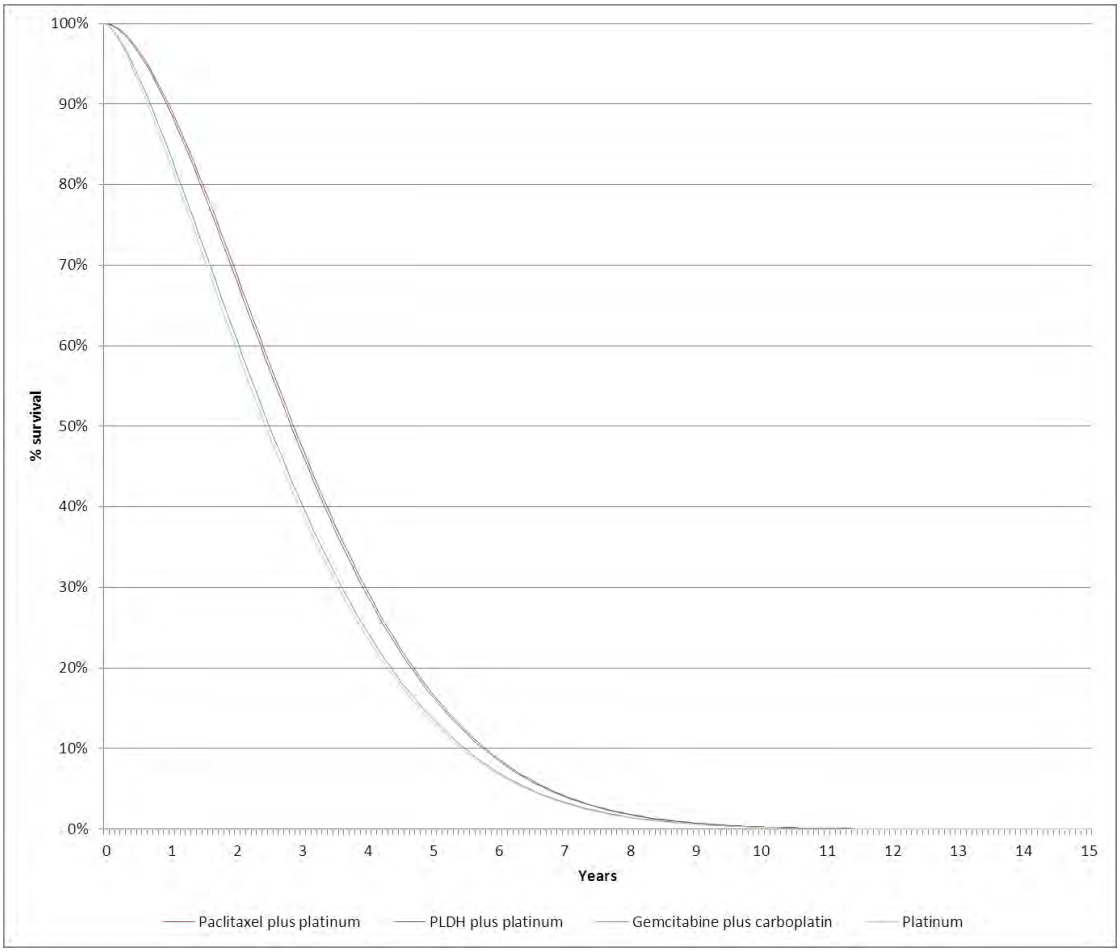
Appendix 9: Survival curves for the TAG economic model

Platinum sensitive network 1

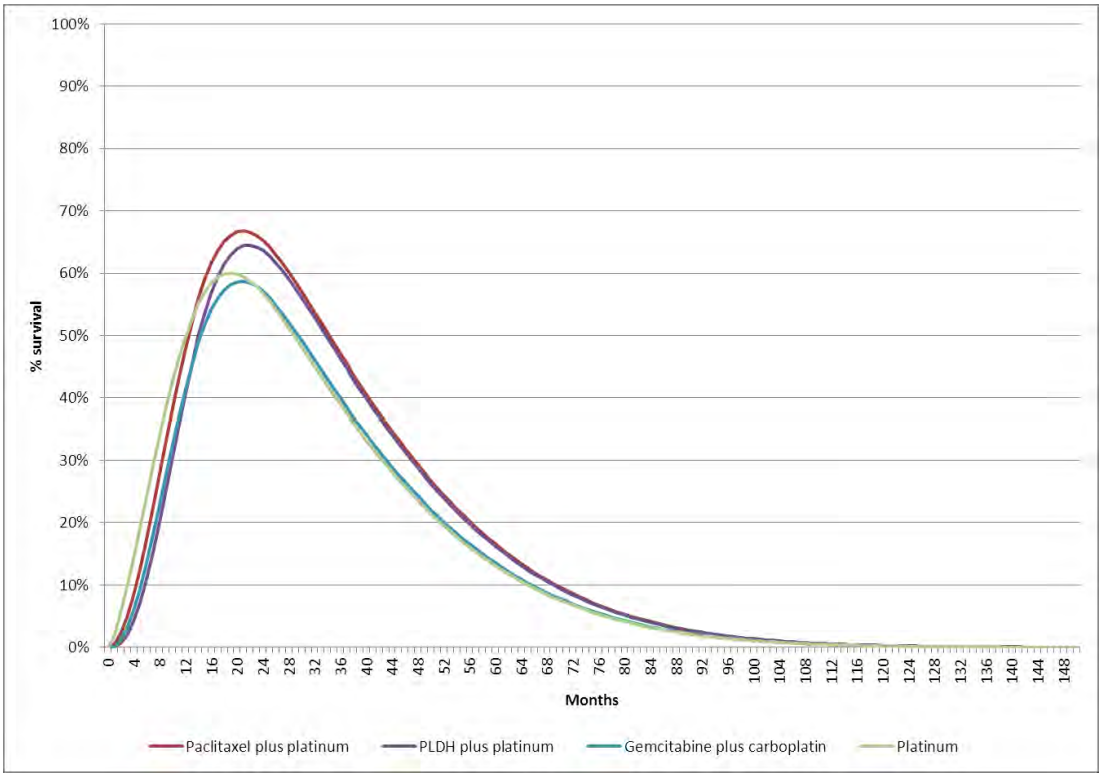
Progression free survival proportions for platinum sensitive network 1



Overall survival proportions for platinum sensitive network 1

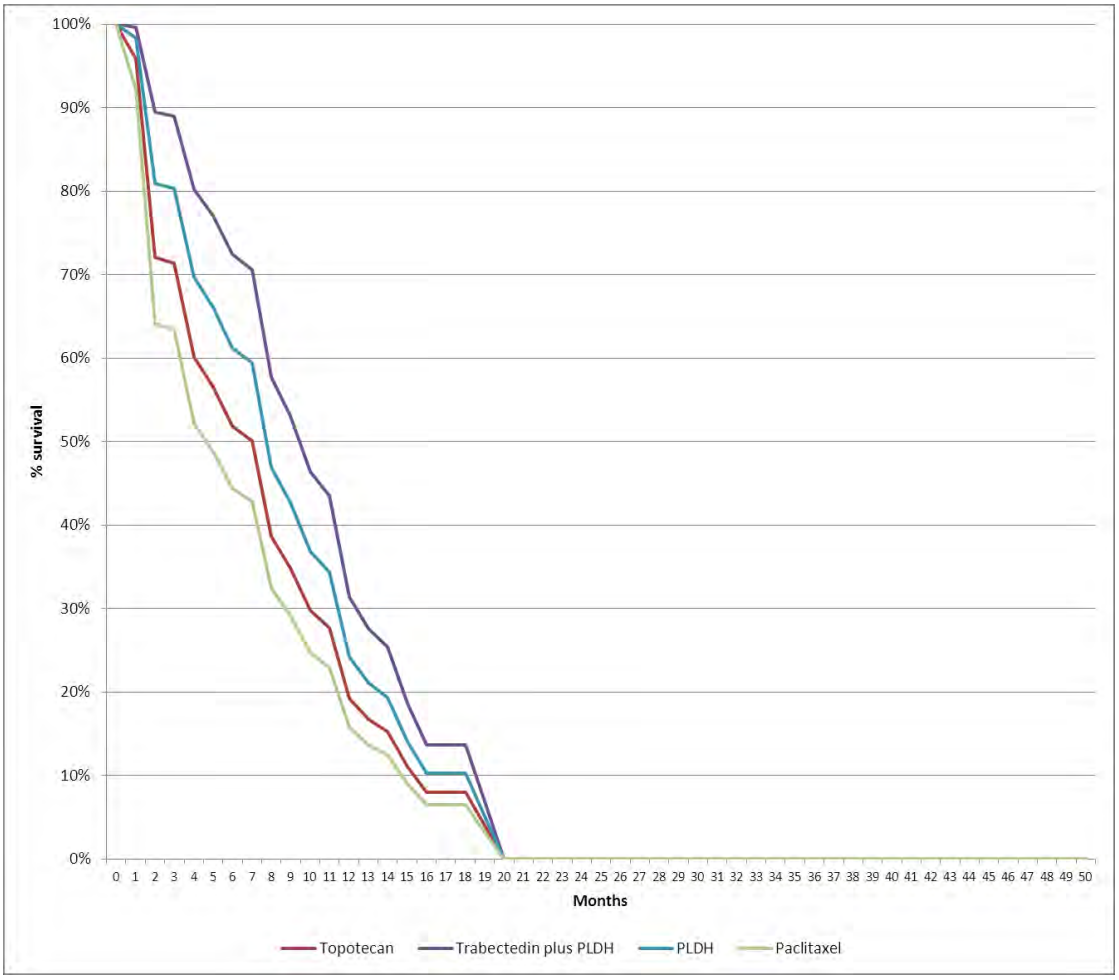


Progressed disease proportions for platinum sensitive network 1

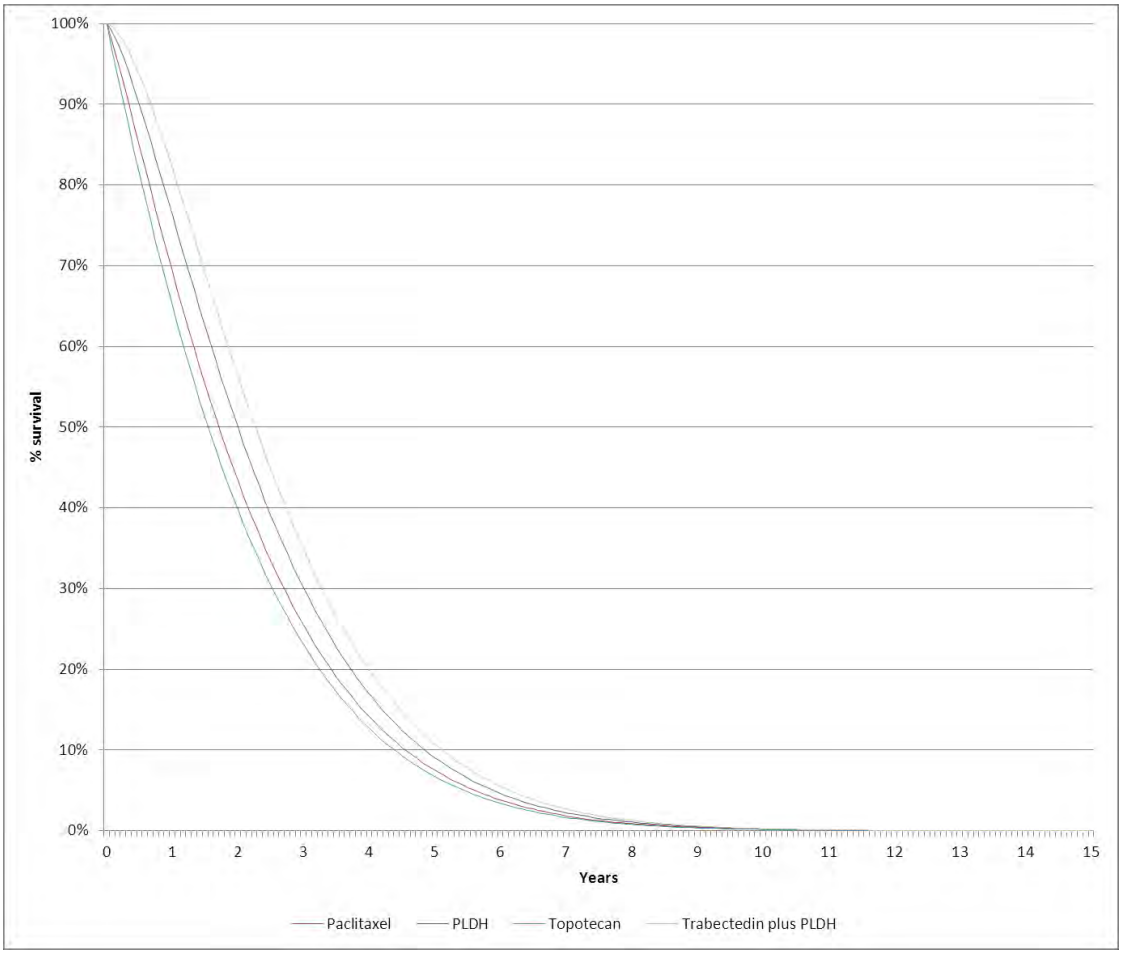


Platinum sensitive network 2

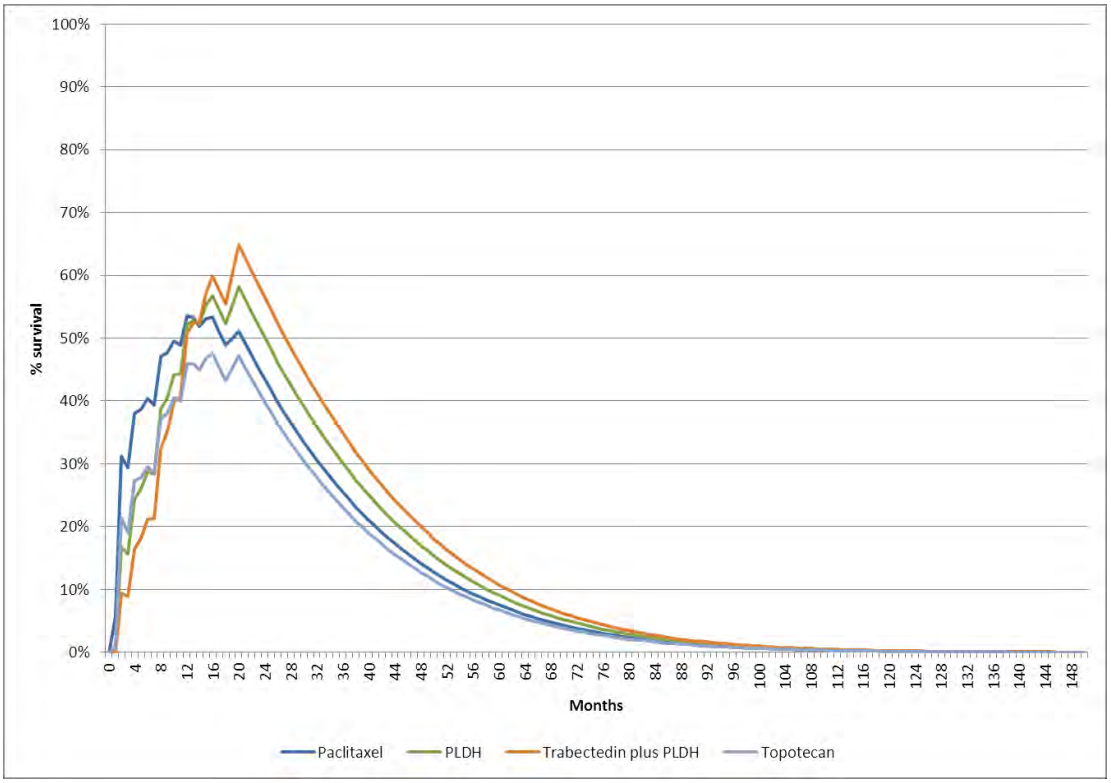
Progression free survival proportions for platinum sensitive network 2



