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Abstract

Topotecan, pegylated liposomal doxorubicin hydrochloride and paclitaxel for second-line or subsequent treatment of advanced ovarian cancer: a systematic review and economic evaluation

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Objectives: To examine the clinical effectiveness and cost-effectiveness of intravenous formulations of topotecan monotherapy, pegylated liposomal doxorubicin hydorocholoride (PLDH) monotherapy and paclitaxel used alone or in combination with a platinum-based compound for the second-line or subsequent treatment of advanced ovarian cancer.
Data sources: Electronic databases covering publication years 2000–4. Company submissions.
Review methods: Seventeen databases were searched for randomised controlled trials (RCTs) and systematic reviews for the clinical effectiveness of PLDH, topotecan and paclitaxel and economic evaluations of the cost-effectiveness of PLDH, topotecan and paclitaxel. Selected studies were quality assessed and data extracted, as were the three company submissions. A new model was developed to assess the costs of the alternative treatments, the differential mean survival duration and the impact of health-related quality of life. Monte-Carlo simulation was used to reflect uncertainty in the cost-effectiveness results.
Results: Nine RCTs were identified. In five of these trials, both the comparators were used within their licensed indications. Of these five, three included participants with both platinum-resistant and platinum-sensitive advanced ovarian cancer, and a further two only included participants with platinum-sensitive disease. The comparators that were assessed in the three trials that included both subtypes of participants were PLDH versus topotecan, topotecan versus paclitaxel and PLDH versus paclitaxel. In the further two trials that included participants with the subtype of platinum-sensitive disease, the comparators that were assessed were single-agent paclitaxel versus a combination of cyclophosphamide, doxorubicin and cisplatin (CAP) and paclitaxel plus platinum-based chemotherapy versus conventional platinum-based therapy alone. A further four trials were identified and included in the review in which one of the comparators in the trial was used outside its licensed indication. The comparators assessed in these trials were oxaliplatin versus paclitaxel, paclitaxel given weekly versus every 3 weeks, paclitaxel at two different dose levels and oral versus intravenous topotecan. Four studies met the inclusion criteria for the cost-effectiveness review. The review of the economic evidence from the literature and industry submissions identified a number of significant limitations in existing studies assessing the cost-effectiveness of PLDH, topotecan and paclitaxel. Analysis 1 assessed the cost-effectiveness of PLDH, topotecan and paclitaxel administered as monotherapies. Sensitivity analysis was undertaken to explore the impact of patient heterogeneity (e.g. platinum-sensitive and platinum-resistant/refractory patients), the inclusion of additional trial data and alternative assumptions regarding treatment and monitoring costs. In the base-case results for Analysis 1, paclitaxel monotherapy emerged as the cheapest treatment. When the incremental cost-effectiveness ratios (ICERs) were estimated, topotecan was dominated by PLDH. Hence the options considered in the estimation of the ICERs were paclitaxel and PLDH. The ICER for PLDH compared with paclitaxel was £7033 per quality-adjusted life-year (QALY) in the overall patient population (comprising platinum-sensitive, -refractory and -resistant patients). The ICER

was more favourable in the platinum-sensitive group (£5777 per QALY) and less favourable in the platinum-refractory/resistant group (£9555 per QALY). The cost-effectiveness results for the base-case analysis were sensitive to the inclusion of additional trial data. Incorporating the results of the additional trial data resulted in less favourable estimates for the ICER for PLDH versus paclitaxel compared with the base-case results. The ICER of PLDH compared with paclitaxel was £20,620 per QALY in the overall patient population, £16,183 per QALY in the platinum-sensitive population and £26,867 per QALY in the platinum-resistant and -refractory population. The results from Analysis 2 explored the cost-effectiveness of the full range of treatment comparators for platinum-sensitive patients. The treatment options considered in this model comprised PLDH, topotecan, paclitaxel–monotherapy, CAP, paclitaxel/platinum combination therapy and platinum monotherapy. Owing to the less robust approaches that were employed to synthesise the available evidence and the heterogeneity between the different trials, the reliability of these results should be interpreted with some caution. Topotecan, paclitaxel monotherapy and PLDH were all dominated by platinum monotherapy (i.e. higher costs and lower QALYs). After excluding these alternatives, the treatments that remained under consideration were platinum monotherapy, CAP and paclitaxel–platinum combination therapy. Of these three alternatives, platinum monotherapy was the least costly and least effective. The ICER for CAP compared with platinum monotherapy was £16,421 per QALY. The ICER for paclitaxel–platinum combination therapy compared with CAP was £20,950 per QALY.

Conclusions: For participants with platinum-resistant disease there was a low probability of response to treatment with PLDH, topotecan or paclitaxel. Furthermore, there was little difference between the three comparators in relation to overall survival. The comparators did, however, differ considerably in their toxicity profiles. Given the low survival times and response rates, it appears that the maintenance of quality of life and the control of symptoms and toxicity are paramount in this patient group. As the three comparators differed significantly in terms of their toxicity profiles, patient and physician choice is also an important element that should be addressed when decisions are made regarding second-line therapy. It can also be suggested that this group of patients may benefit from being included in further clinical trials of new drugs. For participants with platinum-sensitive disease there was a considerable range of median survival times observed across the trials. The most favourable survival times and response rates were observed for paclitaxel and platinum combination therapy. This suggests that treatment with combination therapy may be more beneficial than treatment with a single-agent chemotherapeutic regimen. In terms of single-agent compounds, the evidence suggests that PLDH is more effective than topotecan. Evidence from a further trial that compared PLDH and paclitaxel suggests that there is no significant difference between these two comparators in this trial. The three comparators did, however, differ significantly in terms of their toxicity profiles across the trials. Although treatment with PLDH may therefore be more beneficial than that with topotecan, patient and physician choice as to the potential toxicities associated with each of the comparators and the patient's ability and willingness to tolerate these are of importance. Assuming the NHS is willing to pay up to £20,000–40,000 per additional QALY, PLDH appears to be cost-effective compared with topotecan and paclitaxel monotherapy, in terms of the overall patient population and the main subgroups considered. The cost-effectiveness results for the base-case analysis were sensitive to the inclusion of additional trial data. Incorporating the results of additional trial data gave less favourable estimates for the ICER for PLDH versus paclitaxel monotherapy, compared with the base-case results. Although the ICER of PLDH compared with paclitaxel monotherapy was less favourable, PLDH was still cost-effective compared with topotecan and paclitaxel monotherapy. For platinum-sensitive patients, the combination of paclitaxel and platinum appears to be cost-effective. On the strength of the evidence reviewed here, it can be suggested that participants with platinum-resistant disease may benefit from being included in further clinical trials of new drugs. To assess the effectiveness of combination therapy against a single-agent non-platinum-based compound, it can be suggested that a trial that compared paclitaxel in combination with a platinum-based therapy versus single-agent PLDH would be a reasonable option.