Overall survival proportions for platinum sensitive network 2

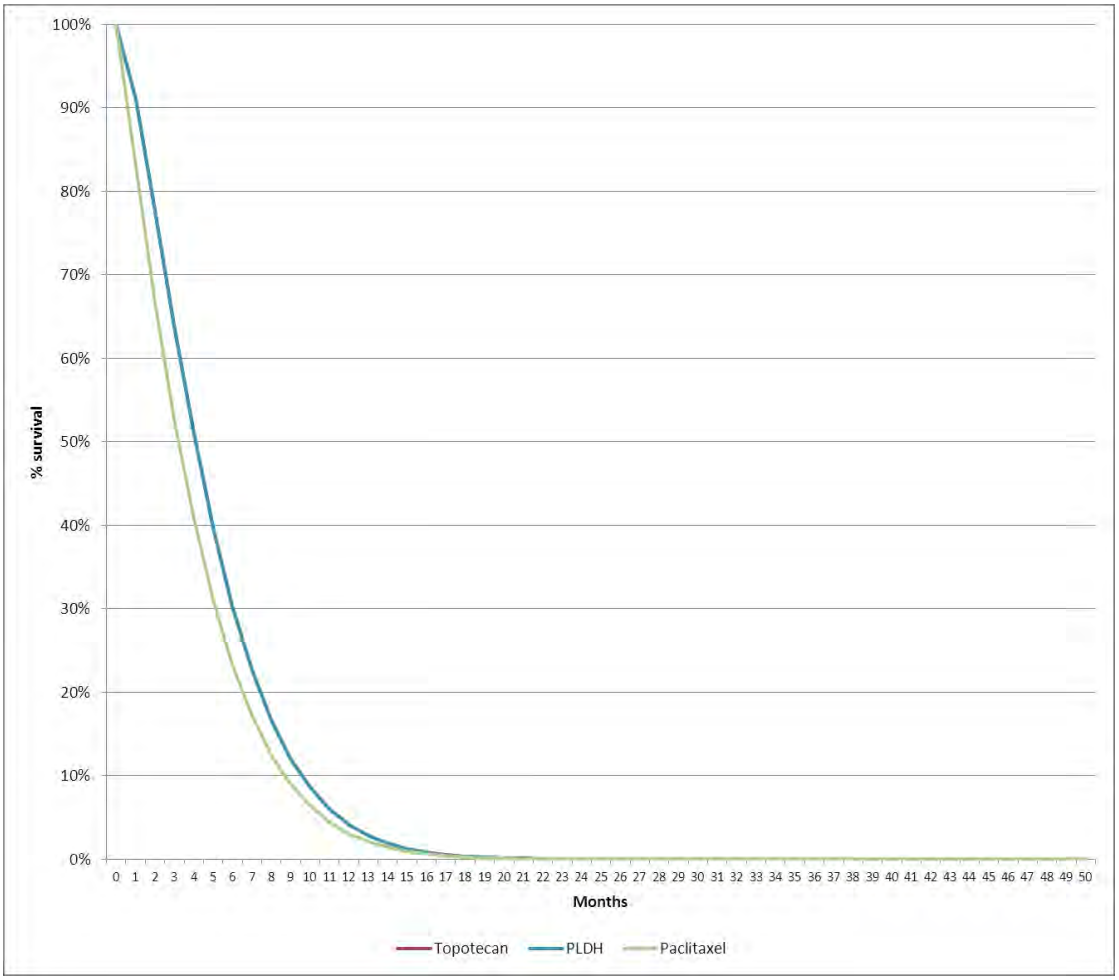


Progressed disease proportions for platinum sensitive network 2



Platinum resistant/refractory network

Progression free survival proportions for platinum resistant/refractory network



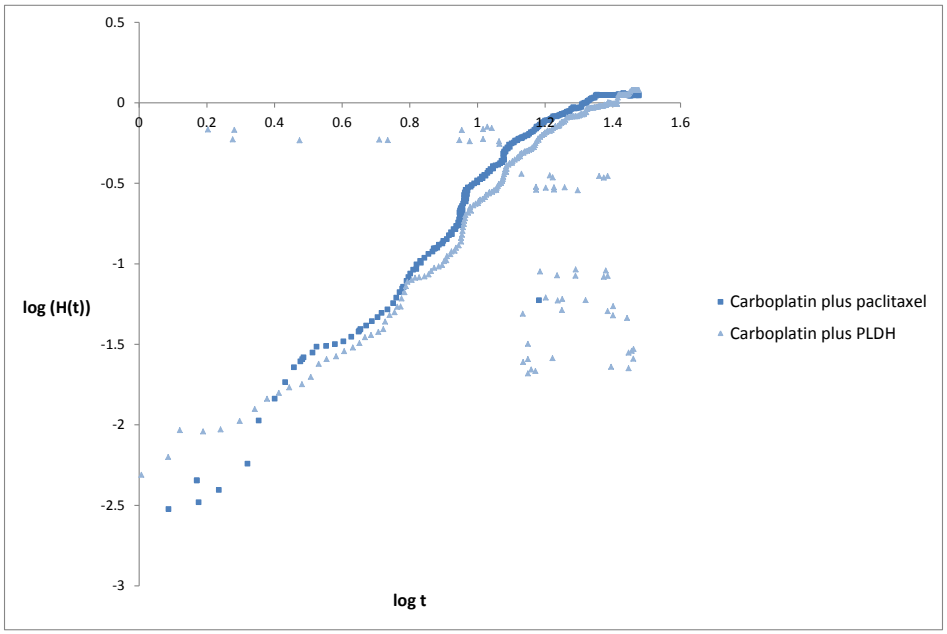
[redacted]

[redacted]

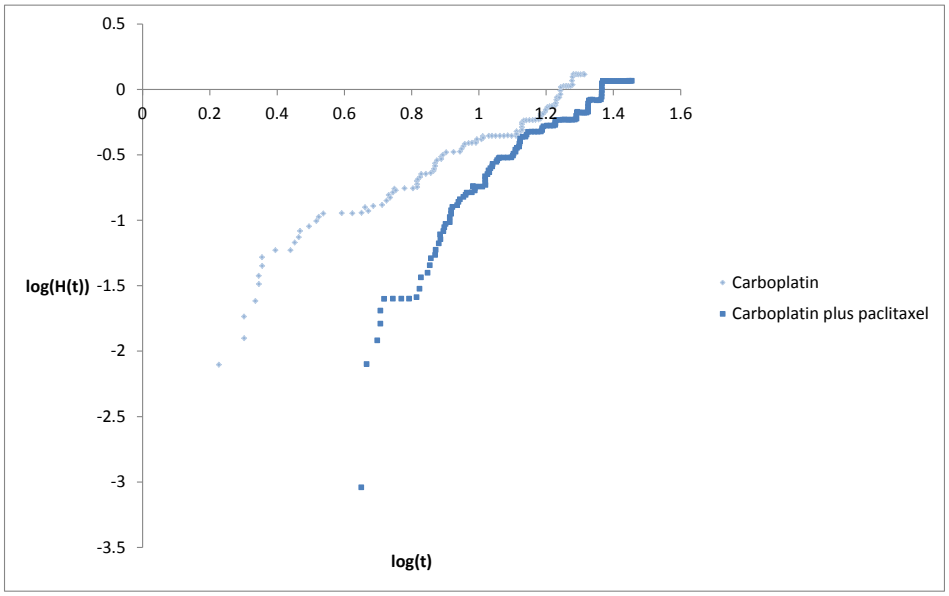
Appendix 10: Cumulative log-hazard plots

Platinum sensitive network 1

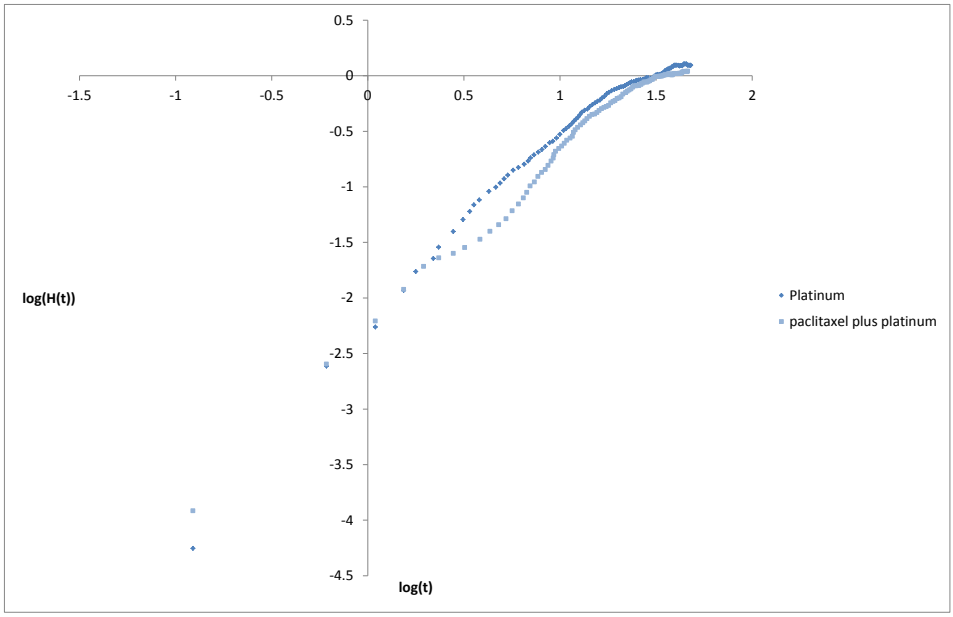
Cumulative log hazards associated with Kaplan-Meier progression free survival data for carboplatin plus paclitaxel versus carboplatin plus PLDH



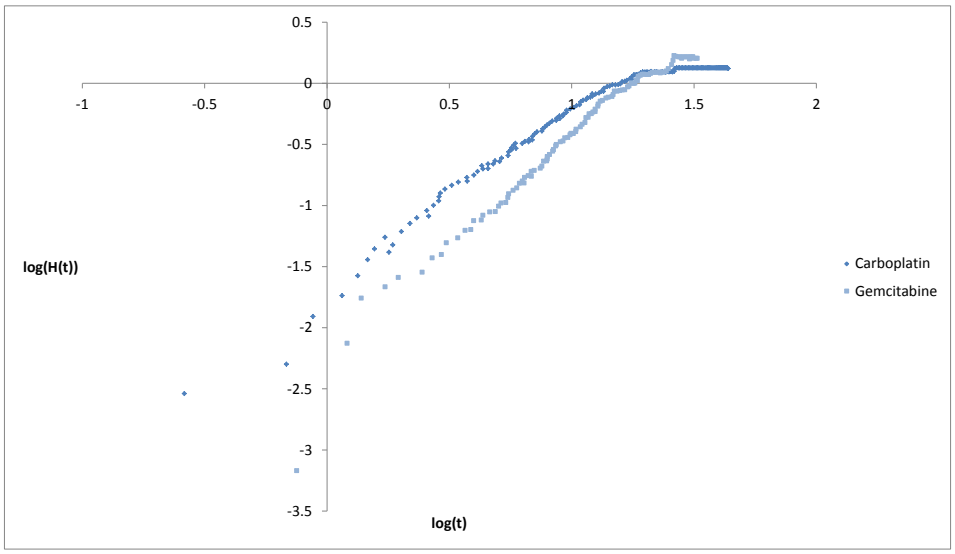
Cumulative log hazards associated with Kaplan-Meier progression free survival data for carboplatin versus carboplatin plus paclitaxel



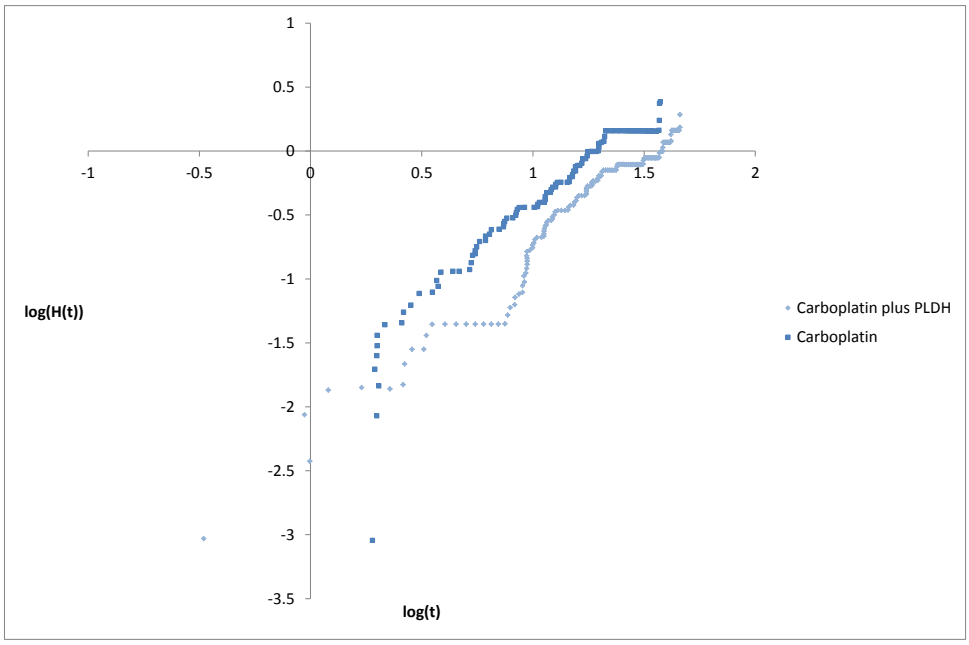
Cumulative log hazards associated with Kaplan-Meier progression free survival data for platinum versus paclitaxel plus platinum


0.5
0
-1.5
-1
-0.5
0
0.5
1
1.5
2
-0.5
-1
-1.5
-2
-2.5
-3
-3.5
-4
-4.5
log(H(t))
log(t)
Platinum
paclitaxel plus platinum

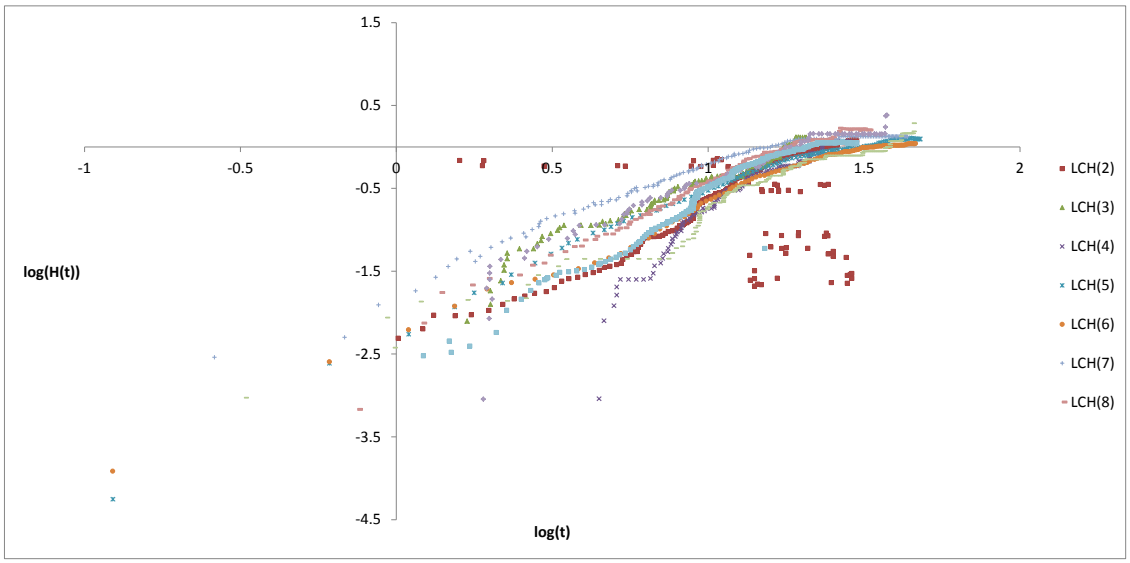
Cumulative log hazards associated with Kaplan-Meier progression free survival data for carboplatin versus gemcitabine plus carboplatin



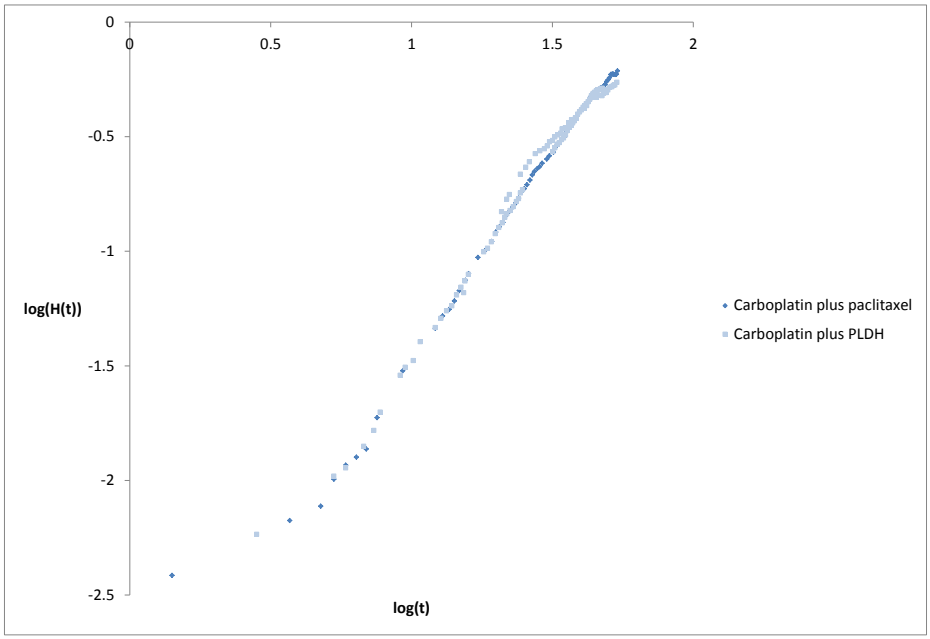
Cumulative log hazards associated with Kaplan-Meier progression free survival data for carboplatin plus PLDH versus carboplatin



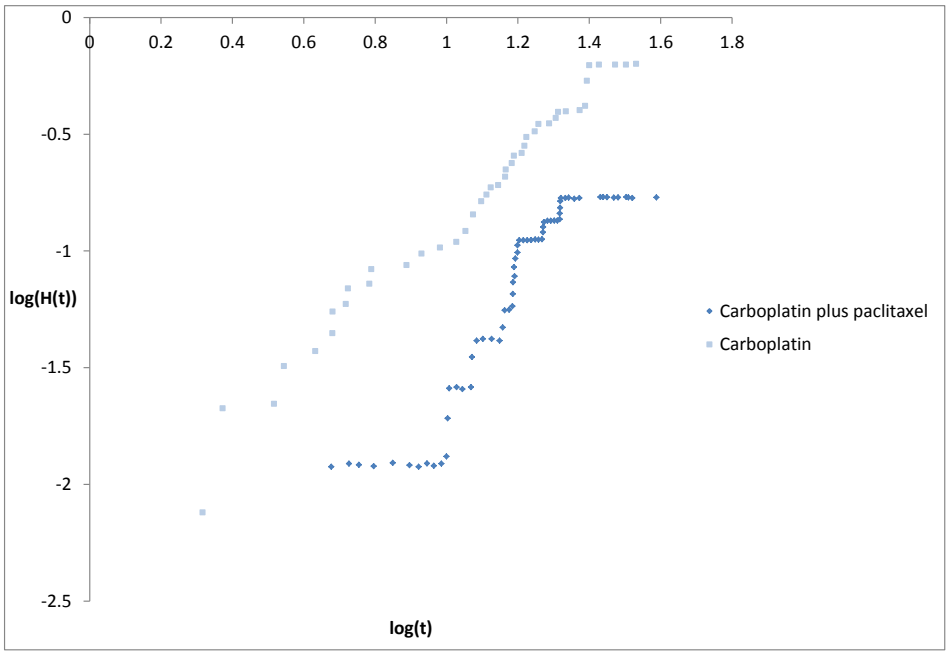
Cumulative log hazards associated with Kaplan-Meier progression free survival data for all treatments considered



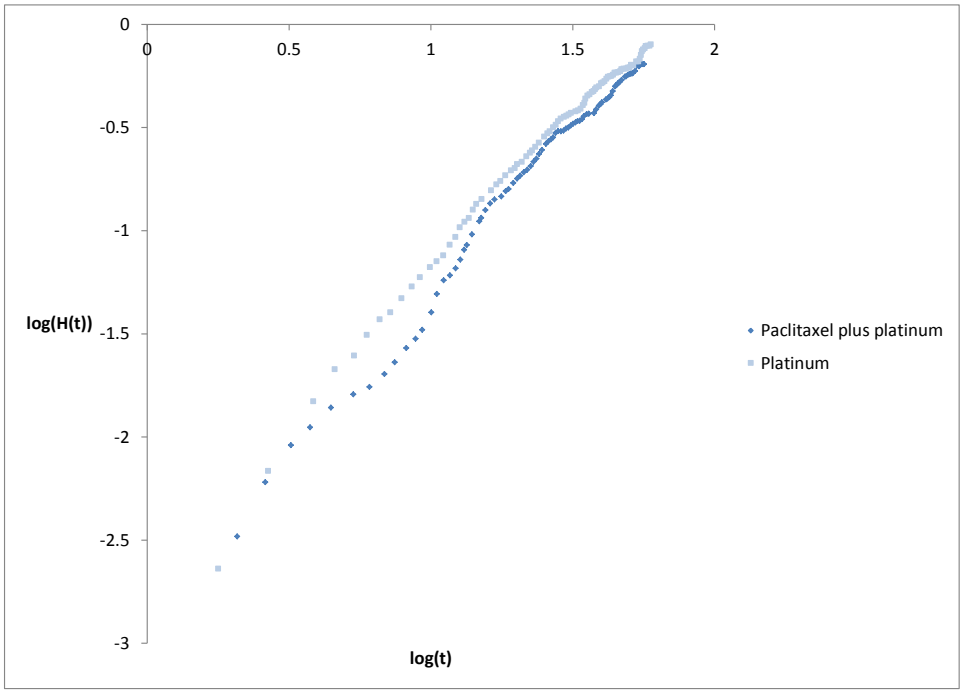
Cumulative log hazards associated with Kaplan-Meier overall survival data for carboplatin plus paclitaxel versus carboplatin plus PLDH



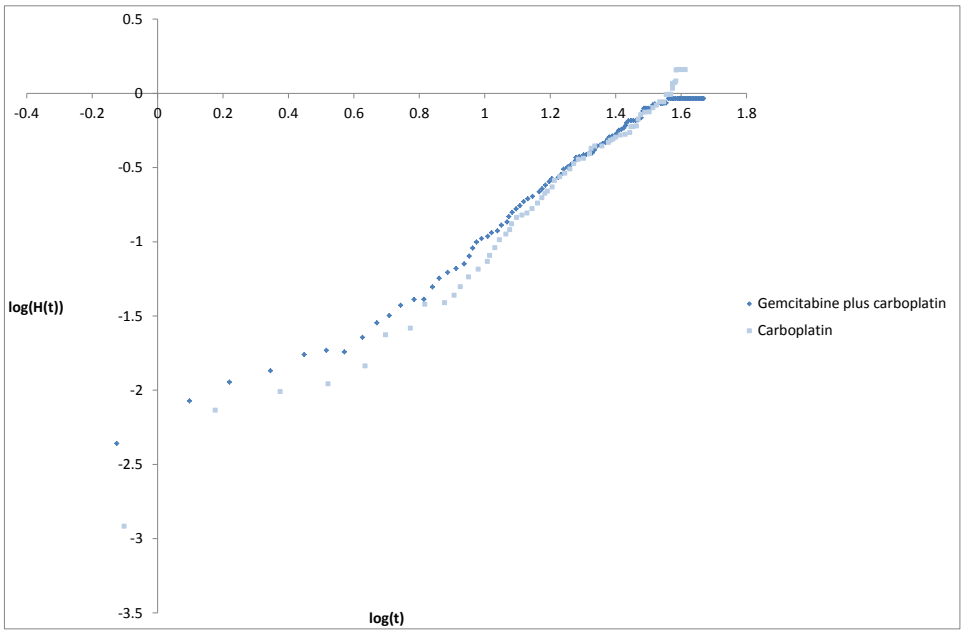
Cumulative log hazards associated with Kaplan-Meier overall survival data for carboplatin versus carboplatin plus paclitaxel



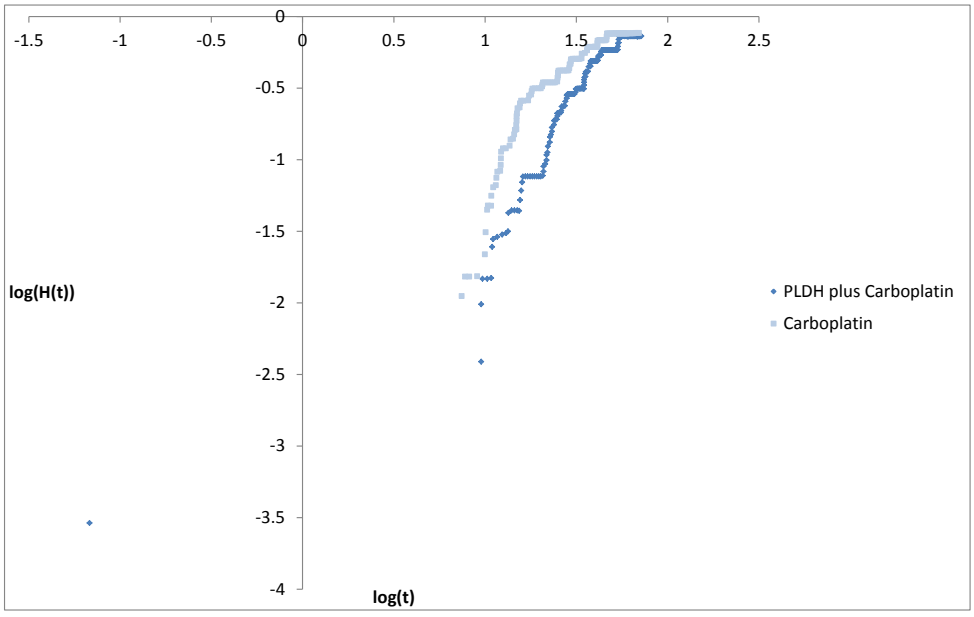
Cumulative log hazards associated with Kaplan-Meier overall survival data for platinum versus paclitaxel plus platinum



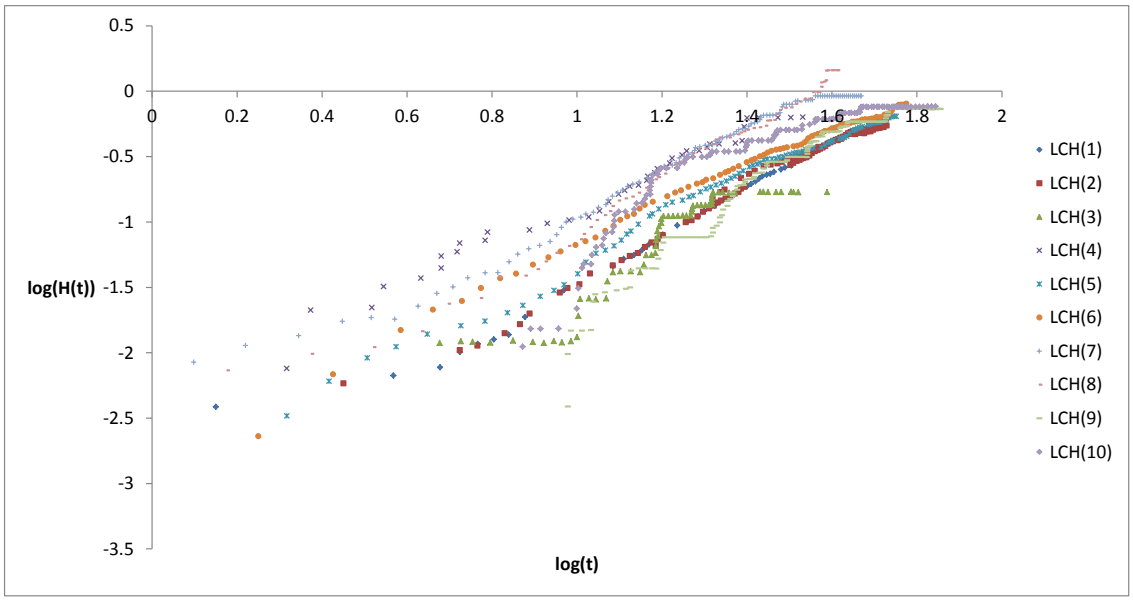
Cumulative log hazards associated with Kaplan-Meier overall survival data for carboplatin versus gemcitabine plus carboplatin



Cumulative log hazards associated with Kaplan-Meier overall survival data for carboplatin plus PLDH versus carboplatin

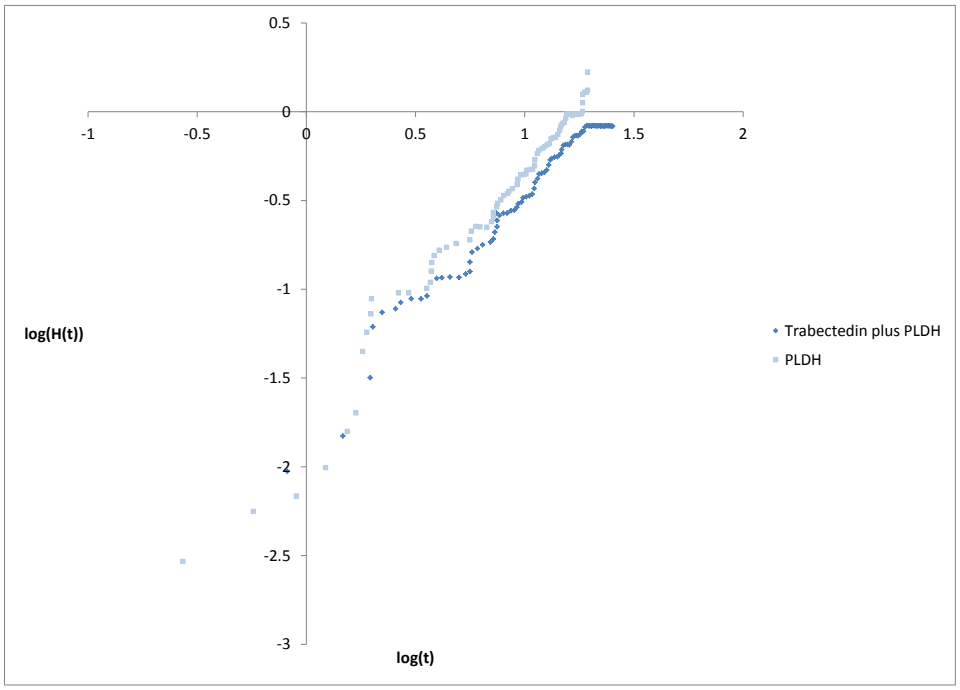


Cumulative log hazards associated with Kaplan-Meier overall survival data for all treatments considered

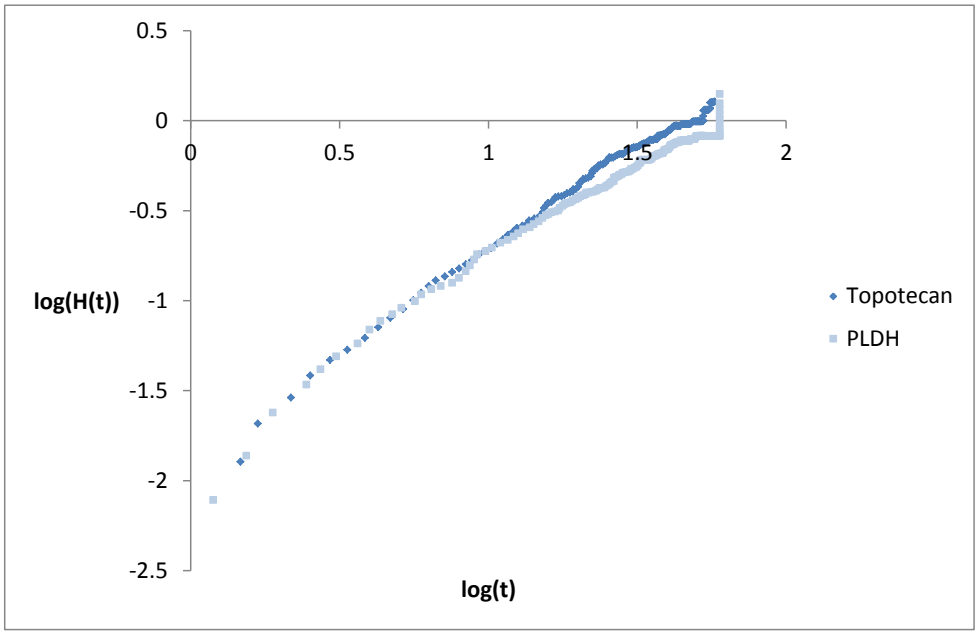


Platinum sensitive network 2

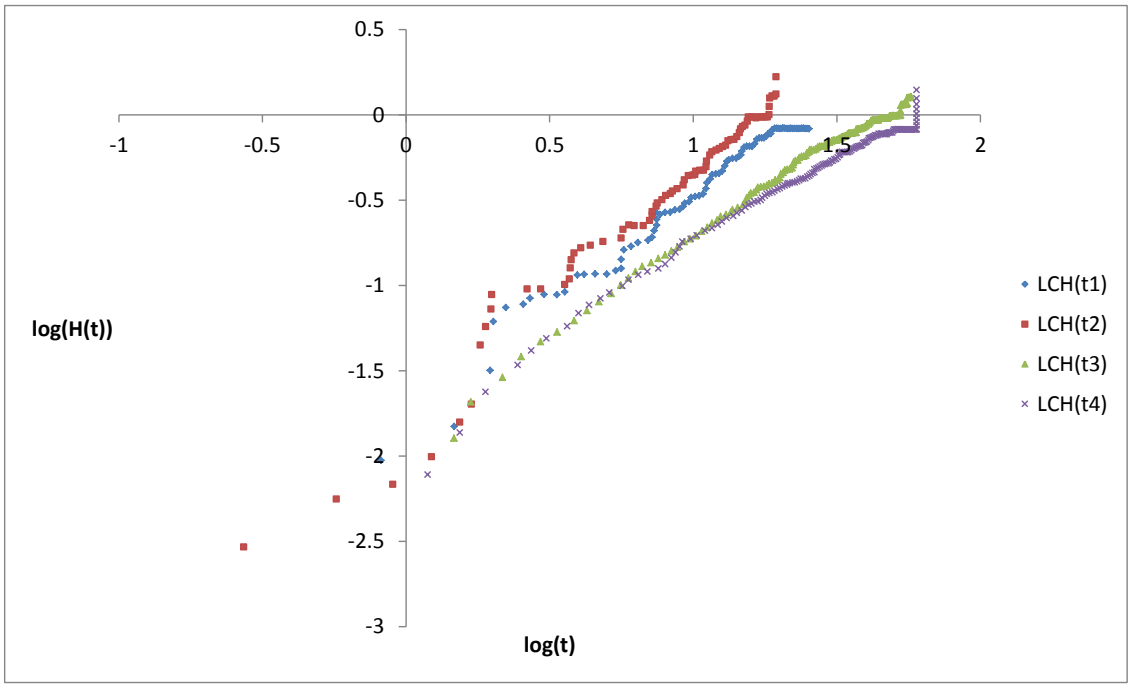
Cumulative log hazards associated with Kaplan-Meier progression free survival data for trabectedin plus PLDH versus PLDH



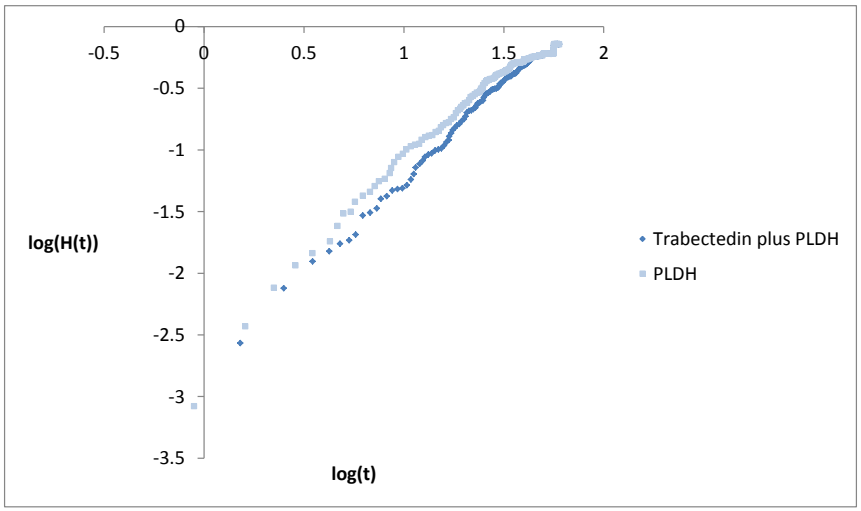
Cumulative log hazards associated with Kaplan-Meier progression free survival data for topotecan versus PLDH



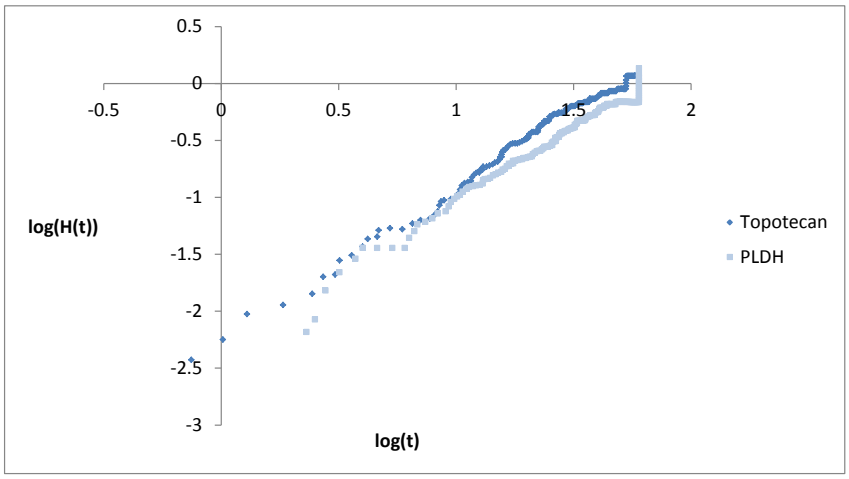
Cumulative log hazards associated with Kaplan-Meier progression free survival data for all treatments considered



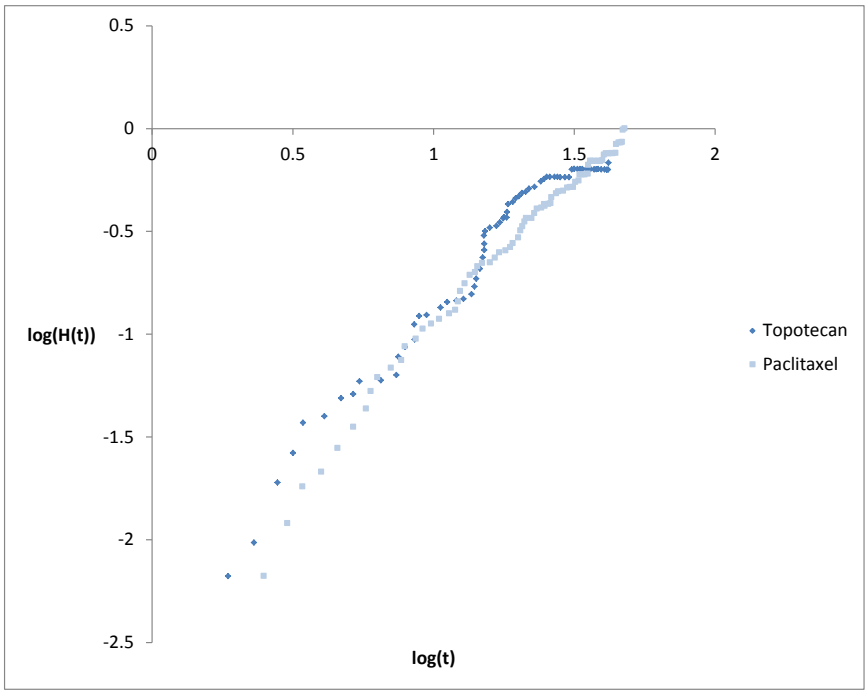
Cumulative log hazards associated with Kaplan-Meier overall survival data for trabectedin plus PLDH versus PLDH