Contents

Glossary and list of abbreviations

Glossary

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

Absolute risk reduction (ARR) The difference between the event rates in the two groups; where the adverse event rate is less in the intervention group this suggests the intervention is beneficial.

Adverse effect/adverse event An abnormal or harmful effect caused by, and attributable to, exposure to a chemical (e.g. a drug), which is indicated by some result such as death, a physical symptom or a visible illness. An event may be classified as adverse if it causes functional or anatomical damage, causes irreversible changes in the homeostasis of the organism or increases the susceptibility of the organism to other chemical or biological stress.

Alopecia Baldness/loss of body hair.

Anaemia An abnormally low level of red blood cells in the blood. Red blood cells are responsible for carrying oxygen around the body.

Anthracyclines A group of antibiotics that have a tetrahydronaphthacenedione ring structure attached by a glycosidic linkage to a sugar molecule. These antibiotics have potent antineoplastic activity. They intercalate with DNA, and so adversely affect many DNA functions. Furthermore, they interact with cell membranes, thereby altering their functions and generating hydrogen peroxide and hydroxy radicals, which are highly destructive to cells.

Antineoplastic Inhibiting or preventing the development of neoplasms and checking the maturation and proliferation of malignant cells.

Arthralgia Joint pain.

Bias Deviation of results or inferences from the truth, or processes leading to such deviation. Any trend in the collection, analysis, interpretation, publication or review of data that can lead to conclusions that are systematically different from the truth.

Blinding A procedure used in clinical trials to avoid the possible bias that might be introduced if the patient and/or doctor knew which treatment the patient would be receiving. If neither the patient nor the doctor is aware of which treatment has been given, the trial is termed 'double-blind'. If only one of the patient or doctor is aware, the trial is called 'single-blind'.

CA-125 A cell surface marker found in serum.

Carcinoma A cancerous growth.

Censored data Censorship means that the event does not occur during the period of observation and the time of event is unknown, but these cases are incorporated into the analysis. Those whose event is unknown, or who are lost to the study (right censored) or new patients introduced into the study (left censored), add to the information on patients whose event time is known (uncensored) at each time interval.

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

Co-intervention In a randomised controlled trial, the application of additional diagnostic of therapeutic procedures to members of either the experimental or reference group, or to both groups.

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

continued

Glossary *continued*

Confidence interval (CI) A measure of precision of statistical estimate

Confounding (1) The masking of an actual association or (2) false demonstration of an apparent association between the study variables when no real association between them exists.

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.

Cycle Chemotherapy is usually administered at regular intervals. A cycle is a course of chemotherapy followed by a period in which the body recovers from the adverse events of the drug(s).

Cytotoxic Toxic to cells. This term is used to describe drugs that kill cancer cells or slow their growth.

Debulking Removal by surgery 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.

End-point A clearly defined outcome or event associated with an individual in a medical investigation.

EORTC The European Organization for Research and Treatment of Cancer (EORTC) is an organisation set up to conduct, develop, coordinate and stimulate laboratory and clinical research in Europe to improve the management of cancer and related problems by increasing survival but also quality of life of patients.

Evaluable disease Unidimensionally measurable lesions, masses with margins not clearly defined, lesions with both diameters = 0.5 cm, lesions on scan with either diameter smaller than the distance between cuts, palpable lesions with either diameter $\geqslant$ 2 cm; malignant ascites or pleural effusion in conjunction with serum levels of CA-125 >100 U/ml in the absence of cirrhosis (CA-125 is a glycoprotein antigen expressed by some ovarian cancers).

External validity The ability to generalise the results from a particular experiment to a larger population.

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.

Forest plot The way in which results from a meta-analysis are often presented. Results are displayed graphically as horizontal lines representing the 95% or 99% confidence intervals of the effect of each trial (strictly the 95% or 99% confidence intervals of a relative risk of the intervention group compared with the control group).

Hazard ratio Measure of relative risk used in survival studies.

Heterogeneous Of differing origins or different types.

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

continued

Glossary *continued*

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

Histology The examination of the cellular characteristics of a tissue.

Incidence The number of new events (new cases of a disease) in a defined population, within a specified period of time.

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.

Intention-to-treat analysis method An analysis of a clinical trial where participants are analysed according to the group to which they were initially randomly allocated, regardless of whether or not they dropped out, fully complied with the treatment or crossed over and received the other treatment.

Interim analysis A formal statistical term indicating an analysis of data part-way through a study.

Internal validity The degree to which a study is logically sound and free of confounding variables.

International Federation of Gynaecologists and Obstetricians (FIGO) This organisation defines staging in gynaecological cancer and collates information about treatment and survival from a group of collaborating European centres (including some in the UK).

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

Localised disease Disease that is confined to a small part of an organ or tissue.

Leucopenia An abnormally low level of leucocytes in the blood. Leucocytes are white blood cells which help to fight infections within the body.

Lymph nodes Small organs that act as filters in the lymphatic system. Lymph nodes close to a primary tumour are often the first sites to which a tumour spreads.

Measurable disease The presence of lesion(s) that can be unidimensionally or bidimensionally measured by physical examination, echography, radiography or computed tomographic scan.

Meta-analysis A quantitative method for combining the results of many studies into one set of conclusions.

Metastasis/metastatic cancer Cancer that has spread to a site distant from the original site.

Mortality rate The proportion of deaths in a population or in a specific number of the population per unit of time.

Myalgia Muscle pain.

Neuropathy A term to describe any disorder of the neurones or nerves of the body.

continued

Glossary *continued*

Neutropenia An abnormally low level of neutrophils in the blood. Neutrophils belong to a group of white blood cells known as granulocytes, which are important in fighting infections within the body.

Number needed to treat (NNT) In clinical treatment regimens, the number of patients with a specified condition who must follow the specified regimen for a prescribed period in order to prevent occurrence of specified complications or adverse outcomes of the condition. Mathematically equal to 1/(risk difference).

Palliative Anything that serves to alleviate symptoms due to the underlying cancer but is not expected to act as a cure.

Palmar–plantar erythrodysesthesia (PPE) A condition characterised by an intense, often painful macular reddening that primarily involves the palms of the hands and soles of the feet. The skin changes may range from a painful desquamating dermatitis, with mild erythema and hyperaemia, to severe crusting, ulceration and epidermal necrosis. The mechanism of this condition is not known but is believed to be a result of microtrauma within the tissue leading to leaky blood vessels.

Paresthesia Numbness/tingling or 'pins and needles' sensation of the skin.

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.

Placebo A 'dummy' treatment administered to the reference group in a controlled clinical trial in order to distinguish the specific and non-specific effects of the experimental treatment (i.e. the experimental treatment must produce better results than the placebo in order to be considered effective).