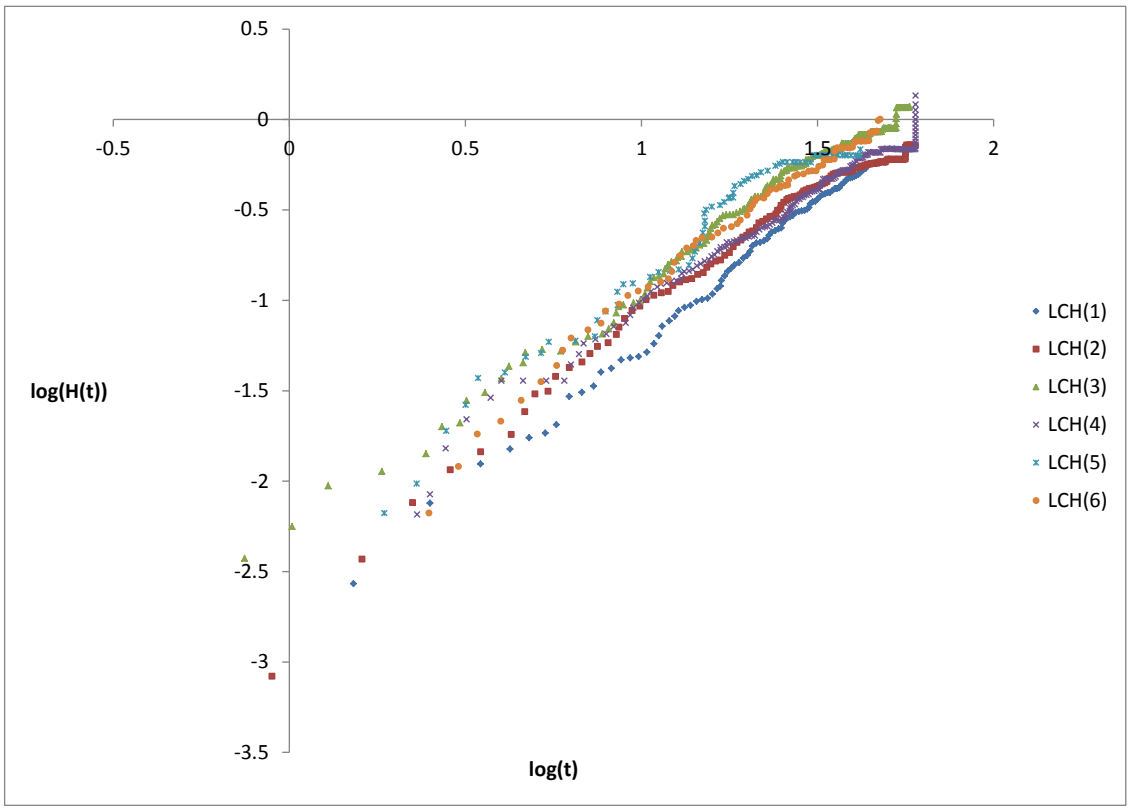
Cumulative log hazards associated with Kaplan-Meier overall survival data for topotecan versus PLDH



Cumulative log hazards associated with Kaplan-Meier overall survival data for topotecan versus paclitaxel

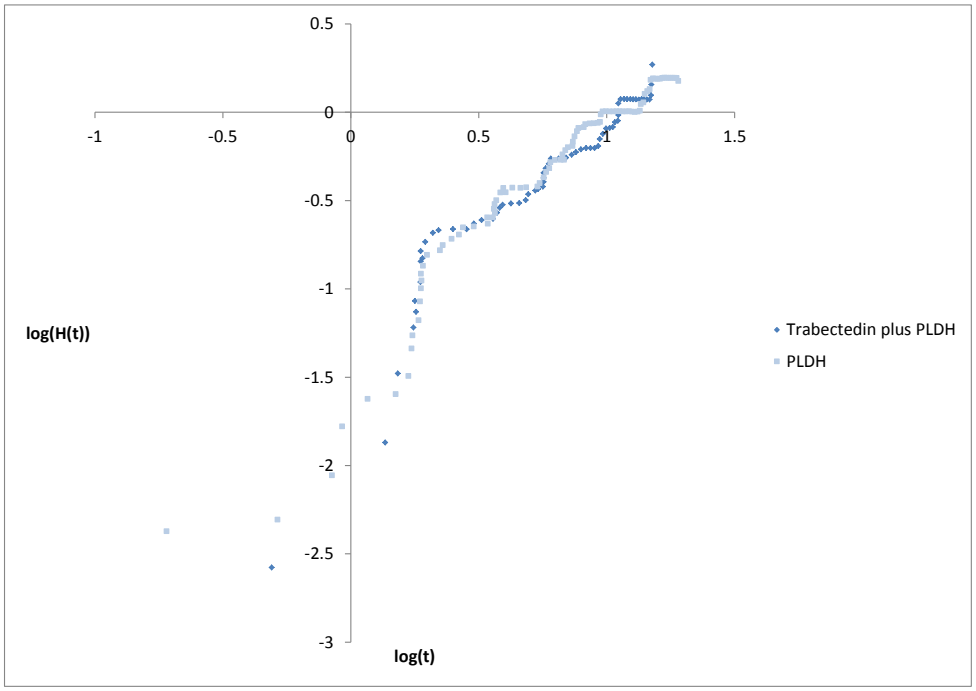


Cumulative log hazards associated with Kaplan-Meier overall survival data for all treatments considered

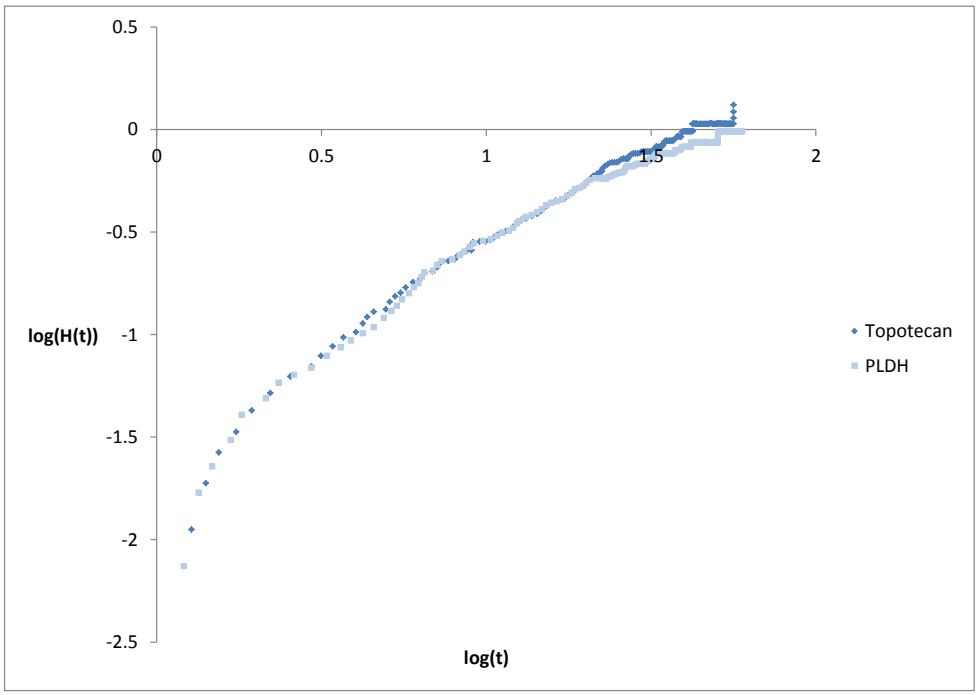


Platinum resistant/refractory network

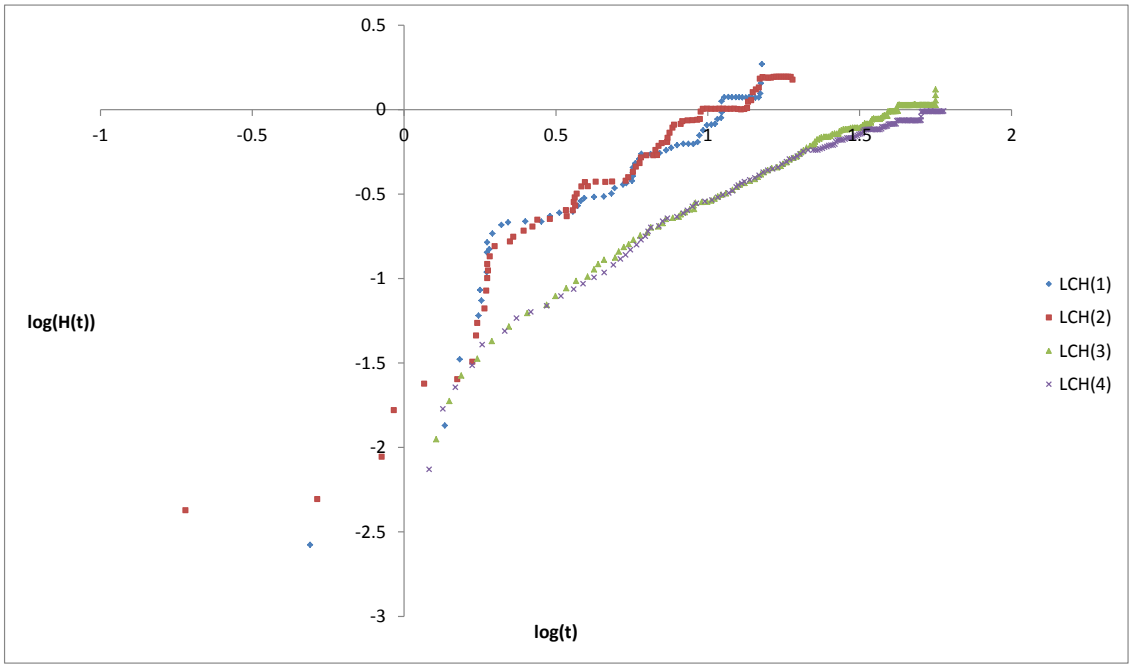
Cumulative log hazards associated with Kaplan-Meier progression free survival data for trabectedin plus PLDH versus PLDH



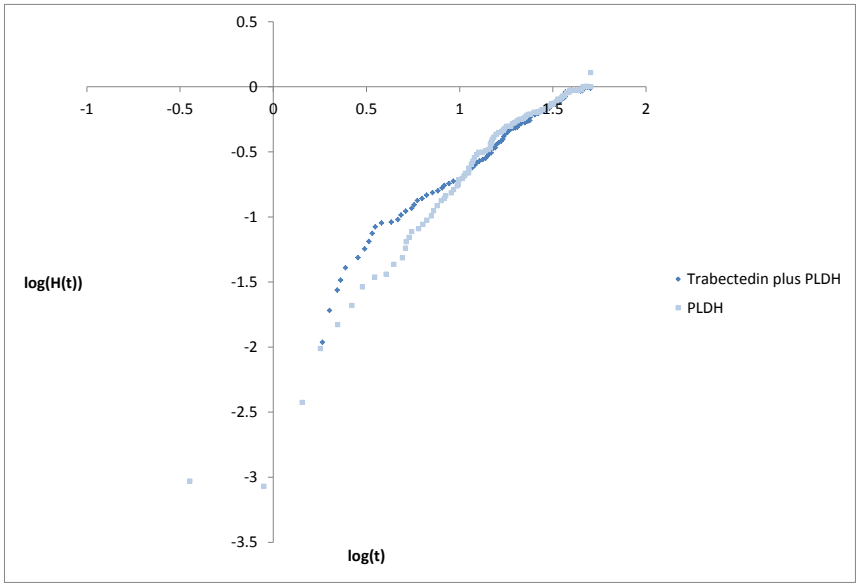
Cumulative log hazards associated with Kaplan-Meier progression free survival data for topotecan versus PLDH



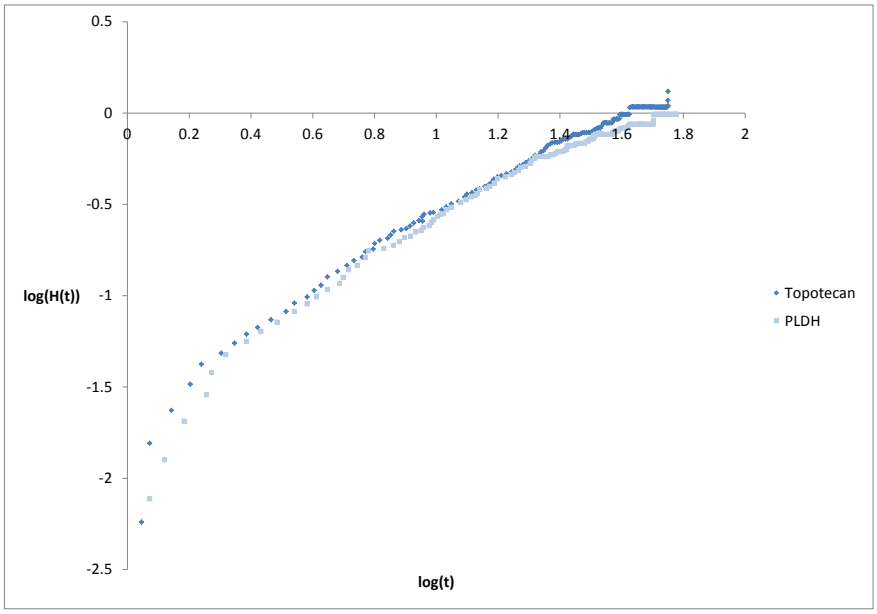
Cumulative log hazards associated with Kaplan-Meier progression free survival data for all treatments considered



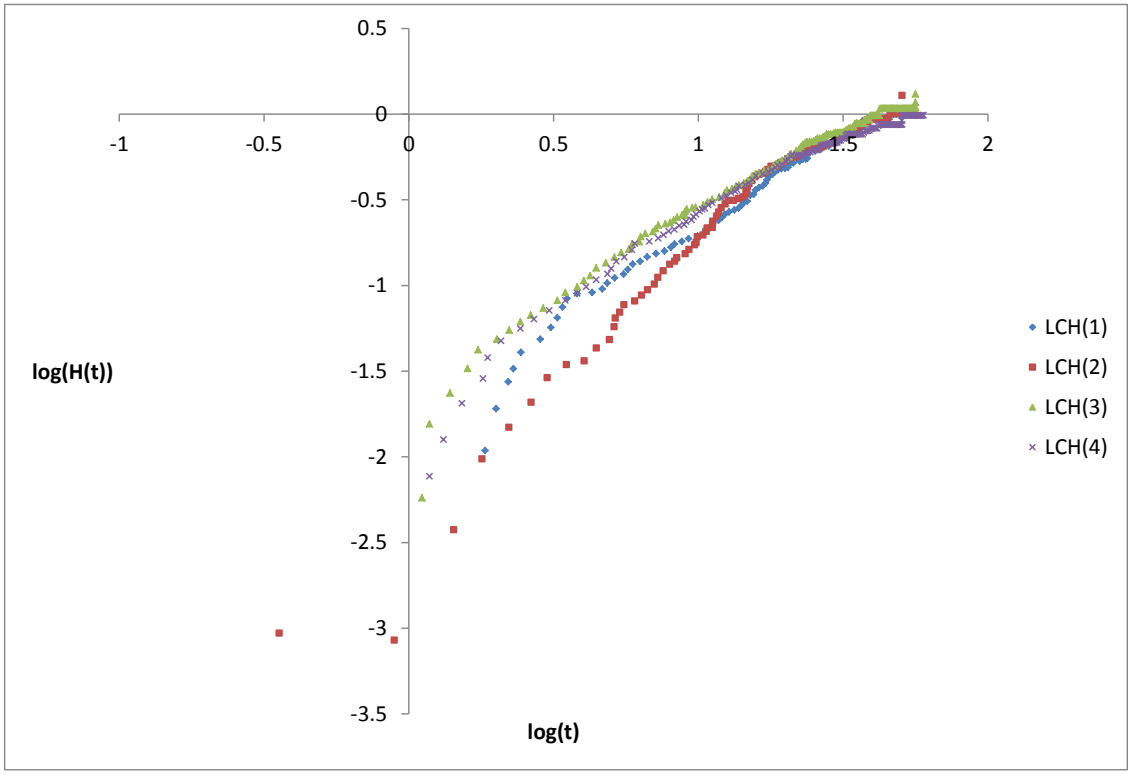
Cumulative log hazards associated with Kaplan-Meier overall survival data for trabectedin plus PLDH versus PLDH



Cumulative log hazards associated with Kaplan-Meier overall survival data for topotecan versus PLDH



Cumulative log hazards associated with Kaplan-Meier overall survival data for all treatments considered



Appendix 11: Scenario analysis results

Deterministic scenario analyses, results for platinum sensitive network 1

Scenario	Outcomes	Platinum	Gemcitabine plus carboplatin	Paclitaxel plus platinum	PLDH plus platinum
Base-case	**Total discounted cost**	£15,949	£20,381	£21,643	£22,620
	Total discounted QALYs	1.80	1.84	2.03	2.02
	ICER (vs next non-dominated option)	–	Extendedly dominated	£24,361	Strictly dominated
Costs associated with a 50 mg rather than 40 mg dose of PLDH	Total discounted cost	£16,155	£20,581	£21,871	£22,839
	Total discounted QALYs	1.80	1.84	2.03	2.02
	ICER*	–	Extendedly dominated	£24,455	Strictly dominated
Patient weight (used to inform drug costs) estimated from the HSE, 2011	Total discounted cost	£16,015	£20,432	£21,713	£22,689
	Total discounted QALYs	1.80	1.84	2.03	2.02
	ICER*	–	Extendedly dominated	£24,377	Strictly dominated
Branded costs of drugs (Abraxane)	Total discounted cost	£15,949	£20,381	£22,940	£22,620
	Total discounted QALYs	1.80	1.84	2.03	2.02
	ICER*	–	Extendedly dominated	£29,912	Extendedly dominated
Branded costs of drugs (Taxol)	Total discounted cost	£15,949	£20,381	£24,384	£22,620
	Total discounted QALYs	1.80	1.84	2.03	2.02
	ICER*	–	Extendedly dominated	£36,092	Extendedly dominated
Branded costs of drugs (Gemzar)	Total discounted cost	£15,949	£20,555	£21,643	£22,620
	Total discounted QALYs	1.80	1.84	2.03	2.02
	ICER*	–	Extendedly dominated	£24,361	Strictly dominated
Calculating cost based upon the selection of vials that resulted in the least number of vials used	Total discounted cost	£16,293	£21,329	£22,128	£22,979
	Total discounted QALYs	1.80	1.84	2.03	2.02
	ICER*	–	Extendedly dominated	£24,961	Strictly dominated

Vial sharing	Total discounted cost	£15,896	£20,348	£21,484	£22,025
	Total discounted QALYs	1.80	1.84	2.03	2.02
	ICER*	–	Extendedly dominated	£23,908	Strictly dominated
Baseline PFS survival curve network 1 using alternative functional forms (log logistic)	Total discounted cost	£15,768	£20,184	£21,430	£22,361
	Total discounted QALYs	1.80	1.84	2.04	2.02
	ICER*	–	Extendedly dominated	£24,213	Strictly dominated
Baseline PFS survival curve network 1 using alternative functional forms (exponential)	Total discounted cost	£15,379	£19,104	£20,436	£21,036
	Total discounted QALYs	1.80	1.84	2.04	2.03
	ICER*	–	Extendedly dominated	£21,239	Strictly dominated
Baseline PFS survival curve network 1 using alternative functional forms (log normal)	Total discounted cost	£15,806	£20,209	£21,455	£22,360
	Total discounted QALYs	1.80	1.84	2.04	2.02
	ICER*	–	Extendedly dominated	£24,177	Strictly dominated
Baseline PS PFS survival curve network 1 using Parmar (rather than Pujade) fitted with a Weibull extrapolation	Total discounted cost	£11,861	£15,213	£16,536	£16,817
	Total discounted QALYs	1.84	1.89	2.09	2.08
	ICER*	–	Extendedly dominated	£19,113	Strictly dominated
Baseline OS survival curve network 1 using alternative functional forms (log logistic)	Total discounted cost	£17,672	£22,144	£23,779	£24,709
	Total discounted QALYs	1.97	2.02	2.25	2.23
	ICER*	–	Extendedly dominated	£22,064	Strictly dominated
Baseline OS survival curve network 1 using alternative functional forms (exponential)	Total discounted cost	£17,329	£21,974	£24,063	£24,994
	Total discounted QALYs	1.96	2.02	2.30	2.28
	ICER*	–	Extendedly dominated	£19,927	Strictly dominated
Baseline OS survival curve network 1 using alternative functional forms (log normal)	Total discounted cost	£16,165	£20,483	£21,125	£22,158
	Total discounted QALYs	1.80	1.83	1.96	1.95
	ICER*	–	Extendedly dominated	£30,084	Strictly dominated

Baseline OS survival curve network 1 using Parmar (rather than Wagner) fitted with a Weibull extrapolation	Total discounted cost	£15,544	£19,984	£21,296	£22,267
	Total discounted QALYs	1.76	1.80	2.00	1.99
	ICER*	–	Extendedly dominated	£24,030	Strictly dominated
Alternative discount rates for costs and benefits (costs at 1%)	Total discounted cost	£16,584	£21,030	£22,414	£23,375
	Total discounted QALYs	1.80	1.84	2.03	2.02
	ICER*	–	Extendedly dominated	£24,944	Strictly dominated
Alternative discount rates for costs and benefits (costs at 6%)	Total discounted cost	£15,376	£19,796	£20,948	£21,940
	Total discounted QALYs	1.80	1.84	2.03	2.02
	ICER*	–	Extendedly dominated	£23,841	Strictly dominated
Alternative discount rates for costs and benefits (benefits at 1%)	Total discounted cost	£15,949	£20,381	£21,643	£22,620
	Total discounted QALYs	1.86	1.91	2.11	2.10
	ICER*	–	Extendedly dominated	£22,970	Strictly dominated
Alternative discount rates for costs and benefits (benefits at 6%)	Total discounted cost	£15,949	£20,381	£21,643	£22,620
	Total discounted QALYs	1.74	1.78	1.96	1.95
	ICER*	–	Extendedly dominated	£25,755	Strictly dominated
Disutilities for adverse events applied	Total discounted cost	£15,949	£20,381	£21,643	£22,620
	Total discounted QALYs	1.80	1.84	2.03	2.02
	ICER*	–	Extendedly dominated	£24,446	Strictly dominated
Nausea and vomiting probabilities estimated from clinical expert opinion for network 1	Total discounted cost	£15,962	£20,399	£21,672	£22,638
	Total discounted QALYs	1.80	1.84	2.03	2.02
	ICER*	–	Extendedly dominated	£24,429	Strictly dominated
Half cycle correction	Total discounted cost	£15,859	£20,286	£21,553	£22,542
	Total discounted QALYs	1.77	1.81	2.00	1.99
	ICER*	–	Extendedly dominated	£24,326	Strictly dominated

* ICER vs next, non-dominated option

Abbreviations used in table: HSE, Health Survey for England; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression free survival; PLDH, pegylated

liposomal doxorubicin hydrochloride; QALY, quality-adjusted life year.

Deterministic scenario analyses, results for platinum sensitive network 2

Scenario	Outcomes	Paclitaxel	PLDH	Topotecan	Trabectedin plus PLDH
Base-case	**Total discounted cost**	£15,668	£19,599	£23,793	£32,640
	Total discounted QALYs	1.40	1.56	1.32	1.72
	ICER (vs next non-dominated option)	–	£23,733	Strictly dominated	£85,212
Costs associated with a 50 mg rather than 40 mg dose of PLDH	Total discounted cost	£15,878	£21,049	£23,987	£32,878
	Total discounted QALYs	1.40	1.56	1.32	1.72
	ICER*	–	£31,222	Strictly dominated	£77,290
Patient weight (used to inform drug costs) estimated from the HSE, 2011	Total discounted cost	£15,689	£19,621	£23,813	£32,665
	Total discounted QALYs	1.40	1.56	1.32	1.72
	ICER*	–	£23,740	Strictly dominated	£85,223
Branded costs of drugs (Abraxane)	Total discounted cost	£16,736	£19,599	£23,793	£32,640
	Total discounted QALYs	1.40	1.56	1.32	1.72
	ICER*	–	£17,285	Strictly dominated	£85,212
Branded costs of drugs (Taxol)	Total discounted cost	£17,925	£19,599	£23,793	£32,640
	Total discounted QALYs	1.40	1.56	1.32	1.72
	ICER*	–	£10,106	Strictly dominated	£85,212
Branded costs of drugs (Hycamtine)	Total discounted cost	£15,668	£19,599	£24,534	£32,640
	Total discounted QALYs	1.40	1.56	1.32	1.72
	ICER*	–	£23,733	Strictly dominated	£85,212
Calculating cost based upon the selection of vials that resulted in the least number of vials used	Total discounted cost	£15,880	£19,717	£23,910	£33,277
	Total discounted QALYs	1.40	1.56	1.32	1.72
	ICER*	–	£23,167	Strictly dominated	£88,605

Vial sharing	Total discounted cost	£15,505	£18,951	£22,343	£31,612
	Total discounted QALYs	1.40	1.56	1.32	1.72
	ICER*	–	£20,810	Strictly dominated	£82,723
Baseline PFS survival curve network 2 using alternative functional forms (Weibull)	Total discounted cost	£15,791	£19,690	£24,086	£32,959
	Total discounted QALYs	1.40	1.56	1.32	1.72
	ICER*	–	£23,565	Strictly dominated	£86,700
Baseline PFS survival curve network 2 using alternative functional forms (log logistic)	Total discounted cost	£15,044	£18,366	£23,144	£31,234
	Total discounted QALYs	1.42	1.59	1.34	1.75
	ICER*	–	£19,188	Strictly dominated	£78,954
Baseline PFS survival curve network 2 using alternative functional forms (exponential)	Total discounted cost	£15,148	£18,640	£22,737	£31,478
	Total discounted QALYs	1.40	1.57	1.32	1.72
	ICER*	–	£20,694	Strictly dominated	£82,280
Baseline PFS survival curve network 2 using alternative functional forms (log normal)	Total discounted cost	£15,313	£18,772	£23,448	£31,805
	Total discounted QALYs	1.40	1.57	1.32	1.73
	ICER*	–	£20,465	Strictly dominated	£83,213
Baseline OS survival curve network 2 using alternative functional forms (log logistic)	Total discounted cost	£17,965	£22,333	£25,868	£35,859
	Total discounted QALYs	1.63	1.84	1.53	2.05
	ICER*	–	£20,660	Strictly dominated	£66,604
Baseline OS survival curve network 1 using alternative functional forms (exponential)	Total discounted cost	£15,939	£20,191	£23,922	£33,584
	Total discounted QALYs	1.44	1.63	1.34	1.82
	ICER*	–	£21,550	Strictly dominated	£71,009
Baseline OS survival curve network 1 using alternative functional forms (log normal)	Total discounted cost	£17,242	£21,536	£25,193	£34,998
	Total discounted QALYs	1.56	1.77	1.46	1.96
	ICER*	–	£20,974	Strictly dominated	£68,262
Alternative discount rates for costs and benefits (costs at 1%)	Total discounted cost	£16,090	£20,097	£24,175	£33,217
	Total discounted QALYs	1.40	1.56	1.32	1.72
	ICER*	–	£24,196	Strictly dominated	£85,726

Alternative discount rates for costs and benefits (costs at 6%)	Total discounted cost	£15,286	£19,148	£23,446	£32,118
	Total discounted QALYs	1.40	1.56	1.32	1.72
	ICER*	–	£23,316	Strictly dominated	£84,750
Alternative discount rates for costs and benefits (benefits at 1%)	Total discounted cost	£15,668	£19,599	£23,793	£32,640
	Total discounted QALYs	1.44	1.62	1.36	1.78
	ICER*	–	£22,669	Strictly dominated	£80,986
Alternative discount rates for costs and benefits (benefits at 6%)	Total discounted cost	£15,668	£19,599	£23,793	£32,640
	Total discounted QALYs	1.36	1.52	1.28	1.66
	ICER*	–	£24,779	Strictly dominated	£89,400
Disutilities for adverse events applied	Total discounted cost	£15,668	£19,599	£23,793	£32,640
	Total discounted QALYs	1.40	1.56	1.31	1.71
	ICER*	–	£23,635	Strictly dominated	£87,916
Head-to-head comparison of trabectedin plus PLDH versus PLDH using adjusted PFS and OS estimates directly from the PharmaMar submission	Total discounted cost	N/A	£21,063	N/A	£34,569
	Total discounted QALYs	N/A	1.70	N/A	2.08
	ICER*	N/A	–	N/A	£35,646
Analysis of the results considering the partially platinum sensitive HRs for OS	Total discounted cost	N/A	£19,599	£22,705	£34,610
	Total discounted QALYs	N/A	1.56	1.20	1.96
	ICER*	N/A	–	Strictly dominated	£37,691
Half cycle correction	Total discounted cost	£15,250	£19,238	£23,044	£32,323
	Total discounted QALYs	1.37	1.54	1.29	1.69
	ICER*	–	£24,050	Strictly dominated	£85,377

* ICER vs next non-dominated option

Abbreviations used in table: HSE, Health Survey for England; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression free survival; PLDH, pegylated liposomal doxorubicin hydrochloride; QALY, quality-adjusted life year.

Deterministic scenario analyses, results for the platinum resistant/refractory network

Scenario	Outcomes	PLDH	Paclitaxel	Topotecan
Base-case	**Total discounted cost**	£14,320	£15,095	£21,271
	Total discounted QALYs	1.00	0.97	1.02
	ICER	–	Strictly dominated	£449,553
Costs associated with a 50 mg rather than 40 mg dose of PLDH	Total discounted cost	£15,442	£15,095	£21,271
	Total discounted QALYs	1.00	0.97	1.02
	ICER	£10,480 (vs paclitaxel)	–	£376,985 (vs PLDH)
Patient weight (used to inform drug costs) estimated from the HSE, 2011	Total discounted cost	£14,320	£15,095	£21,271
	Total discounted QALYs	1.00	0.97	1.02
	ICER	–	Strictly dominated	£449,553
Branded costs of drugs (Abraxane)	Total discounted cost	£14,320	£17,635	£21,271
	Total discounted QALYs	1.00	0.97	1.02
	ICER	–	Strictly dominated	£449,553
Branded costs of drugs (Taxol)	Total discounted cost	£14,320	£18,074	£21,271
	Total discounted QALYs	1.00	0.97	1.02
	ICER	–	Strictly dominated	£449,553
Branded costs of drugs (Hycamtine)	Total discounted cost	£14,320	£15,095	£22,011
	Total discounted QALYs	1.00	0.97	1.02
	ICER	–	Strictly dominated	£497,418
Calculating cost based upon the selection of vials that resulted in the least number of vials used	Total discounted cost	£14,320	£15,794	£21,284
	Total discounted QALYs	1.00	0.97	1.02
	ICER	–	Strictly dominated	£450,435
Vial sharing	Total discounted cost	£13,808	£14,824	£19,901
	Total discounted QALYs	1.00	0.97	1.02
	ICER	–	Strictly dominated	£394,035

Baseline PFS survival curve using alternative functional forms (log logistic)	Total discounted cost	£14,101	£15,055	£21,195
	Total discounted QALYs	1.01	0.97	1.02
	ICER	–	Strictly dominated	£458,313
Baseline PFS survival curve using alternative functional forms (exponential)	Total discounted cost	£13,681	£14,267	£20,115
	Total discounted QALYs	1.01	0.97	1.02
	ICER	–	Strictly dominated	£415,929
Baseline PFS survival curve using alternative functional forms (log normal)	Total discounted cost	£14,227	£15,156	£21,304
	Total discounted QALYs	1.00	0.97	1.02
	ICER	–	Strictly dominated	£457,727
Baseline OS survival curve using alternative functional forms (log logistic)	Total discounted cost	£15,394	£16,114	£22,375
	Total discounted QALYs	1.11	1.07	1.13
	ICER	–	Strictly dominated	£374,963
Baseline OS survival curve using alternative functional forms (exponential)	Total discounted cost	£14,459	£15,210	£21,422
	Total discounted QALYs	1.02	0.98	1.04
	ICER	–	Strictly dominated	£414,866
Baseline OS survival curve using alternative functional forms (log normal)	Total discounted cost	£14,927	£15,670	£21,896
	Total discounted QALYs	1.07	1.03	1.08
	ICER	–	Strictly dominated	£402,379
Alternative discount rates for costs and benefits (costs at 1%)	Total discounted cost	£14,522	£15,288	£21,478
	Total discounted QALYs	1.00	0.97	1.02
	ICER	–	Strictly dominated	£449,873
Alternative discount rates for costs and benefits (costs at 6%)	Total discounted cost	£14,135	£14,918	£21,081
	Total discounted QALYs	1.00	0.97	1.02
	ICER	–	Strictly dominated	£449,261
Alternative discount rates for costs and benefits (benefits at 1%)	Total discounted cost	£14,320	£15,095	£21,271
	Total discounted QALYs	1.02	0.99	1.04
	ICER	–	Strictly dominated	£435,381

Alternative discount rates for costs and benefits (benefits at 6%)	Total discounted cost		£14,320		£15,095		£21,271	
	Total discounted QALYs		0.99		0.95		1.00	
	ICER		–		Strictly dominated		£463,366	
Disutilities for adverse events applied	Total discounted cost		£14,320		£15,095		£21,271	
	Total discounted QALYs		1.00		0.97		1.02	
	ICER		–		Strictly dominated		£503,885	
Half cycle correction	Total discounted cost		£13,782		£14,290		£20,266	
	Total discounted QALYs		0.98		0.94		0.99	
	ICER		–		Strictly dominated		£418,861	
Equivalent efficacy assumed for all therapies outlined within the NICE scope for patients with resistant/refractory disease (cost analysis only)		Etoposide	Best supportive care	Etoposide plus platinum	PLDH	Paclitaxel	Paclitaxel plus platinum	Topotecan
	Total discounted cost	£8,194	£12,622	£13,095	£14,320	£15,822	£18,023	£21,114
Abbreviations used in table: HSE, Health Survey for England; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression free survival; PLDH, pegylated liposomal doxorubicin hydrochloride; QALY, quality-adjusted life year.								

Appendix 12. Protocol

TECHNOLOGY ASSESSMENT REPORT COMMISSIONED BY THE NIHR HTA PROGRAMME ON BEHALF OF THE NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

FINAL PROTOCOL

Date: 28 November 2012. Revised 14 January 2013 (trabectedin in combination with pegylated liposomal doxorubicin hydrochloride added as an intervention for patients with people with ovarian cancer who are allergic to platinum-based chemotherapy)

1 Title of the project

Topotecan, pegylated liposomal doxorubicin hydrochloride, paclitaxel, trabectedin and gemcitabine for the treatment of recurrent ovarian cancer

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3 Plain English Summary

Ovarian cancer is a common gynaecological cancer affecting women in the UK. The outcome of ovarian cancer is generally poor, with an overall 5-year survival rate of less than 40%. Although ovarian cancer usually responds to first-line therapy, in a large proportion of patients the cancer eventually comes back. This is defined as recurrent ovarian cancer. There are several different treatment options for recurrent ovarian cancer on the market with the aim of controlling the disease for as long as possible.

The aim of this project is to review all technologies for treatment of recurrent ovarian cancer, in a multiple technology appraisal (MTA). This will include a review of TA91 (Paclitaxel, pegylated liposomal doxorubicin hydrochloride and topotecan for second-line or subsequent treatment of advanced ovarian cancer) and TA222 (Trabectedin for the treatment of relapsed ovarian cancer). In addition, this MTA will also cover gemcitabine. The medical benefit and risks associated with these treatments will be assessed and compared across the treatments and against available standard drug treatments for recurrent ovarian cancer. In addition, this project will include an assessment of whether these drugs are likely to be considered good value for money for the National Health Service (NHS).