Platinum-based chemotherapy Treatment with platinum-based drugs such as cisplatin or carboplatin.

Platinum-resistant disease Disease which responded to first-line platinum-based chemotherapy but relapsed within 6 months.

Platinum-sensitive disease Disease which responded to first-line platinum-based therapy but which relapsed after longer than 6 months.

Prevalence The measure of the proportion of people in a population who have some attribute or disease at a given point in time or during some period.

Progressive disease Used to describe a tumour that continues to grow or where a patient develops more metastatic sites.

Progression-free survival The time from the start of study drug administration to documented disease progression or death due to any cause while the participant was on study drug or during the long-term follow-up period.

Prophylaxis/prophylactic treatment An intervention (i.e. any act, procedure, drug or equipment) used to guard against or prevent an unwanted outcome.

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.

continued

Glossary *continued*

***p*-Value** In the context of significant tests, the *p*-value represents the probability that a given difference is observed in a study sample, when such a difference does not exist in the relevant population. Small *p*-values indicate stronger evidence to reject the null hypothesis of no difference.

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.

Quality of Life Questionnaire (QLQ-C30) A self-administered quality of life questionnaire developed by the EORTC for the measurement of health-related quality of life. The questionnaire consists of nine scales – one global QoL scale, five function scales (physical, role, emotional, cognitive and social), and three symptom scales (fatigue, pain and nausea/vomiting) and questions on six single items (dyspnoea, sleep disturbance, appetite loss, constipation, diarrhoea and financial impact). Higher scores on the function scales indicate better functioning and QoL, whereas higher scores on the symptom scales indicate the presence of more symptoms.

Random allocation A method of allocation to ensure that the treatment assignment is unpredictable.

Randomised controlled trial (RCT) (also randomised clinical trial) These are designed to measure the efficacy and safety of particular types of healthcare interventions, by randomly assigning people to one of two or more treatment groups and, where possible, blinding them and the investigators to the treatment that they are receiving. The outcome of interest is then compared between the treatment groups. Such studies are designed to minimise the possibility of an association due to confounding and remove the many sources of bias present in other study designs.

Relative risk (RR) Also called the risk ratio. A common way of estimating the risk of experiencing a particular effect or result. An RR >1 means a person is estimated to be at an increased risk, whereas an RR <1 means a person is apparently at decreased risk. An RR of 1.0 means there is no apparent effect on risk at all, e.g. if RR = 4.0, the result is about four times as likely to happen, and 0.4 means it is four times less likely to happen. The RR is expressed with confidence intervals, e.g. RR = 3.0 (95% CI: 2.5 to 3.8). This means the result is three times as likely to happen – anything from 2.5 times as likely, to 3.8 times as likely. It is statistically significant. On the other hand, RR = 3.0 (95% CI: 0.5 to 8.9), means it is also estimated to be three times as likely, but it is not statistically significant. The chances go from half as likely to happen (0.5 a decreased chance), to nearly nine times as likely to happen (8.9 an increased chance).

Relative risk reduction (RRR) Alternative way of expressing relative risk. It is calculated as follows: RRR = (1 – RR) × 100%. The RRR can be interpreted as the proportion of the initial or baseline 'risk' which was eliminated by a given treatment or intervention, or by avoidance of exposure to a risk factor.

Recurrent disease Disease that reappears after a period during which it has shown no measurable/detectable signs.

Refractory disease Disease which does not respond or progresses during first-line platinum-based chemotherapy.

Risk difference The difference (absolute) in the proportion with the outcome between the treatment and control groups. If the outcome represents an adverse event and the risk difference is negative (below zero), this suggests that the treatment reduces the risk – referred to as the absolute risk reduction.

continued

Glossary *continued*

Salvage therapy Any therapy given in the hope of getting a response when the 'standard' therapy has failed. This may overlap with 'second-line' therapy, but could also include therapy given for patients with refractory disease, i.e. disease that has never responded to first-line therapy.

Second-line therapy 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. Depending on the circumstances, patients may be treated with the same regimen again, or a different regimen. In either case this is defined as second-line therapy.

Stable disease No change or less than a 25% change in measurable lesions for at least 4–8 weeks with no new lesions appearing.

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.

Stomatitis Inflammation/ulceration of the mouth.

Taxane naïve Patients who had not received a taxane as part of first-line therapy.

Thrombocytopenia An abnormally low level of platelets in the blood. Platelets play a role in the blood clotting process.

Time to progression The length of time from the start of treatment (or time from randomisation within the context of a clinical trial) until tumour progression.

Topoisomerase inhibitors Drugs that target the DNA topoisomerase I enzyme which is involved in the replication of DNA. This leads to the inhibition of cell division.

Utility A measure of the strength of an individual's preference for a given health state or outcome. Utilities assign numerical values on a scale from 0 (death) to 1 (optimal or 'perfect' health), and provide a single number that summarises health-related quality of life. Hence utility has been described as a global measure of health-related quality of life. Sometimes 'utility' is only used to refer to preferences (on the 0–1 scale) that are elicited using methods which introduce risky scenarios to the respondent (standard gamble), with the term 'values' used to refer to other types of preferences.

Values An alternative measure of the strength of an individual's preference for a given health state or outcome. In contrast to utilities, values reflect preferences elicited in a risk-less context.

List of abbreviations

ACER	average cost-effectiveness ratio
ASCO	American Society of Clinical Oncology
AUC	area under the curve
BMS	Bristol Myers Squibb
BNF	British National Formulary
CAP	cyclophosphamide, doxorubicin and cisplatin
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
COSTART	Coding Symbols for Thesaurus of Adverse Reactions Terms
CR	complete response
CT	computed tomography
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organization for Research and Treatment of Cancer
FIGO	International Federation of Gynaecologists and Obstetricians
G-CSF	granulocyte colony-stimulating factor
GFR	glomerular filtration rate
GSK	GlaxoSmithKline
HR	hazard ratio
ICER	incremental cost-effectiveness ratio
IRFMN	Instituto Mario Negri
ITT	intention-to-treat
KPS	Karnofsky performance status
LYG	life-year gained
MCUE	micturating cystourogram
MRC CTU	Medical Research Council Clinical Trials Unit
MRI	magnetic resonance imaging
MTC	mixed treatment comparison
NC	no change
NCI CTC	National Cancer Institute Common Toxicity Criteria
NE	not evaluable
NICE	National Institute for Health and Clinical Excellence
NR	no response
OR	odds ratio
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PLDH	pegylated liposomal doxorubicin hydrochloride
PPE	palmar–plantar erythrodysesthesia
PR	partial response
Pt-r	platinum-refractory (disease)
QALY	quality-adjusted life-year
QLQ-C30	quality of life questionnaire C30

continued

List of abbreviations *continued*

QoL	quality of life
Q-TwiST	quality-adjusted time without symptoms or toxicity
RCT	randomised controlled trial
RR	relative risk
SD	stable disease
TTP	time to progression
TwiST	time without symptoms or toxicity
WTP	willingness to pay

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Executive summary

Background

Ovarian cancer is the most common gynaecological cancer, with an annual incidence of 21.9 per 100,000 women in England and 26.7 per 100,000 in Wales (2000 figures). The prognosis is generally poor, owing to the advanced stage of disease at detection in most cases, and the UK 5-year survival rate is only around 30%. The current guidance issued by the National Institute for Health and Clinical Excellence is that first-line chemotherapy should include either paclitaxel in combination with a platinum-based chemotherapy regimen, or a platinum-based regimen alone (carboplatin or cisplatin). As the majority of patients ultimately relapse and require treatment with second-line therapy, the guidance is that patients who have received recommended first-line therapy should not be treated with the same agents. Pegylated liposomal doxorubicin hydrocholoride (PLDH), topotecan and paclitaxel may therefore be considered alongside other drugs licensed for second-line therapy in advanced ovarian cancer. Participants who had not received paclitaxel as a component of first-line therapy may receive it as second-line.

Objectives of the review

The objectives were to examine the clinical effectiveness and cost-effectiveness of intravenous formulations of topotecan monotherapy, PLDH monotherapy and paclitaxel used alone or in combination with a platinum-based compound for the second-line or subsequent treatment of advanced ovarian cancer.

Methods

Search strategy

Seventeen databases were searched for randomised controlled trials (RCTs) and systematic reviews for the clinical effectiveness of PLDH, topotecan and paclitaxel and economic evaluations of the cost-effectiveness of PLDH, topotecan and paclitaxel. Previous searches were conducted up to 2000. The current searches were therefore limited to publication years 2000–4.

Inclusion/exclusion criteria

Two reviewers independently screened all titles and/or abstracts including economic evaluations. The full text of any study judged to be relevant by either reviewer was obtained and assessed for inclusion or exclusion. Disagreements were resolved through discussion. For the assessment of clinical effectiveness, RCTs that compared topotecan monotherapy, PLDH monotherapy or paclitaxel administered alone or in combination with a platinum-based compound with any other comparator including usual supportive care were included. For the assessment of cost-effectiveness, a broader range of studies was considered.

Data extraction and quality assessment

Data from included studies were extracted by one reviewer and independently checked for accuracy by a second reviewer. Individual studies were assessed for quality by one reviewer and independently checked for accuracy by a second.

Methods of analysis/synthesis

The results of the data extraction and quality assessment of the RCTs were presented in structured tables and as a narrative summary. For the cost-effectiveness section of the report, details of each identified published economic evaluation, together with a critical appraisal of its quality, were presented in structured tables.

Handling company submissions

All the clinical effectiveness data included in the company submissions from Bristol Myers Squibb, GlaxoSmithKline and Schering-Plough Ltd were assessed. Where this met the inclusion criteria it was included in the clinical effectiveness review. All economic evaluations (including accompanying models) included in the company submissions were assessed and a detailed assessment of the assumptions underlying the submitted analyses was undertaken. A new model was developed to assess the costs of the alternative treatments, the differential mean survival duration and the impact of health-related quality of life. Monte-Carlo simulation was used to reflect uncertainty in the cost-effectiveness results.

Results

A total of 2542 titles and abstracts were screened for inclusion in the review of clinical and cost-effectiveness; 194 studies were ordered as full papers and assessed in detail. Nine RCTs were identified. In five of these trials, both the comparators were used within their licensed indications. Of these five trials, three of the trials included participants with both platinum-resistant and platinum-sensitive advanced ovarian cancer, and a further two trials only included participants with platinum-sensitive disease. The comparators that were assessed in the three trials that included both subtypes of participants were PLDH versus topotecan, topotecan versus paclitaxel and PLDH versus paclitaxel. In the further two trials that included participants with the subtype of platinum-sensitive disease, the comparators that were assessed were single-agent paclitaxel versus a combination of cyclophosphamide, doxorubicin and cisplatin (CAP) and paclitaxel plus platinum-based chemotherapy versus conventional platinum-based therapy alone.

A further four trials were identified and included in the review in which one of the comparators in the trial was used outside its licensed indication. The comparators assessed in these trials were oxaliplatin versus paclitaxel, paclitaxel given weekly versus every 3 weeks, paclitaxel at two different dose levels and oral versus intravenous topotecan.

Clinical effectiveness

Trials including participants with refractory, resistant and platinum-sensitive disease

PLDH versus topotecan

PLDH was marginally more effective than topotecan in terms of overall survival in the total trial population that included both participants with platinum-sensitive and platinum-resistant disease. However, this result appears to be driven by the more highly significant benefit of PLDH treatment in the platinum-sensitive subgroup of participants. For participants with platinum-resistant disease there was no statistically significant difference in overall survival between the PLDH and topotecan treatment groups. There were also no statistically significant differences between the PLDH and topotecan groups in terms of progression-free survival, response or quality of life.

In terms of toxicities reported during the trial, the rates of grade 3 stomatitis, palmar-plantar erythrodysesthesia (PPE), mucous membrane disorder and rash were significantly higher in the PLDH treatment arm. In the topotecan arm the rates of grade 3 and 4 haematological toxicities and grade 3 alopecia and fever were significantly higher.

Topotecan versus paclitaxel

There were no statistically significant differences between the two treatment groups in terms of overall survival, time to progression, response rate or response duration. The point estimates for all of these outcomes favoured treatment with topotecan over paclitaxel. However, there was a significant difference between the two treatment groups in terms of time to response, favouring paclitaxel.

In this trial, treatment with topotecan was associated with significantly more grade 3 and 4 haematological toxicities compared with paclitaxel. In addition, grades 3 and 4 nausea, vomiting, constipation, abdominal pain, asthenia, fatigue and fever/infection were significantly higher in this group. Treatment with paclitaxel was associated with significantly more grade 3 and 4 alopecia, arthralgia, myalgia and skeletal pain compared with the topotecan treatment arm.

PLDH versus paclitaxel

In relation to overall survival, there was no significant difference between the PLDH and paclitaxel treatment groups. Treatment with PLDH was associated with significantly more grade 3 PPE, ascites, stomatitis and dyspnoea compared with treatment with paclitaxel. Treatment with paclitaxel was associated only with a higher incidence of grade 3 alopecia relative to PLDH. This trial was terminated prematurely, therefore the results should be interpreted with caution.

Trials including participants with platinum-sensitive disease only

Paclitaxel versus CAP

CAP was more effective than paclitaxel in terms of both overall and progression-free survival. There were no significant differences between the two treatment regimens in terms of response. However, the incidence of grade 3 and 4 haematological toxicities and grade 2 nausea and vomiting was significantly higher in the CAP treatment arm. Treatment with paclitaxel was associated with significantly higher rates of alopecia and allergic reactions relative to treatment with CAP.