4 Decision problem

4.1 Purpose

Ovarian cancer is the fifth most common cancer in women in the UK.[(1)] Almost 7,000 women are diagnosed with ovarian cancer each year.[(2)] The risk of developing ovarian cancer increases with age, and most women are post-menopause when they develop the disease.[(1)] Ovarian cancer comprises a group of tumours in different tissues within the ovary. The most common type is epithelial ovarian cancer, which is the diagnosis for almost 9 out of 10 ovarian cancer tumours.[(1)] Ovarian cancer often spreads from the ovary to any surface within the abdominal cavity and eventually to other parts of the body. Symptoms of ovarian cancer are usually vague and can be related to other much less serious conditions. The symptoms can include abdominal pain and bloating, loss of appetite, and irregular bleeding.[(1)] Most women are therefore not diagnosed until they have advanced stage disease, that is, the disease has spread away from the ovary to other parts of the body. The outcome is generally poor with an overall 5-year survival rate of around 40%.[(2)]

Although a significant proportion of women with ovarian cancer respond to the initial chemotherapy, many of these women relapse within 2 years of completing treatment. Recurrent ovarian cancer may be classified based on the time from initial chemotherapy to recurrence of disease into: platinum-sensitive, when the cancer responds to initial chemotherapy but recurs 6 months or more after completion of the regimen; and platinum-resistant, when the cancer recurs within 6 months of completion of initial chemotherapy. Platinum-sensitive ovarian cancer can be further divided into fully platinum-sensitive (when the recurrence-free interval is 12 months or more) and partially platinum-sensitive (when the interval is between 6 and 12 months). Patients may also have refractory disease, which does not respond to first-line therapy. However, in practice there is a time-dependent continuum of platinum sensitivity, and categorisation by level of platinum sensitivity is not rigid.

This MTA will appraise the clinical and cost-effectiveness of topotecan, PLDH, paclitaxel, trabectedin and gemcitabine within their licensed indications for the treatment of recurrent or refractory ovarian cancer.

4.2 Interventions

The five pharmaceutical interventions that are the focus of this MTA all have marketing authorisations in the UK for the treatment of several types of cancer, including ovarian cancer. Paclitaxel (various manufacturers) is licensed for first-line treatment of ovarian cancer in combination with cisplatin (platinum-based chemotherapy), and as second-line treatment of ovarian cancer after failure of standard platinum-based therapy.[3] PLDH (Caelyx, Jansen-Cilag) and topotecan (various manufacturers) are licensed for the treatment of advanced ovarian cancer after failure of first-line platinum-based therapy.[4;5] Gemcitabine (Gemzar, Lilly) is licensed in combination with carboplatin (platinum-based chemotherapy), and trabectedin (Yondelis, PharmaMar) is licensed in combination with PLDH, as second-line treatment of ovarian cancer in patients with relapsed platinum-sensitive disease.[6;7] All the interventions are administered by intravenous infusion.

4.3 Place of the interventions in the treatment pathway

For patients with relapsed, recurrent or refractory ovarian cancer NICE has issued guidance that encompasses PLDH, paclitaxel, and topotecan,[8] and it has appraised evidence on trabectedin.[9] The recommended options for patients with platinum-sensitive or partially platinum-sensitive advanced ovarian cancer are paclitaxel in combination with a platinum-based compound (carboplatin or cisplatin), or single-agent PLDH (only for partially platinum-sensitive ovarian cancer). Trabectedin in combination with PLDH is not recommended.[8] The recommended options for patients with platinum-resistant or platinum-refractory ovarian cancer are single-agent paclitaxel, PLDH, or topotecan (for patients for whom PLDH and paclitaxel are considered inappropriate). At present there is no published guidance regarding the use of gemcitabine for treatment of ovarian cancer. However, combined with carboplatin, gemcitabine is licensed for the treatment of relapsed ovarian cancer in patients with platinum-sensitive or partially platinum-sensitive disease.[6]

4.4 Relevant comparators

For patients with platinum-sensitive ovarian cancer the relevant comparators are:

- the interventions licensed for platinum-sensitive disease in comparison with each other;

- bevacizumab in combination with platinum-containing chemotherapy;
- single-agent platinum chemotherapy.

For patients with platinum-resistant or platinum-refractory ovarian cancer the relevant comparators are:

- the interventions licensed for platinum-resistant or platinum-refractory disease in comparison with each other;
- etoposide alone or in combination with platinum chemotherapy;
- best supportive care.

For patients with ovarian cancer, who are allergic to platinum-based chemotherapy the relevant comparators are:

- the interventions licensed as single agents, without platinum-containing chemotherapy, in comparison with each other;
- etoposide;
- best supportive care.

4.5 Population and relevant subgroups

The population of interest to the current appraisal is women with ovarian cancer that has recurred after treatment with, or that did not respond to, first-line (or subsequent) platinum-based chemotherapy. If the evidence allows, the use of the interventions will be considered separately in the subgroups of:

- patients with platinum-sensitive disease: who respond to first-line platinum-based chemotherapy but relapse after 6 months or more;
- patients with platinum-resistant disease: who respond to first-line platinum-based chemotherapy but relapse within 6 months and/or patients with refractory disease who do not respond or whose disease progresses on first-line platinum-based chemotherapy;
- patients with relapsed ovarian cancer, for whom platinum-based chemotherapy is not suitable because of allergy or intolerance.

4.6 Outcomes to be addressed

Evidence on the following outcome measures will be considered:

- overall survival;
- progression-free survival;
- response rate;

- adverse effects of treatment;
- health-related quality of life (HRQoL);
- cost-effectiveness.

5 Report methods for synthesis of evidence of clinical effectiveness

This MTA will include a review of topotecan, PLDH, paclitaxel, trabectedin and gemcitabine for the treatment of recurrent ovarian cancer. It will include a review of TA91 and TA222.[8;9] The MTA will be undertaken following the general principles published by the NHS Centre for Reviews and Dissemination.[10]

5.1 Search strategy

To update the literature search on topotecan, PLDH, and paclitaxel from TA91, the search for these interventions will be carried out from April 2004.[8] As trabectedin and gemcitabine were not included in the scope of TA91, a second search will be carried out with no restriction on search date to identify randomised controlled trials (RCTs) evaluating these interventions. Should the randomised evidence base be insufficient to inform the decision problem that is the focus of this MTA, a search for non-randomised trials will be conducted. Any non-RCT evidence identified will be considered for suitability and recommended methods[11] used to minimise the introduction of bias.

To identify relevant RCTs, a comprehensive search strategy will be designed and used to search multiple electronic databases including MEDLINE, EMBASE, CENTRAL, and DARE. Bibliographies of retrieved studies (RCTs and systematic reviews) identified as relevant will be manually reviewed for potentially eligible studies. Ongoing clinical trials will be identified by searching clinical trial registries, including ClinicalTrials.gov and the EU Clinical Trials Register. The Index to Scientific and Technical Proceedings will be searched to identify relevant conference proceedings. Appropriate organisational websites, databases, and registers will also be searched. In addition, experts in the field will be contacted with a request for details of published and unpublished studies of which they may have knowledge. Furthermore, submissions provided by manufacturers will be assessed for unpublished data.

No language restrictions will be applied to the search strategy. Full details of the terms used in the scoping search are presented in Appendix 9.1. All searches will be updated when the draft report is under peer review, prior to submission of the final report.

5.2 Study selection criteria and procedures

Two reviewers will independently screen all titles and abstracts according to the inclusion criteria (see Table 1). It is anticipated that relevant manufacturers will provide submissions

that may include unpublished data that will be considered. Full paper manuscripts of any titles/abstracts that may be relevant will be obtained where possible and the relevance of each study assessed. Discrepancies will be resolved by consensus, with involvement of a third reviewer when necessary.

Table 1. Inclusion criteria

	Inclusion criteria
Study design	Randomised controlled trials
Population	People with ovarian cancer that has recurred after first-line (or subsequent) platinum-based chemotherapy or is refractory to platinum-based chemotherapy
Interventions	For people with platinum-sensitive ovarian cancer: • paclitaxel as monotherapy or in combination with platinum-based chemotherapy; • PLDH as monotherapy or in combination with platinum-based chemotherapy; • gemcitabine in combination with carboplatin; • trabectedin in combination with PLDH; • topotecan monotherapy. For people with platinum-resistant or platinum-refractory ovarian cancer: • paclitaxel as monotherapy or in combination with platinum-based chemotherapy; • PLDH monotherapy; • topotecan monotherapy. For people with ovarian cancer who are allergic to platinum-based chemotherapy: • paclitaxel monotherapy; • PLDH monotherapy; • trabectedin in combination with PLDH; • topotecan monotherapy.
Comparators	For people with platinum-sensitive ovarian cancer: • the interventions listed above in comparison with each other; • bevacizumab in combination with platinum-containing chemotherapy (subject to NICE appraisal); • single-agent platinum chemotherapy. For people with platinum-resistant or platinum-refractory ovarian cancer: • the interventions listed above in comparison with each other; • etoposide as monotherapy or in combination with platinum-based chemotherapy; • best supportive care. For people with ovarian cancer who are allergic to platinum-based chemotherapy: • the interventions listed above in comparison with each other; • etoposide monotherapy; • best supportive care.
Abbreviations used in table: PLDH, pegylated liposomal doxorubicin hydrochloride; NICE, National Institute for Health and Clinical Excellence	

5.3 Subgroups

If the evidence allows, the use of the interventions in the subgroup of patients with relapsed ovarian cancer that is platinum-sensitive will be considered separately from that of patients who are platinum-resistant or refractory, or who are allergic to platinum-based compounds.

5.4 Outcomes

Data on the following outcome measures will be assessed:

- overall survival;
- progression-free survival;
- response rate;
- adverse effects of treatment；
- HRQoL.

5.5 Data extraction strategy

Full paper manuscripts of any included reference will be obtained where possible. Data will be extracted independently by two reviewers using a standardised data extraction form (see Appendix 9.2). Information extracted will include details of the study's design and methodology, baseline characteristics of participants and results including any adverse events reported. Where there is incomplete information the study authors will be contacted to gain further details. Discrepancies will be resolved by discussion, with involvement of a third reviewer when necessary.

5.6 Quality assessment strategy

The quality of the clinical effectiveness studies will be assessed by one reviewer, and independently checked for agreement by a second reviewer. Any disagreements will be resolved by consensus and if necessary a third reviewer will be consulted. The study quality will be assessed according to recommendations by the NHS Centre for Reviews and Dissemination[10] and *Cochrane Handbook for Systematic Reviews of Interventions*.[12] This will include assessing the following factors:

- random sequence generation;
- allocation concealment;
- blinding of participants, personnel and outcome assessment;
- incomplete outcome data;
- selective outcome reporting; and
- other bias.

5.7 Methods of analysis/synthesis

Extracted data and quality assessment for each study of clinical effectiveness will be presented in structured tables and as a narrative summary. The possible effects of study quality on the effectiveness data and review findings will be discussed. Should sufficient comparable data be identified, standard pair-wise comparisons and mixed-treatment comparisons will be performed to evaluate the clinical effectiveness. Treatment effects will be presented as odds ratios for dichotomous data, weighted mean differences for continuous data or as hazard ratios where appropriate. Mixed-treatment comparisons will be performed using a Bayesian Markov Chain Monte Carlo (MCMC) simulation.[13] Meta-analysis will be carried out using Comprehensive Meta Analysis software, with the use of fixed- and/or random-effects model appropriate to the assembled datasets. Statistical heterogeneity between included studies will be assessed by I^2 test. In the presence of heterogeneity (I^2 > 30%) possible sources will be investigated, including differences between individual studies in study populations, methods or interventions. Where feasible, the possibility of publication bias and/or small study effects will be investigated using funnel plots and Egger's tests.

6 Report methods for synthesising evidence of cost-effectiveness

The purpose of this MTA will be to assess the cost-effectiveness of topotecan, PLDH, paclitaxel, trabectedin and gemcitabine within their licensed indications for second-line or subsequent treatment of relapsed ovarian cancer in the UK. These interventions will be compared with each other and with routine and best practice or supportive care currently used in the NHS. This overarching objective will be met through identification and appraisal of:

- published economic evaluations from the literature or submitted economic evaluations from manufacturers' submissions (MSs);
- HRQoL studies of people with ovarian cancer including safety data.
- UK specific resource use data, non-UK sources will be considered if there is insufficient UK specific information;

Should the published or submitted economic evaluations prove insufficient to answer the review question; an independent *de novo* economic model will be developed.

6.1 Search strategy

As outlined in Section 5, this MTA is, in part, an update of an earlier systematic review (search date of April 2004) that evaluated the clinical and cost-effectiveness of topotecan, PLDH, and paclitaxel.[8] The cost-effectiveness search will aim to identify full economic

evaluations, costing studies and HRQoL studies. The following electronic databases will be searched in order to identify economic evaluations and quality of life studies for the interventions considered:

- MEDLINE (Ovid);
- EMBASE (Ovid);
- Database of Reviews of Effects (DARE);
- NHS Economic Evaluations Database (NHS EED).

Databases will be searched from inception for evidence on trabectedin and gemcitabine, while searches for evidence on topotecan, PLDH, and paclitaxel will be carried out from April 2004 onwards.

The details of the search strategy are presented in full in Appendix 9.1. The search strategy will combine terms capturing the interventions or comparators of interest and the target condition (ovarian cancer). Health economic and quality of life search terms will be applied to capture the study designs of interest (cost-effectiveness, cost and quality of life, health state utility values [HSUVs]). No language (to assess volume of foreign language studies available), setting or country restrictions will be applied to the search strategy. In addition, experts in the field will be contacted with a request for details of published and unpublished studies of which they may have knowledge. Furthermore, identified systematic reviews and manufacturers' submissions will be searched for additional references. All searches will be updated when the draft report is under peer review, prior to submission of the final report.

6.2 Inclusion and exclusion criteria

The titles and abstracts of papers identified through the searches outlined above will be independently assessed for inclusion by two reviewers using the following criteria:

Inclusion criteria:

- all economic evaluations (cost-effectiveness, cost-benefit, cost-consequence or cost minimisation);
- any setting (to be as inclusive as possible);
- intervention or comparators as per the final scope;
- study outcomes reported in terms of life-years gained (LYG) or quality adjusted life years (QALYs);
- full publications in English (numbers of relevant non-English studies will be reported);
- quality of life studies in ovarian or gynaecological cancers.
- costing/resource use studies in ovarian cancer (for resource use review)

Exclusion criteria:

- abstracts with insufficient methodological details;
- systematic reviews.

6.3 Data extraction strategy

Data will be extracted by one reviewer using a standardised data extraction table and checked by a second reviewer for accuracy. Disagreement will be resolved by discussion, however, if no consensus is reached, a third reviewer will be consulted. In cases where there are missing data or unclear reporting in the published or submitted economic evidence or quality of life studies, attempts will be made to contact authors. Studies published in the UK will be reported in greater detail than non-UK studies as they are more likely to be relevant to the NHS. Tables 2 and 3 show the health economic evaluation and quality of life data that will be sought from each study. In addition, the reason for exclusion of each excluded study will be documented (Table 4).

Table 2. Health economic evaluation data extraction table

Author, year, country	**Perspective, discounting & cost year**	**Model type**	**Patient population**	**Intervention/ comparator**	**Outcomes**	**Results ICER (per QALY gained) incl uncertainty**
Reviewer's comments:						
Abbreviations used in table: QALY, quality adjusted life year						

Table 3. Quality of life data extraction table

Author, year, country	**Sample size**	**Patient population**	**Instrument (Valuation)**	**Utility results**
Reviewer's comments:				
Abbreviations used in table:				

Table 4. Data exclusion table

Bibliographic reference	**Reasons for exclusion**
Abbreviations used in table:	

6.4 Quality assessment strategy

All published economic evaluations identified within the review and any economic evaluations submitted by manufacturers to NICE will be subject to critical appraisal. The methodological quality of each economic evaluation will be assessed against NICE's reference checklist for economic evaluations[(11)] together with the Philips checklist[(14)] on mathematical models used in technology assessments (see Appendix 9.3). Each economic

evaluation will be assessed by one health economist and the details of the assessment checked by a second health economist.

6.5 Methods of analysis

Published and submitted economic evaluations

A narrative summary and accompanying data extraction tables will be presented to summarise evidence from published or submitted economic evaluations.

Economic modelling

Should the economic evidence identified prove insufficient to answer the review question; a *de novo* economic model will be developed. The structure of the *de novo* model will be informed by economic evaluations identified in the published literature and MSs; all structural assumptions will be documented and accompanying rationales provided. It is anticipated that the model used in the previous MTA will be the most informative in the development of any *de novo* economic evaluation.[8] However, in addition to the interventions considered by Main *et al*. trabectedin and gemcitabine will be considered in any *de novo* economic evaluation. The clinical effectiveness parameters required for the economic model will be informed by the review of clinical effectiveness discussed in Section 5. The clinical effectiveness section evaluates all the technologies for recurrent ovarian cancer, and includes a review of TA91 and TA222. In addition, parameters such as estimates of quality of life (utility data) will be informed by the published literature, identified in the review. In cases where parameters required to populate the model are not available from published studies or MSs, expert clinical opinion will be considered.

The cost-effectiveness of the interventions will be estimated in terms of an incremental cost per additional QALY gained, as well as the incremental cost per LYG. As appropriate, cost data will be obtained from NHS reference costs[15], British National Formulary[16], Unit Costs of Health and Social Care[17], published sources or MSs. Costs will consist of direct medical costs (e.g. drug costs and cost of adverse events, monitoring and administering chemotherapy) and direct non-medical costs (e.g. healthcare professional's costs). Resource use and costs will be valued from the NHS and Personal Social Services perspective. Both costs and outcomes will be discounted at 3.5% per annum after the first year in accordance with NICE methods guidance.[11] The time horizon for the economic analysis will be lifetime in order to reflect the chronic and advanced nature of recurrent ovarian cancer disease.

6.6 Methods for estimating quality of life

The third Consensus Conference on Ovarian Cancer held in Baden-Baden in September 2004 stated that "the main goals of the treatment of patients with relapsing ovarian cancer are to provide disease control, i.e., survival prolongation, together with symptom palliation and an emphasis on *patient quality of life*".[18] Ideally, evidence of the impact of treatments included in this review on HRQoL will be available directly from identified trials. In the absence of such evidence, any *de novo* economic model may use indirect evidence on quality of life from alternative literature sources, such as related technology appraisals or clinical guidelines. In accordance with NICE methods guidance, utility values will be taken from studies that have been based on "public" preferences elicited using a choice-based method.[11] Utility data will also be adjusted for age using data from the Health Survey of England.[19]

6.7 Analysis of uncertainty

As a standard, the model will be probabilistic; that is, all relevant input parameters will be entered as probability distributions to reflect their imprecision and Monte Carlo simulation will be used to reflect this uncertainty in the model's results. In addition, uncertainty will also be explored through one-way sensitivity analysis. The outputs of probabilistic sensitivity analysis (PSA) will be presented in the cost-effectiveness plane and through the use of cost-effectiveness acceptability curves. One way sensitivity analysis outputs will be presented in tables and tornado diagrams. Where possible, uncertainty pertaining to the structural assumptions used will be assessed in scenario analyses using alternative structural assumptions. If data permits, the impact of patient heterogeneity (e.g. platinum sensitive vs. platinum resistant/refractory) on cost-effectiveness results will be explored in subgroup analyses.