Paclitaxel in combination with platinum-based chemotherapy versus platinum-based therapy alone
Paclitaxel in combination with platinum-based chemotherapy was more effective than platinum monotherapy in relation to both overall survival and progression-free survival. However, there was no significant treatment benefit observed for combination therapy for response rates or overall quality of life.

Treatment with paclitaxel in combination with platinum was associated with significantly higher rates of grades 2–4 neurological toxicity and alopecia. Treatment with platinum monotherapy was associated with significantly higher rates of haematological toxicity.

Trials in which one of the comparators was used outside the licensed indication
Paclitaxel versus oxaliplatin
There were no statistically significant differences between the paclitaxel and oxaliplatin treatment groups in terms of overall survival, time to progression, response rate, response duration or quality of life. Treatment with paclitaxel was associated with a higher incidence of severe neutropenia, whereas oxaliplatin was associated with higher rates of thrombocytopenia.

Paclitaxel given weekly versus every 3 weeks
There was no significant treatment benefit for either of these regimens as assessed by overall survival, time to progression, response or response duration. Treatment with paclitaxel every 3 weeks was associated with a significantly higher incidence of grade 3 and 4 neutropenia and alopecia, whereas treatment every week was associated with problems with nail changes.

Paclitaxel 175 versus 250 mg/m^2
There were no statistically significant differences between participants treated with the lower dose regimen and those treated with the higher dose regimen for overall survival or progression-free survival. There was a significant benefit in favour of the higher dose regimen for response rates. However, the reporting of grade 3 and 4 haematological toxicities was more common in the higher dose treatment group.

Oral versus intravenous topotecan
There was a significant benefit in favour of intravenous topotecan for overall survival. However, no further significant difference between the two treatment regimens was found for time to progression, response rate, response duration and time to response. Neutropenia and leucopenia occurred frequently in both treatment groups, but were higher in the intravenous treatment group. The rates of grade 3 and 4 nausea, vomiting, diarrhoea and fever were all significantly higher in the oral treatment regimen group compared with the intravenous treatment arm.

Cost-effectiveness

Four studies met the inclusion criteria for the cost-effectiveness review. In addition, separate submissions were received from Bristol Myers Squibb, GlaxoSmithKline and Schering-Plough Ltd. The review of the economic evidence from the literature and industry submissions identified a number of significant limitations in existing studies assessing the cost-effectiveness of PLDH, topotecan and paclitaxel. A new model was developed to address the limitations identified in these sources and to provide a direct comparison of the full range of possible strategies that are relevant to the NHS. The model explored a range of uncertainties and sources of variability that were not fully addressed in existing data sources. Two separate analyses (Analysis 1 and Analysis 2) were required in order to reflect the heterogeneity identified in the different trials and the difficulties encountered in obtaining robust estimates using a consistent approach for the methods of evidence synthesis of the relative treatment effects.

Analysis 1 assessed the cost-effectiveness of PLDH, topotecan and paclitaxel administered as monotherapies. Sensitivity analysis was undertaken to explore the impact of patient heterogeneity (e.g. platinum-sensitive and platinum-resistant/refractory patients), the inclusion of additional trial data (30-57) and alternative assumptions regarding treatment and monitoring costs. In the base-case results for Analysis 1, paclitaxel monotherapy emerged as the cheapest treatment. When the incremental cost-effectiveness ratios (ICERs) were estimated, topotecan was dominated by PLDH. Hence the options considered in the estimation of the ICERs were paclitaxel and PLDH. The ICER for PLDH compared with paclitaxel was £7033 per quality-adjusted life-year (QALY) in the overall patient population (comprising platinum-sensitive, -refractory and -resistant patients). The ICER was more favourable in the platinum-sensitive group (£5777 per QALY) and less favourable in the platinum-refractory/resistant group (£9555 per QALY). The cost-effectiveness results for the base-case analysis were sensitive to the inclusion of trial 30-57. Incorporating the results of trial 30-57 resulted in less favourable estimates for the ICER

for PLDH versus paclitaxel compared with the base-case results. The ICER of PLDH compared with paclitaxel was £20,620 per QALY in the overall patient population, £16,183 per QALY in the platinum-sensitive population and £26,867 per QALY in the platinum-resistant and -refractory population.

The results from Analysis 2 explored the cost-effectiveness of the full range of treatment comparators for platinum-sensitive patients. The treatment options considered in this model comprised PLDH, topotecan, paclitaxel–monotherapy, CAP, paclitaxel/platinum combination therapy and platinum monotherapy. Owing to the less robust approaches that were employed to synthesise the available evidence and the heterogeneity between the different trials, the reliability of these results should be interpreted with some caution. Topotecan, paclitaxel monotherapy and PLDH were all dominated by platinum monotherapy (i.e. higher costs and lower QALYs). After excluding these alternatives, the treatments that remained under consideration were platinum monotherapy, CAP and paclitaxel–platinum combination therapy. Of these three alternatives, platinum monotherapy was the least costly and least effective. The ICER for CAP compared with platinum monotherapy was £16,421 per QALY. The ICER for paclitaxel–platinum combination therapy compared with CAP was £20,950 per QALY.

Conclusions

Clinical effectiveness

Participants with platinum-resistant disease

For participants with platinum-resistant disease there was a low probability of response to treatment with PLDH, topotecan or paclitaxel. Furthermore, there was little difference between the three comparators in relation to overall survival. The comparators did, however, differ considerably in their toxicity profiles. Given the low survival times and response rates, it appears that the maintenance of quality of life and the control of symptoms and toxicity are paramount in this patient group. As the three comparators differed significantly in terms of their toxicity profiles, patient and physician choice is also an important element that should be addressed when decisions are made regarding second-line therapy. It can also be suggested that this group of patients may benefit from being included in further clinical trials of new drugs.

Participants with platinum-sensitive disease

For participants with platinum-sensitive disease there was a considerable range of median survival times observed across the trials. The most favourable survival times and response rates were observed for paclitaxel and platinum combination therapy. This suggests that treatment with combination therapy may be more beneficial than treatment with a single-agent chemotherapeutic regimen. In terms of single-agent compounds, the evidence suggests that PLDH is more effective than topotecan. Evidence from a further trial that compared PLDH and paclitaxel suggests that there is no significant difference between these two comparators in this trial. The three comparators did, however, differ significantly in terms of their toxicity profiles across the trials. Although treatment with PLDH may therefore be more beneficial than that with topotecan, patient and physician choice as to the potential toxicities associated with each of the comparators and the patient's ability and willingness to tolerate these are of importance.

Cost-effectiveness

The following conclusions are possible assuming the NHS is willing to pay up to £20,000–40,000 per additional QALY:

- PLDH appears to be cost-effective compared with topotecan and paclitaxel monotherapy, in terms of the overall patient population and the main subgroups considered.
- The cost-effectiveness results for the base-case analysis were sensitive to the inclusion of trial 30-57. Incorporating the results of trial 30-57 gave less favourable estimates for the ICER for PLDH versus paclitaxel monotherapy, compared with the base-case results. Although the ICER of PLDH compared with paclitaxel monotherapy was less favourable, PLDH was still cost-effective compared with topotecan and paclitaxel monotherapy.
- For platinum-sensitive patients, the combination of paclitaxel and platinum appears to be cost-effective.

Research recommendations

Participants with platinum-resistant disease

On the strength of the evidence reviewed in this assessment, it can be suggested that participants with platinum-resistant disease may benefit from being included in further clinical trials of new drugs.

Participants with platinum-sensitive disease

To assess the effectiveness of combination therapy against a single-agent non-platinum based compound, it can be suggested that a trial that compared paclitaxel in combination with a platinum-based therapy versus single-agent PLDH would be a reasonable option.

Chapter 1

Aim of the review

This review examined the clinical effectiveness and cost-effectiveness of intravenous formulations of topotecan monotherapy (Hycamtin®, GlaxoSmithKline), pegylated liposomal doxorubicin hydrochloride (PLDH) monotherapy (Caelyx®, Schering-Plough, UK; Doxil®, Alza Corporation, USA), and paclitaxel, used alone or in combination with a platinum-based compound (Taxol®, Bristol-Myers Squibb; Paxene®, Mayne Pharma) for the second-line or subsequent treatment of advanced ovarian cancer. The patient population that the review addressed were women who had failed first-line platinum-based chemotherapy.

Chapter 2
Background

Description of underlying health problem

Epidemiology

Ovarian cancer is the most common gynaecological cancer in England and Wales and the fourth most common cause of cancer death in women, accounting for a total of 6% of female cancer deaths. In 2000 there were 5512 new cases in England and 399 in Wales, giving age-standardised rates per 100,000 women of 17.9 [95% confidence interval (CI) 17.4 to 18.4) and 20.6 (95% CI 18.6 to 22.7), respectively.[1] In 2002–3, ovarian cancer accounted for 34,086 hospital episodes, totalling 104,750 bed days, in England.[2] There were 4687 deaths from ovarian cancer in England and Wales in 2000.[1]

Aetiology, pathology and prognosis

Ovarian cancer is generally staged using the International Federation of Gynaecologists and Obstetricians (FIGO) criteria, under which stage I refers to malignant growth which is restricted to the ovaries, and stage IV refers to disease where distant metastasis can be detected (further details of the FIGO staging criteria are available in Appendix 1). Ovarian cancer is often asymptomatic in its early stages and, as a result, over 75% of patients are diagnosed with advanced (stage III or IV) disease. As a result, the 5-year survival rate is significantly poorer than that for other gynaecological cancers at only ~30%.[2]

There are three principal types of ovarian cancers, determined by the primary cell type. The majority of the cancers are epithelial, primarily mucinous or serous carcinomas. Epithelial cancer is by far the most common, accounting for 80% of the cancers observed, and stromal or germ cell tumours each account for around a further 10% of cases.

The primary risk factor for developing ovarian cancer is age, with 80% of cases occurring in women over the age of 50 years and the highest incidence rates in those over the age of 70 years.[3,4] Between 5 and 10% of all cases occur amongst women who are known to be at high risk of the disease due to mutations in the genes BRCA1 and BRCA2, or who carry the hereditary non-polyposis colorectal cancer (HNPCC) gene.

In the 90% of ovarian cancers which are not linked to these genetic bases, a link with incessant ovarian function has been proposed. Factors suspected to be associated with an increased risk, other than age, include an early age at menarche, a late menopause, infertility and the use of fertility drugs.[5]

The factors that are reported to be protective include parity, with nulliparous women having a higher risk than parous women and there being an inverse relationship between parity and risk.[6,7] Breastfeeding may also have a protective effect,[8–10] and the use of oral contraceptives,[11,12] tubal ligation[13] and hysterectomy[13] have all been reported as associated with a reduced risk of ovarian cancer.

Prognostic factors, which may influence both survival and response to treatment, include stage of the disease at diagnosis, level of residual disease after debulking surgery, the grade and histology of the tumour, performance status and age at diagnosis.[14]

An elevated CA125 level is used as a marker in the detection and diagnosis of ovarian cancer, as around 80% of malignant ovarian masses are associated with an elevated CA125 level. Raised levels are also correlated with disease progression. However, CA125 is not specific to ovarian tumours and raised levels also occur in association with other tumours including tumours of the breast.[15]

Current service provision

The majority of patients will be treated with surgery as a first-line intervention. However, it is usually not possible to excise the tumour completely and further therapy is required in the majority of patients. This therapy generally takes the form of first-line platinum-based chemotherapy. Current National Institute for Health and Clinical Excellence (NICE) guidance[16] is that first-line chemotherapy should include either paclitaxel in combination with a platinum-based chemotherapy regimen, or a platinum-based regimen alone. At the present time, about 75% of patients receive paclitaxel and platinum combination therapy as their first-line

chemotherapy regimen and the remainder receive platinum alone or in combination with a different chemotherapeutic agent.

Although first-line chemotherapy achieves a response in ~70–80% of patients, the majority of these will eventually relapse and require second-line therapy. Between 55 and 75% of those who respond to first-line therapy will relapse within 2 years of completing treatment. On the whole, treating a patient who is platinum sensitive with a platinum-based regimen a second or subsequent time can produce a response, but fewer patients will respond and their responses will be of shorter duration. The response to first-line therapy is predictive of the response to second and subsequent courses of treatment with platinum-based therapy. In particular, the length of treatment-free interval and the extent of relapse (the number and volume of tumour sites involved) have been found to be predictive of response to second and subsequent courses of therapy.

Eventually, whether it is while still receiving a first cycle of platinum-based therapy or after a number of such treatments with the same platinum-based regimen, the majority of patients will fail to respond adequately. This is when second-line therapy can be offered. Such treatment is palliative, with the aims of alleviating symptoms and prolonging survival. At this stage of treatment a cure is generally not achieved, and maintenance of quality of life is a key objective of treatment. As the agents used in second-line chemotherapy are likely to cause a range of adverse effects, this consideration is critical. NICE guidance currently recommends the use of either combination paclitaxel–platinum therapy or platinum-therapy alone for the first-line treatment of advanced ovarian cancer.[16] The guidance further recommends that paclitaxel should not be administered as second-line therapy to women who have received this in combination with first-line platinum-based therapy. Where patients have been treated with first-line platinum monotherapy or another chemotherapeutic regimen, paclitaxel may be considered as an option for second-line therapy. Further NICE guidance recommends that topotecan[17] and PLDH[18] be considered alongside other licensed chemotherapeutic agents for second-line therapy following the failure of platinum-based mono- or combination first-line chemotherapy.