7 Handling the company submission(s)

All data submitted by the drug manufacturers/sponsors will be considered if received by the TAR group on or before 20/03/2013. Data arriving after this date will not be considered. Data meeting the inclusion criteria for the review will be extracted and quality assessed in accordance with the procedures outlined in this protocol. Any economic evaluation included in the manufacturer(s)'s submission(s), provided it complies with NICE's advice on presentation, will be assessed for clinical validity, reasonableness of assumptions and appropriateness of the data used in the economic model. If the TAR group judges that the existing economic evidence is not robust, then further work will be undertaken, either by adapting what already exists or developing a *de-novo* model.

Any 'commercial in confidence' data taken from a manufacturer's submission, and specified as confidential in the supplied check list, will be [redacted] in the assessment report (followed by an indication of the relevant manufacturer name, for

example, in brackets). Any 'academic in confidence' data taken from a manufacturer's submission, and specified as confidential in the supplied check list, will be [redacted] in the assessment report.

8 Competing interests of authors

None.

9 Appendices

Appendix 9.1. Draft search strategy

Clinical draft search strategy

Database: MEDLINE (Ovid host); search run: 25/10/2012
Records retrieved: 2698
Limits:

- Date limit applied to update search run for previous NICE TAR for topotecan, pegylated liposomal doxorubicin hydrochloride and paclitaxel (from April 2004)
- All years were searched for trabectedin and gemcitabine
- Animal-only studies excluded
- No limits applied for study design or language

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1 exp ovarian neoplasms/ (59446)
2 (ovar$ adj4 (cancer$ or tumo?r$ or malignan$ or oncolog$ or carcinoma$ or neoplas$ or mass$ or growth$ or cyst$)).mp. [mp=title, abstract, name of substance, mesh subject heading] (77917)
3 (adenexa$ adj4 mass$).mp. [mp=title, abstract, name of substance, mesh subject heading] (5)
4 or/1-3 (79681)
5 topotecan/ (1693)
6 topotecan.mp. [mp=title, abstract, name of substance, mesh subject heading] (2350)
7 (hycam$ or potactasol).mp. [mp=title, abstract, name of substance, mesh subject heading] (72)
8 or/5-7 (2353)
9 exp doxorubicin/ (40006)
10 (doxorubicin hydrochloride or doxorubicin hcl).mp. [mp=title, abstract, name of substance, mesh subject heading] (536)
11 liposomal doxorubicin.mp. [mp=title, abstract, name of substance, mesh subject heading] (1201)
12 liposome encapsulated doxorubicin.mp. [mp=title, abstract, name of substance, mesh subject heading] (85)
13 doxil.mp. [mp=title, abstract, name of substance, mesh subject heading] (256)
14 caelyx.mp. [mp=title, abstract, name of substance, mesh subject heading] (156)
15 or/9-14 (40342)
16 exp paclitaxel/ (17628)
17 paclitaxel.mp. [mp=title, abstract, name of substance, mesh subject heading] (21432)
18 taxol.mp. [mp=title, abstract, name of substance, mesh subject heading] (5750)
19 or/16-18 (22887)
20 limit 8 to ed=20040401-20121025 (1177)
21 limit 15 to ed=20040401-20121025 (13829)
22 limit 19 to ed=20040401-20121025 (12895)
23 trabectedin/ (0)
24 trabectedin.mp [mp=title, abstract, name of substance, mesh subject heading] (362)

25 (yondelis).mp. [mp=title, abstract, name of substance, mesh subject heading] (90)
26 or/23-25 (368)
27 gemcitabine/ (0)
28 gemcitabine.mp. [mp=title, abstract, name of substance, mesh subject heading] (8348)
29 (gemzar).mp. [mp=title, abstract, name of substance, mesh subject heading] (207)
30 or/27-29 (8359)
31 20 or 21 or 22 or 26 or 30 (34100)
32 4 and 31 (2764)
33 animal/ not (animal/ and human/) (3705460)
34 32 not 33 (2698)

Health economics draft search strategy

Database: MEDLINE (Ovid host); search run: 23/10/12
Records retrieved: 101

1 exp Ovary Cancer/ (59382)
2 (adenexa$ adj4 mass$).mp. (5)
3 genital neoplasms, female/ or ovarian neoplasms/ (67028)
4 exp Carcinoma/ (454999)
5 exp ovarian neoplasms/ (59382)
6 (ovar$ adj4 (cancer$ or tumo?r$ or malignan$)).ti. (26128)
7 (ovar$ adj4 (cancer$ or tumo?r$ or malignan$)).ab. (38904)
8 (ovar$ adj4 (oncolog$ or carcinoma$)).ab. (11836)
9 or/1-8 (516972)
10 Topotecan/ (1691)
11 topotecan.mp. (2348)
12 (hycamtin or hycamptamine).mp. (69)
13 or/10-12 (2350)
14 exp Doxorubicin/ (39977)
15 doxil.mp. (256)
16 (doxorubicin hydrochloride or doxorubicin hcl).mp. (536)
17 liposomal doxorubicin.mp. (1199)
18 (caelyx or adriamycin or rubex).mp. (13576)
19 liposome encapsulated doxorubicin.mp. (85)
20 or/14-19 (44024)
21 Paclitaxel/ (17606)
22 paclitaxel.mp. (21404)
23 docetaxel.mp. (7850)
24 taxol.mp. (5746)
25 taxotere.mp. (911)
26 or/21-25 (27636)
27 exp Trabectedin/ (0)
28 ecteinascidin 743.mp. (126)
29 ET-743.mp. (166)
30 or/27-29 (218)
31 exp Gemcitabine/ (0)
32 Carboplatin/ (8292)
33 (carboplatin or paraplatin).mp. (11106)
34 or/32-33 (11106)
35 Cisplatin/ (37564)
36 (cisplatin or platinol).mp. (48141)
37 or/35-36 (48141)
38 13 or 20 or 26 or 30 or 34 or 37 (111012)
39 animal/ not (animal/ and human/) (3703336)

40 38 not 39 (94456)
41 economics/ (26627)
42 exp costs/ and cost analysis/ (40236)
43 exp economics, hospital/ (18252)
44 economics, medical/ (8491)
45 economics, pharmaceutical/ (2377)
46 (economic$ or pharmaeconomic$ or pharmacoeconomic$ or pharmaco-economic$).tw. (126456)
47 (cost or costs or costly or costing or costed).tw. (268651)
48 value for money.tw. (778)
49 cost utility/ (0)
50 cost effectiveness/ (55464)
51 or/41-50 (430154)
52 limit 51 to yr=2004-2012 (184620)
53 40 and 52 (584)
54 9 and 53 (101)

Appendix 9.2. Data extraction form

Data extraction form clinical effectiveness studies

Study information	
Study name	
Study references (insert citations from reference manager)	
Country(ies) where the clinical trial was conducted	
Multicentre trial (number, location)	
Trial sponsors	
Date the clinical trial was conducted	
Trial design (e.g. parallel, crossover, or cluster trial)	
Trial duration (treatment duration and follow-up)	
Inclusion criteria	
Exclusion criteria	
Concomitant medications	
Outcomes	
Subgroups	
Criteria for disease progression (e.g. CA 125, RECIST criteria or both)	
Abbreviations used in table: RECIST, Response Evaluation Criteria for Solid Tumors.	

Patient characteristics	**Intervention**	**Control**	**Total**
N randomised			
N withdrawals (%)			
Age (mean SD, or age range)			
Platinum sensitive ovarian cancer			
Platinum resistant ovarian cancer			
Refractory ovarian cancer			
Primary site (e.g. ovarian, fallopian tube, primary peritoneal			
Previous treatment (summary of drugs or other			

treatments)			
Ethnicity			
Abbreviations used in table: SD, standard deviation			

	Intervention	Control
Drug name		
Delivery		
Dose		
Formulation		
Number of cycles		
Length per cycle		
Note		
Abbreviations used in table:		

Outcome	Risk of Bias	Low	Unclear	High	Comments
	Random sequence generation				
	Allocation concealment				
	Blinding (who [participants, personnel], and method)				
Overall survival	Blinding of outcome assessment				
	Incomplete outcome data (patients who discontinued/ changed treatment, patients lost to follow-up)				
	Selective reporting				
Response rate	Blinding of outcome assessment				
	Incomplete outcome data				
	Selective reporting				
Adverse events	Blinding of outcome assessment				
	Incomplete outcome data				
	Selective reporting				
Progression-free survival	Blinding of outcome assessment				
	Incomplete outcome data				
	Selective reporting				
Quality of life	Blinding of outcome assessment				
	Incomplete outcome data				
	Selective reporting				
Abbreviations used in table:					

Outcome	Intervention	Control
N randomised		
Overall survival		

Response rate		
Adverse events		
febrile neutropenia		
thrombocytopenia		
anaemia		
palmar-plantar erythrodyesthesia (PPE)		
nausea		
diarrhoea		
constipation		
stomatitis		
abdominal pain		
leukopaenia		
mucositis		
rash		
fatigue		
asthenia		
alopecia		
anorexia		
malaise		
raised blood pressure		
proteinuria		
bowel perforation		
peripheral neuropathy		
Time frame (e.g. end of study, weeks)		
Abbreviations used in table:		

Outcome	**Intervention**			**Control**		
N randomised						
	mean	**95% CI**	**N**	**mean**	**95% CI**	**N**
Progression-free survival						
Quality of life						
Time frame (e.g., end of study, weeks)						
Abbreviations used in table:						

Appendix 9.3. Health economic evaluation study quality assessment

NICE reference case ([11])

Attribute	**Reference case**	**Reviewer's comments**
Decision problem	The scope developed by NICE	
Comparator(s)	Alternative therapies routinely used in the NHS	
Perspective costs	NHS and Personal Social Services	
Perspective benefits	All health effects on individuals	
Form of economic evaluation	Cost-utility analysis	
Time horizon	Sufficient to capture differences in costs and outcomes	

Synthesis of evidence on outcomes	Systematic review	
Outcome measure	QALYs	
Health states for QALY	Described using a standardised and validated instrument	
Benefit valuation	Time-trade off or standard gamble	
Source of preference data for valuation of changes in HRQoL	Representative sample of the public	
Discount rate	An annual rate of 3.5% on both costs and health effects	
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	
Sensitivity analysis	Probabilistic sensitivity analysis	
Abbreviations used in table: NICE, National Institute for Health and Clinical Excellence; NHS, National Health Service; QALY, quality adjusted life year.		

Philips checklist ([14])

Dimension of quality	Reviewers comments
Structure	
S1 Statement of decision problem/objective	
S2 Statement of scope/perspective	
S3 Rationale for structure	
S4 Structural assumptions	
S5 Strategies/comparators	
S6 Model type	
S7 Time horizon	
S8 Disease states/pathways	
S9 Cycle length	
Data	
D1 Data identification	
D2 Premodel data analysis	
D2a Baseline data	
D2b Treatment effects	
D2d Quality of life weights (utilities)	
D3 Data incorporation	
D4 Assessment of uncertainty	
D4a Methodological	
D4b Structural	
D4c Heterogeneity	
D4d Parameter	
Consistency	
C1 Internal consistency	
C2 External consistency	
Abbreviations used in table:	

Additional information that is needed by NETSCC, HTA and NICE.
Please send this as a WORD document when you submit your protocol to Htatar@soton.ac.uk.

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Please indicate to whom you wish all correspondence to be addressed

Please send all correspondences to the lead, Steve Edwards, and the main reviewer, Sam Barton.

Timetable/milestones

A Progress Report (to NETSCC, HTA who forward it to NICE within 24hr) will be submitted 27 March 2013

A draft Assessment Report (simultaneously to NICE and NETSCC, HTA) will be submitted 22 May 2013

The Assessment Report (simultaneously to NICE and NETSCC, HTA) will be submitted 1 July 2013

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Appendix 13. Quality assessment

Quality assessment of the clinical evidence

Alberts *et al*.[20]

Outcome	Risk of Bias	Low	Unclear	High	Comments
	Random sequence generation		✓		No details reported.
	Allocation concealment		✓		No details reported.
	Selective reporting	✓			
	Other bias		✓		
Overall survival	Blinding (who [participants, personnel], and method)		✓		No details reported.
	Blinding of outcome assessment	✓			OS is associated with a low risk of bias
	Incomplete outcome data	✓			Modified ITT analysis
Progression-free survival	Blinding (who [participants, personnel], and method)		✓		No details reported.
	Blinding of outcome assessment		✓		
	Incomplete outcome data	✓			
Response rate	Blinding (who [participants, personnel], and method)		✓		No details reported.
	Blinding of outcome assessment		✓		
	Incomplete outcome data	✓			
Adverse events	Blinding (who [participants, personnel], and method)		✓		No details reported.
	Blinding of outcome assessment		✓		
	Incomplete outcome data	✓			

OVA-301[21;22]

Outcome	Risk of Bias	Low	Unclear	High	Comments
	Random sequence generation	✓			Permuted block
	Allocation concealment		✓		No details given
	Selective reporting	✓			All outcomes mentioned are reported
	Other bias		✓		
Overall survival	Blinding (who [participants, personnel], and method)			✓	Open label.
	Blinding of outcome assessment	✓			OS is associated with a low risk of bias as an outcome measure
	Incomplete outcome data (patients who discontinued/ changed treatment, patients lost to follow-up)	✓			

Progression-free survival	Blinding (who [participants, personnel], and method)			✓	Open label.
	Blinding of outcome assessment	✓			Blinded independent radiology and oncology review
	Incomplete outcome data	✓			
Response rate	Blinding (who [participants, personnel], and method)			✓	Open label.
	Blinding of outcome assessment	✓			Blinded independent radiology and oncology review
	Incomplete outcome data	✓			ITT analysis
Quality of life	Blinding (who [participants, personnel], and method)			✓	Open label.
	Blinding of outcome assessment		✓		
	Incomplete outcome data		✓		
Adverse events	Blinding (who [participants, personnel], and method)			✓	Open label.
	Blinding of outcome assessment		✓		Independent data monitoring committee
	Incomplete outcome data	✓			

CARTAXHY (Lortholary *et al*.[23])

Outcome	Risk of Bias	Low	Unclear	High	Comments
	Random sequence generation		✓		No details reported.
	Allocation concealment		✓		No details reported.
	Selective reporting	✓			
	Other bias		✓		
Overall survival	Blinding (who [participants, personnel], and method)			✓	Open label.
	Blinding of outcome assessment	✓			OS is associated with a low risk of bias.
	Incomplete outcome data (patients who discontinued/ changed treatment, patients lost to follow-up)	✓			
Progression-free survival	Blinding (who [participants, personnel], and method)			✓	Open label.
	Blinding of outcome assessment		✓		No details reported as to level of masking of assessor
	Incomplete outcome data	✓			
Response rate	Blinding (who [participants, personnel], and method)			✓	Open label.
	Blinding of outcome assessment		✓		No details reported as to level of masking of

					assessor
	Incomplete outcome data	✓			
Quality of life	Blinding (who [participants, personnel], and method)			✓	Open label.
	Blinding of outcome assessment		✓		
	Incomplete outcome data		✓		Limited details reported on proportion of patients returning questionnaire and scores on completed questionnaires
Adverse events	Blinding (who [participants, personnel], and method)			✓	Open label.
	Blinding of outcome assessment		✓		No details reported
	Incomplete outcome data	✓			

Pfisterer *et al*.[24]

Outcome	Risk of Bias	Low	Unclear	High	Comments
	Random sequence generation		✓		Random assignment through central office, using “block size of 10”. No additional details reported.
	Allocation concealment		✓		No details reported.
	Selective reporting	✓			
	Other bias		✓		
Overall survival	Blinding (who [participants, personnel], and method)			✓	Open label.
	Blinding of outcome assessment	✓			OS is associated with a low risk of bias
	Incomplete outcome data (patients who discontinued/ changed treatment, patients lost to follow-up)	✓			
Progression-free survival	Blinding (who [participants, personnel], and method)			✓	Open label.
	Blinding of outcome assessment		✓		No details reported as to level of masking of assessor
	Incomplete outcome data	✓			ITT analysis
Response rate	Blinding (who [participants, personnel], and method)			✓	Open label.
	Blinding of outcome assessment		✓		No details reported as to level of masking of assessor
	Incomplete outcome data	✓			

Quality of life	Blinding (who [participants, personnel], and method)			✓	Open label.
	Blinding of outcome assessment		✓		No details reported as to level of masking of assessor
	Incomplete outcome data		✓		Limited details reported on proportion of patients returning questionnaire and scores on completed questionnaires
Adverse events	Blinding (who [participants, personnel], and method)			✓	Open label.
	Blinding of outcome assessment		✓		
	Incomplete outcome data	✓			

Piccart *et al*.[25]

Outcome	Risk of Bias	Low	Unclear	High	Comments
	Random sequence generation		✓		Not reported
	Allocation concealment		✓		Assigned by European Organisation for Research and Treatment of Cancer Data Centre. Method not reported.
	Selective reporting	✓			
	Other bias		✓		
Overall survival	Blinding (who [participants, personnel], and method)			✓	Open label.
	Blinding of outcome assessment	✓			OS is associated with a low risk of bias
	Incomplete outcome data (patients who discontinued/ changed treatment, patients lost to follow-up)	✓			
Progression-free survival	Blinding (who [participants, personnel], and method)			✓	Open label.
	Blinding of outcome assessment		✓		Verified by two independent radiologists. Level of masking unclear
	Incomplete outcome data	✓			
Response rate	Blinding (who [participants, personnel], and method)			✓	Open label.
	Blinding of outcome assessment		✓		Verified by two independent radiologists. Level of masking unclear
	Incomplete outcome data	✓			

Quality of life	Blinding (who [participants, personnel], and method)			✓	Open label.
	Blinding of outcome assessment		✓		
	Incomplete outcome data		✓		Limited details reported on proportion of patients returning questionnaire and scores on completed questionnaires
Adverse events	Blinding (who [participants, personnel], and method)			✓	Open label.
	Blinding of outcome assessment		✓		
	Incomplete outcome data	✓			

Bafaloukos *et al*.[26]

Outcome	Risk of Bias	Low	Unclear	High	Comments
	Random sequence generation		✓		Performed at central HeCOG Data Office. No further details reported.
	Allocation concealment		✓		No details reported.
	Selective reporting	✓			
	Other bias		✓		
Overall survival	Blinding (who [participants, personnel], and method)		✓		No details reported.
	Blinding of outcome assessment	✓			OS is associated with a low risk of bias
	Incomplete outcome data (patients who discontinued/ changed treatment, patients lost to follow-up)	✓			
Time to progression	Blinding (who [participants, personnel], and method)		✓		No details reported.
	Blinding of outcome assessment		✓		No details reported
	Incomplete outcome data	✓			
Response rate	Blinding (who [participants, personnel], and method)		✓		No details reported.
	Blinding of outcome assessment		✓		No details reported
	Incomplete outcome data	✓			
Adverse events	Blinding (who [participants, personnel], and method)		✓		No details reported.
	Blinding of outcome assessment		✓		