Description of new intervention

The interval between the end of first-line chemotherapy and the start of second-line chemotherapy (treatment-free interval) has been widely used for over 10 years to stratify patients entering clinical trials and to influence the clinical management of patients. Patients who relapse after less than 6 months are considered to have platinum-resistant disease, whereas those who relapse after a longer period are considered to have platinum-sensitive disease. Patients who do not respond, or who progress while receiving first-line therapy, are classified as having platinum-refractory disease.

Interventions

The following section of the report summarises the product characteristics for topotecan, PLDH and paclitaxel available from the electronic Medicine Compendium (www.medicines.org.uk/). Further details of the current manufacturers' information provided for health professionals are available in Appendix 2.[19]

Topotecan (Hycamtin)

Topotecan is a water-soluble analogue of camptothecin, which is derived from the oriental tree *Camptotheca acuminta* and is a topoisomerase I inhibitor. This class of drugs inhibits the topoisomerase I enzyme, which is involved in DNA replication and is therefore critically involved in cell replication. Topotecan is currently licensed for use in patients with metastatic ovarian cancer following the failure of first-line or subsequent therapy.

It is usually administered intravenously over a 30-minute period on five consecutive days. The initial recommended dose is 1.5 mg m^2 of body surface area. Treatment is normally given every 3 weeks, and although the recommended minimum treatment is 4 cycles, treatment may continue until disease progression occurs if it is well tolerated.

Contraindications

- A history of severe hypersensitivity reaction to topotecan and/or its excipients.
- Pregnancy or breastfeeding.
- Severe bone marrow depression with baseline neutrophils $<1.5 \times 10^9$/l and/or platelet count $\leq 100 \times 10^9$/l.

Special warnings and special precautions for use

- Topotecan should only be used in units specialised in the administration of cytotoxic chemotherapy and should only be administered under the supervision of a physician experienced in the use of chemotherapy.
- Since haematological toxicity is dose related, full blood counts including platelets should be subject to regular monitoring.

- The use of topotecan in patients with severe renal impairment (creatinine clearance <20 ml/minute) or severe hepatic impairment (serum bilirubin ≥ 10 mg/dl) is not recommended.

Adverse events
- Haematological toxicity is a dose-limiting adverse occurrence. Severe neutropenia, thrombocytopenia and moderate to severe anaemia occur in substantial proportions of patients, but are reversible and do not appear to result in cumulative toxicity.
- Non-haematological adverse events occurring in >5% of patients include nausea, vomiting, diarrhoea, constipation, stomatitis, abdominal pain, fatigue, asthenia and alopecia.

PLDH (Caelyx, Doxil)

PLDH is a stealth liposome-encapsulated form of doxorubicin. Doxorubicin is isolated from cultures of *Streptomyces peucetius* var. *caesius* and is an anthracycline. This is a class of antibiotic that has antineoplastic activity as a result of intercalation with DNA and inhibition of the enzyme topoisomerase II. This class of drugs also affects the fluidity and ion transport function of cell membranes and generates hydroxyl radicals, which are cytotoxic.

PLDH is licensed for the treatment of advanced ovarian cancer in women who have failed a first-line platinum-based chemotherapy regimen. PLDH is usually administered at a dose of 50 mg/m^2 of body surface area once every 4 weeks for as long as disease does not progress and the treatment continues to be tolerated.

Contraindications
- A history of severe hypersensitivity reactions to PLDH and/or its excipients.
- Pregnancy and breastfeeding.

Special warnings and special precautions for use
- It is recommended that all patients receiving PLDH on a regular basis receive regular and frequent electrocardiogram monitoring in conjunction with monitoring of left ventricular ejection fraction by either echocardiography or, preferably, multiple gated arteriography. Where possible injury associated with PLDH therapy is detected, the risk of myocardial injury should be assessed against the benefits of continued therapy.
- Caution should be exercised in treating patients who have impaired cardiac function.
- Caution should be exercised in treating patients who have previously been treated with anthracyclines.

Adverse events
- The principal treatment-related adverse events which are frequently reported are palmar–plantar erythrodysesthesia (PPE) and stomatitis.
- Other adverse events that occur in >5% of patients include nausea, asthenia, rash, vomiting, alopecia, constipation, anorexia, mucous membrane disorder, diarrhoea, abdominal pain, fever, paresthesia, pain, skin discolouration, pharyngitis, dry skin, dyspepsia and somnolence.
- Clinically significant laboratory abnormalities include increases in total bilirubin and serum creatinine levels.

Paclitaxel (Taxol, Paxene)

Paclitaxel is a taxane, a class of drugs that are derived from the Pacific yew tree *Taxus brevifolia*. The taxanes prevent the formation of mitotic spindles interfering with the process of cell division and resulting in cell death. Paclitaxel is licensed in the UK for first-line chemotherapy of ovarian cancer in combination with cisplatin or carboplatin. However, in practice it is usually administered in conjunction with carboplatin for patients who have advanced disease or residual disease following surgery. It is also licensed for second-line chemotherapy after failure of standard platinum first-line therapy. It is usually administered at a dose of 175 mg/m^2 of body surface area as a 3-hour intravenous infusion, followed by a platinum compound. Treatment is usually given every 3 weeks, with patients normally receiving six cycles. Paxene is licensed for the treatment of patients with metastatic carcinoma of the ovary after failure of platinum-containing combination therapy without taxanes.

Contraindications
- A history of severe hypersensitivity reactions to paclitaxel or any other component of the formulation, especially polyethoxylated castor oil.
- Pregnancy or breastfeeding.
- Baseline neutrophils $<1.5 \times 10^9$/l.

Special warnings and special precautions for use
- Paclitaxel should only be administered under the supervision of a physician experienced in the use of cancer chemotherapeutic agents. As significant hypersensitivity reactions may occur, appropriate supportive equipment should be available.
- Patients must be pretreated with corticosteroids, antihistamines and H_2 antagonists.
- Paclitaxel should be administered before cisplatin where they are employed in combination.

- Frequent monitoring of blood counts should be carried out, as bone marrow suppression, and neutropenia in particular, is a dose-limiting toxicity. Patients should not be retreated until neutrophils recover to a level ≥ 1.5×10^9/l and platelets to a level ≥ 10^9/l.
- In patients with mildly abnormal liver function there is no evidence of increased toxicity of paclitaxel when given as a 3-hour infusion. When paclitaxel is given as a longer infusion, increased myelosuppression may be seen in patients with moderate to severe hepatic impairment. Paclitaxel is not recommended for patients with severely impaired hepatic function. No data are available for patients with severe baseline cholestasis.
- Particular care should be taken to avoid the intra-arterial administration of paclitaxel, as animal studies indicated that severe tissue reactions occurred subsequent to intra-arterial administration.
- Severe cardiac abnormalities have been reported rarely. If significant abnormalities develop during paclitaxel administration, appropriate therapy should be instated and continuous cardiac monitoring instated during subsequent therapy. Hypotension, hypertension and bradycardia have been observed during paclitaxel administration, but such patients are usually asymptomatic and do not require treatment. Frequent monitoring of vital signs, especially during the first hour of infusion, is recommended.
- While peripheral neuropathy occurs frequently, the development of severe symptoms is unusual. In such severe cases a dose reduction of 20% is recommended for all subsequent courses of paclitaxel.