	Incomplete outcome data	✓			

Gonzalez Martin *et al*.[27]

Outcome	Risk of Bias	Low	Unclear	High	Comments
	Random sequence generation		✓		Reported to have been carried out at a central data centre. No details reported.
	Allocation concealment		✓		No details reported.
	Selective reporting	✓			
	Other bias		✓		
Overall survival	Blinding (who [participants, personnel], and method)		✓		No details reported.
	Blinding of outcome assessment	✓			OS is associated with a low risk of bias
	Incomplete outcome data (patients who discontinued/ changed treatment, patients lost to follow-up)	✓			
Time to progression	Blinding (who [participants, personnel], and method)		✓		No details reported.
	Blinding of outcome assessment		✓		No details reported
	Incomplete outcome data	✓			
Response rate	Blinding (who [participants, personnel], and method)		✓		No details reported.
	Blinding of outcome assessment		✓		No details reported.
	Incomplete outcome data	✓			
Quality of life	Blinding (who [participants, personnel], and method)		✓		No details reported.
	Blinding of outcome assessment		✓		No details reported
	Incomplete outcome data		✓		Limited details reported on proportion of patients returning questionnaire and scores on completed questionnaires
Adverse events	Blinding (who [participants, personnel], and method)		✓		No details reported.
	Blinding of outcome assessment		✓		No details reported.
	Incomplete outcome data	✓			

Rosenberg *et al*.[28]

Outcome	Risk of Bias	Low	Unclear	High	Comments
	Random sequence generation		✓		Reported to have been carried out at Bristol-Myers Squibb office in Stockholm; no further details reported
	Allocation concealment		✓		No details reported
	Selective reporting	✓			
	Other bias		✓		
Overall survival	Blinding (who [participants, personnel], and method)		✓		No details reported.
	Blinding of outcome assessment	✓			OS is associated with a low risk of bias
	Incomplete outcome data (patients who discontinued/ changed treatment, patients lost to follow-up)	✓			
Time to progression	Blinding (who [participants, personnel], and method)		✓		No details reported.
	Blinding of outcome assessment		✓		No details reported.
	Incomplete outcome data	✓			
Response rate	Blinding (who [participants, personnel], and method)		✓		No details reported.
	Blinding of outcome assessment		✓		No details reported.
	Incomplete outcome data	✓			
Adverse events	Blinding (who [participants, personnel], and method)		✓		No details reported.
	Blinding of outcome assessment		✓		No details reported
	Incomplete outcome data	✓			

CALYPSO (Pujade-Lauraine *et al*.[29])

Outcome	Risk of Bias	Low	Unclear	High	Comments
	Random sequence generation	✓			Permuted blocks of six. Centrally randomised.
	Allocation concealment		✓		
	Selective reporting	✓			
	Other bias		✓		
Overall survival	Blinding (who [participants, personnel], and method)			✓	Open label
	Blinding of outcome assessment	✓			OS is associated with a low risk of bias
	Incomplete outcome data (patients who discontinued/ changed treatment, patients lost to follow-up)	✓			

Progression-free survival	Blinding (who [participants, personnel], and method)			✓	Open label
	Blinding of outcome assessment	✓			Responses reviewed by an independent assessor masked to treatment
	Incomplete outcome data	✓			
Response rate	Blinding (who [participants, personnel], and method)			✓	Open label
	Blinding of outcome assessment	✓			Responses reviewed by an independent assessor masked to treatment
	Incomplete outcome data	✓			
Adverse events	Blinding (who [participants, personnel], and method)			✓	Open label
	Blinding of outcome assessment		✓		No details reported.
	Incomplete outcome data	✓			

Gordon *et al*.[30;31]

Outcome	Risk of Bias	Low	Unclear	High	Comments
	Random sequence generation		✓		No details reported in full publication. TA91 indicated that method of randomisation was robust.[32]
	Allocation concealment		✓		No details reported in full publication. TA91 indicated that allocation of treatment was concealed.[32]
	Selective reporting	✓			
	Other bias		✓		
Overall survival	Blinding (who [participants, personnel], and method)			✓	Open label design.
	Blinding of outcome assessment	✓			OS is associated with a low risk of bias
	Incomplete outcome data (patients who discontinued/ changed treatment, patients lost to follow-up)	✓			
Progression-free survival	Blinding (who [participants, personnel], and method)			✓	Open label design.
	Blinding of outcome assessment		✓		Radiological scans underwent independent radiological review, but level of masking of assessor is unclear

	Incomplete outcome data	✓			

Response rate	Blinding (who [participants, personnel], and method)			✓	Open label design.
	Blinding of outcome assessment		✓		Radiological scans underwent independent radiological review, but level of masking of assessor is unclear
	Incomplete outcome data	✓			
Quality of life	Blinding (who [participants, personnel], and method)			✓	Open label design.
	Blinding of outcome assessment		✓		No details reported
	Incomplete outcome data		✓		Limited details reported on proportion of patients returning questionnaire and scores on completed questionnaires
Adverse events	Blinding (who [participants, personnel], and method)			✓	Open label design.
	Blinding of outcome assessment		✓		No details reported
	Incomplete outcome data	✓			

ICON4/AGO-OVAR2.2 (Parmar *et al*.[33])

Outcome	Risk of Bias	Low	Unclear	High	Comments
	Random sequence generation	✓			Minimisation by computer.
	Allocation concealment		✓		"Telephone or facsimile" – no extra details reported.
	Selective reporting	✓			
	Other bias		✓		
Overall survival	Blinding (who [participants, personnel], and method)		✓		No details reported.
	Blinding of outcome assessment	✓			OS is associated with a low risk of bias
	Incomplete outcome data (patients who discontinued/ changed treatment, patients lost to follow-up)	✓			
Progression-free survival	Blinding (who [participants, personnel], and method)		✓		No details reported.
	Blinding of outcome assessment		✓		No details reported.
	Incomplete outcome data	✓			
Response rate	Blinding (who [participants, personnel], and method)		✓		No details reported.
	Blinding of outcome assessment		✓		No details reported

	Incomplete outcome data		✓		
Quality of life	Blinding (who [participants, personnel], and method)		✓		No details reported.
	Blinding of outcome assessment		✓		No details reported.
	Incomplete outcome data		✓		Limited details reported on proportion of patients returning questionnaire and scores on completed questionnaires
Adverse events	Blinding (who [participants, personnel], and method)		✓		No details reported.
	Blinding of outcome assessment		✓		No details reported.
	Incomplete outcome data	✓			

Gore *et al*.[34]

Outcome	Risk of Bias	Low	Unclear	High	Comments
	Random sequence generation		✓		No others details reported.
	Allocation concealment		✓		Reported to be "by telephone", but no additional details given.
	Selective reporting	✓			
	Other bias		✓		
Overall survival	Blinding (who [participants, personnel], and method)			✓	Open label.
	Blinding of outcome assessment	✓			OS is associated with a low risk of bias
	Incomplete outcome data (patients who discontinued/ changed treatment, patients lost to follow-up)	✓			
Time to progression	Blinding (who [participants, personnel], and method)			✓	Open label.
	Blinding of outcome assessment	✓			Independent, blinded radiological review.
	Incomplete outcome data	✓			
Response rate	Blinding (who [participants, personnel], and method)			✓	Open label.
	Blinding of outcome assessment	✓			Independent, blinded radiological review.
	Incomplete outcome data	✓			
Adverse events	Blinding (who [participants, personnel], and method)			✓	Open label.
	Blinding of outcome assessment		✓		No details reported
	Incomplete outcome data	✓			

ten Bokkel Huinink *et al*.[35;36]

Outcome	Risk of Bias	Low	Unclear	High	Comments
	Random sequence generation		✓		Paper states "telephone randomisation system". No further details given.
	Allocation concealment		✓		No details reported.
	Selective reporting	✓			
	Other bias		✓		
Overall survival	Blinding (who [participants, personnel], and method)			✓	Open label.
	Blinding of outcome assessment	✓			OS associated with low risk of bias
	Incomplete outcome data (patients who discontinued/ changed treatment, patients lost to follow-up)	✓			
Time to progression	Blinding (who [participants, personnel], and method)			✓	Open label.
	Blinding of outcome assessment	✓			Independent, blinded review of response.
	Incomplete outcome data	✓			
Response rate	Blinding (who [participants, personnel], and method)			✓	Open label.
	Blinding of outcome assessment	✓			Independent, blinded review of response.
	Incomplete outcome data	✓			
Quality of life	Blinding (who [participants, personnel], and method)			✓	Open label.
	Blinding of outcome assessment		✓		
	Incomplete outcome data		✓		
Adverse events	Blinding (who [participants, personnel], and method)			✓	Open label.
	Blinding of outcome assessment		✓		No details reported.
	Incomplete outcome data	✓			

Sehouli *et al*.[37]

Outcome	Risk of Bias	Low	Unclear	High	Comments
	Random sequence generation	✓			Central randomisation with permutated blocks.
	Allocation concealment		✓		Phone or fax. No additional details reported.
	Selective reporting	✓			
	Other bias		✓		

Overall survival	Blinding (who [participants, personnel], and method)		✓		No details reported.
	Blinding of outcome assessment	✓			OS is associated with a low risk of bias
	Incomplete outcome data (patients who discontinued/ changed treatment, patients lost to follow-up)		✓		No details reported
Progression-free survival	Blinding (who [participants, personnel], and method)		✓		No details reported.
	Blinding of outcome assessment		✓		Confirmed by second evaluation. No details reported for blinding.
	Incomplete outcome data		✓		
Response rate	Blinding (who [participants, personnel], and method)		✓		No details reported.
	Blinding of outcome assessment		✓		Confirmed by second evaluation. No details reported for blinding.
	Incomplete outcome data		✓		
Quality of life	Blinding (who [participants, personnel], and method)		✓		No details reported.
	Blinding of outcome assessment		✓		
	Incomplete outcome data		✓		
Adverse events	Blinding (who [participants, personnel], and method)		✓		No details reported.
	Blinding of outcome assessment		✓		
	Incomplete outcome data	✓			

Omura *et al.*[38]

Outcome	Risk of Bias	Low	Unclear	High	Comments
	Random sequence generation	✓			Treatment regimens sequentially assigned from stratified, permuted blocks
	Allocation concealment		✓		No details reported
	Selective reporting		✓		
	Other bias		✓		
Overall survival	Blinding (who [participants, personnel], and method)		✓		No details reported
	Blinding of outcome assessment	✓			OS is associated with a low risk of bias
	Incomplete outcome data (patients who discontinued/ changed treatment, patients lost to follow-up)			✓	Not all patients randomised were included in analysis. Reasons for ineligibility not clearly reported
Progression-free survival	Blinding (who [participants, personnel], and method)		✓		No details reported
	Blinding of outcome assessment		✓		No details reported
	Incomplete outcome data			✓	Not all patients randomised were included in analysis. Reasons for ineligibility not clearly reported
Response rate	Blinding (who [participants, personnel], and method)		✓		No details reported
	Blinding of outcome assessment		✓		No details reported
	Incomplete outcome data			✓	Not all patients randomised were included in analysis. Reasons for ineligibility not clearly reported
Adverse events	Blinding (who [participants, personnel], and method)		✓		No details reported
	Blinding of outcome assessment		✓		No details reported
	Incomplete outcome data			✓	Not all patients randomised were included in analysis. Reasons for ineligibility not clearly reported

Trial 30–57 (taken from TA91)[32]

Outcome	Risk of Bias	Low	Unclear	High	Comments
	Random sequence generation	✓			
	Allocation concealment	✓			
	Selective reporting		✓		Unclear whether all outcomes reported
	Other bias		✓		
Overall survival	Blinding (who [participants, personnel], and method)			✓	Personnel and patients not masked
	Blinding of outcome assessment	✓			OS is associated with a low risk of bias
	Incomplete outcome data (patients who discontinued/ changed treatment, patients lost to follow-up)	✓			ITT
Adverse events	Blinding (who [participants, personnel], and method)			✓	
	Blinding of outcome assessment		✓		
	Incomplete outcome data	✓			

Appendix 14. Completed and ongoing clinical trials of interest

Trial title (and URL)	Sponsor	ID	Intervention	Comparator	Status
Phase III International Multicenter Randomized Study Testing the Effect on Survival of Prolonging Platinum-free Interval in Patients With Ovarian Cancer Recurring Between 6 and 12 Months After Previous Platinum Based Chemotherapy	National Cancer Institute, Naples	EudraCT number: 2008-001755-22 ClinicalTrials.gov identifier NCT00657878	a non-platinum based therapy (corresponding to stealth liposomal doxorubicin, or topotecan, or gemcitabine, or any other drug approved in clinical practice for the treatment of patients with ovarian cancer after previous platinum-based chemotherapy) followed by a platinum based chemotherapy at disease progression	platinum based chemotherapy (corresponding to the combination of carboplatin + paclitaxel, or carboplatin + gemcitabine for patients with significant but lower than grade 3 neuropathy at baseline) followed by a non-platinum based chemotherapy at disease progression	Recruiting
An Open, Randomized, Multicenter Study in Patients With Recurrent Epithelian Cancer, Primary Peritoneal Cancer or Fallopian Tube Cancer to Compare the Efficacy and Safety of Paclitaxel (Micellar) Nanoparticles and Paclitaxel (Cremophor® EL)	Oasmia Pharmaceutical AB	EudraCT Number: 2008-002668-32 ClinicalTrials.gov Identifier: NCT00989131	Paclitaxel (Paclical®) plus carboplatin	Paclitaxel (Taxol®) plus carboplatin	Ongoing
Phase III international, randomized study of Trabectedin plus Pegylated Liposomal Doxorubicin (PLD) versus Carboplatin plus PLD in patients with ovarian cancer progressing within 6-12 months of last platinum	IST. DI RICERCHE FARMACOLOG. M. NEGRI	EudraCT number: 2010-022949-17 ClinicalTrials.gov identifier: NCT01379989	Trabectedin plus PLDH	Carboplatin plus PLDH	Suspended due to limited availability of PLDH
An Open-Label Multicenter Randomized Phase 3 Study Comparing the Combination of DOXIL/CAELYX and YONDELIS With DOXIL/CAELYX Alone in Subjects With Advanced Relapsed Ovarian Cancer	Johnson & Johnson Pharmaceutical Research & Development, L.L.C.	NCT00113607	DOXIL + trabectedin	DOXIL	Completed

National, Randomized, Phase II Study Comparing Efficacy of Weekly Administration of Paclitaxel in Monotherapy or in Combination With Topotecan or Carboplatin in Patients With Epithelial Ovarian Cancer in Early Relapse	ARCAGY/GINECO GROUP	NCT00189566	Paclitaxel monotherapy	Paclitaxel combination With Topotecan or Carboplatin	Completed
A Randomized Phase III Study Comparing Gemcitabine Plus Carboplatin Versus Carboplatin Monotherapy in Patients With Advanced Epithelial Ovarian Carcinoma Who Failed First-Line Platinum-Based Therapy	AGO Study Group	NCT00102414	Gemcitabine Plus Carboplatin	Carboplatin Monotherapy	Completed
A Randomized, Open-Label Study Comparing the Combination of YONDELIS and DOXIL/CAELYX With DOXIL/CAELYX Monotherapy for the Treatment of Advanced-Relapsed Epithelial Ovarian, Primary Peritoneal, or Fallopian Tube Cancer	Janssen Research & Development, LLC	NCT01846611	trabectedin + PLDH	PLDH	Not yet recruiting
A Phase II Randomized Controlled Clinical Trial of Carboplatin and Paclitaxel or Carboplatin and Gemcitabine in Platinum-sensitive, Recurrent Ovarian, Fallopian Tube, and Primary Peritoneal Cancer	Korean Gynecologic Oncology Group	NCT01570582	Carboplatin and Paclitaxel	Carboplatin and Gemcitabine	Active, not recruiting
A Randomized Phase II Evaluation of Topotecan Administered Daily x 5 Every 3 Weeks vs Weekly Topotecan in the Treatment of Recurrent Platinum-Sensitive Ovarian, Fallopian Tube, or Primary Peritoneal Cancer	Gynecologic Oncology Group	NCT00114166	Topotecan Administered Daily x 5 Every 3 Weeks	vs Weekly	Completed

Appendix 15. WinBUGS code

OS and PFS

```
model{
for(i in 1:ndp){
prec[i]<- 1/(se[i]*se[i])
lhr[i]~dnorm(md[i],prec[i])
md[i] <- d[t[i]] - d[b[i]]
rhat[i] <- lhr[i] * prec[i]
dev[i] <- (lhr[i] - md[i])*(lhr[i] - md[i])/(se[i]*se[i])
}
resdev <- sum(dev[])
d[1]<-0
for (k in 2:nt){
d[k] ~ dnorm(0,0.001)
}
for (c in 1:nt-1){
for (k in (c+1):nt){
lhzr[c,k] <- d[k] - d[c]
HR[c,k] <- exp(lhzr[c,k])
}
}
}
```

Overall response rate and all safety outcomes

```
model{
for(i in 1:ns){
delta[i,t[i,1]]<-0
mu[i] ~ dnorm(0,0.0001)
for (k in 1:na[i]) {
```

```
r[i,t[i,k]] ~ dbin(p[i,t[i,k]],n[i,t[i,k]])

logit(p[i,t[i,k]])<-mu[i] + delta[i,t[i,k]]

rhat[i,t[i,k]]<- p[i,t[i,k]] * n[i,t[i,k]]

resdev[i,k]<- 2 * (r[i,t[i,k]] * (log(r[i,t[i,k]]) - log(rhat[i,t[i,k]])) + (n[i,t[i,k]] - r[i,t[i,k]]) * (log(n[i,t[i,k]] - r[i,t[i,k]]) - log(n[i,t[i,k]] - rhat[i,t[i,k]])))

}

sumdev[i]<-sum(resdev[i,1:na[i]])

for (k in 2:na[i]) {

delta[i,t[i,k]] <- d[t[i,k]] - d[t[i,1]]

}

}

sumdevtot<- sum(sumdev[])

d[1]<-0

for (k in 2:nt){

d[k] ~ dnorm(0,0.0001)

}

for (i in 1:ns) {

mu1[i] <- mu[i] * equals(t[i,1],1)

}

for (c in 1:(nt-1)) { for (k in (c+1):nt) { or[c,k] <- exp(d[k] - d[c] ) }}

}
```