Adverse events

- Haematological toxicity in the form of neutropenia and leucopenia is a dose-limiting adverse occurrence.
- Other adverse events include peripheral neuropathy, alopecia, gastrointestinal disturbance, myalgia and arthralgia.
- Hypersensitivity reactions characterised by dyspnoea and hypotension requiring treatment, angiodema and generalised urticaria occur, although these can be reduced in frequency by the use of antihistamine- and corticosteroid-based premedication. Where appropriate premedication has been administered, <1% of patients will experience such events. Where severe hypersensitivity reactions occur, paclitaxel therapy should be discontinued immediately and symptomatic therapy initiated. The patient should not be treated with paclitaxel.

Current service cost

Topotecan

The average cost of the minimum number of four cycles is £6250 per patient, rising to £9250 for the mean number of cycles actually received (5.92 in a recent trial). These figures assume that only 2.7 mg of each 4-mg vial is used, as is the case for a patient with average body surface area.

PLDH

The cost per cycle of therapy for a typical patient is £1627, with the overall cost depending on the number of cycles undertaken.

Paclitaxel

Treatment is normally undertaken on an outpatient basis and drug costs are approximately £1100 per cycle, giving a typical total cost of £6600 per patient. This figure excludes the cost of the platinum drugs, premedication, cost of treating adverse events associated with the drug, wider hospital treatment and VAT.

Comparator/alternative technologies

For patients who require second-line therapy, NICE guidance advises the use of platinum-based therapy except in patients who are initially refractory to this regimen or those who become resistant to platinum-based chemotherapy. The guidance also advises that therapy including paclitaxel should be considered except where this has previously failed. Given that guidance for first-line therapy currently recommends the use of platinum and paclitaxel combination therapy, a majority of patients needing retreatment following relapse will now require alternative second-line therapy. Guidance currently recommends that both PLDH and topotecan be considered as therapy in such cases. Chemotherapeutic agents currently licensed for the treatment of advanced ovarian cancer are treosulfan, hexamethylmelamin, cisplatin, carboplatin, epirubicin, cyclophosphamide and methotrexate.

Chapter 3

Methods for literature review of effectiveness and cost-effectiveness

Search strategy

The literature searches for this systematic review aimed to update the searches of previous NICE technology appraisal reviews on the use of topotecan, PLDH and paclitaxel for the treatment of ovarian cancer.

Date limits were applied to the searches according to the date the literature searches for the previous review had been carried out:

1. Topotecan
   (a) Previous searches conducted August–September 2000
   (b) Current searches limited to publication years 2000–4.
2. PLDH
   (a) Previous searches conducted May–June 2001
   (a) Current searches limited to publication years 2001–4.
3. Paclitaxel
   (a) Previous searches conducted October 2001
   (b) Current searches limited to publication years 2001–4.

The searches aimed to retrieve both published references and ongoing studies. Ongoing research studies were limited to research that had been started after 2000.

The literature searches were carried out in April 2004. There were no limits applied by study design. The following databases were searched to identify studies of topotecan, PLDH and paclitaxel.

Published studies

MEDLINE
PREMEDLINE
EMBASE
CINAHL
Database of Abstracts of Reviews of Effects (DARE)
NHS Economic Evaluation database (NHS EED)
Health Technology Assessment (HTA) database
Cochrane Controlled Trials Register
Cochrane Database of Systematic Reviews
Science Citation Index
Index to Scientific and Technical Proceedings
BIOSIS
Office of Health Economics Health Economic Evaluations Database (OHE HEED)

Ongoing studies

National Research Register
Controlled Trials.com
CancerPortfolio.org
Clinical Trials.gov

The literature searches retrieved 2542 unique references after de-duplication. All references were managed using Endnote software version 6. The full details of the search strategies are given in Appendix 3. In addition, a further systematic search was undertaken to identify published economic evaluations relating to the use of PLDH, topotecan and paclitaxel for second-line therapy for relapsed advanced ovarian cancer. The search strategies used to identify studies are given in Appendix 3.

Inclusion and exclusion criteria

Two reviewers independently screened all titles and abstracts. Full paper texts of any titles/abstracts that were considered relevant by either reviewer were obtained where possible. The relevance of each study was assessed according to the criteria set out below. Studies that did not meet all the criteria were excluded and their bibliographic details are listed with reasons for exclusion in Appendix 4. Any discrepancies were resolved by consensus and if necessary a third reviewer was consulted.

Interventions

This review covers the effectiveness of the following three alternative chemotherapeutic agents, used within their respective licensed indications:

- Intravenous topotecan monotherapy (Hycamtin®, GlaxoSmithKline)

- Pegylated liposomal doxorubicin hydrochloride monotherapy (Caelyx®, Schering-Plough, UK; Doxil®, Alza Corporation, USA)
- Paclitaxel, used alone or in combination with a platinum-based compound (Taxol®, Bristol-Myers Squibb; Paxene®, Mayne Pharma).

The interventions were assessed only as second-line or salvage therapy. Second-line therapy was defined as the second chemotherapy regimen administered either as a result of relapse after first-line platinum-based therapy in platinum-sensitive patients or immediately following on from first-line therapy in patients with platinum-insensitive disease. Salvage therapy was defined as any therapy given in hope of getting a response when the 'standard' therapies had failed. This may overlap with 'second-line' therapy, but could also include therapy given for patients with refractory disease that did not respond to first-line therapy. Studies that assessed two different regimens of the same agent, in terms of either dose, cycle length, period of treatment, route of administration or combination, were also included in the review. Studies in which the chemotherapeutic agent was administered as 'maintenance' therapy following directly on from first-line therapy without evidence of disease progression were excluded.

Comparators

The comparators that were considered included both usual supportive care or any of the following chemotherapeutic agents: cisplatin, carboplatin, treosulfan, epirubicin, hexamethylmelamin, cyclophosphamide or methotrexate. Agents that are licensed for use in the treatment of other cancers but that are currently used off-licence for the treatment of advanced ovarian cancer were only included when they were directly compared with either topotecan, paclitaxel or pegylated liposomal doxorubicin hydrochloride.

Participants

The participants were women with resistant or refractory advanced ovarian cancer who had experienced a progression of disease. This could be after the completion of first-line platinum-based therapy or while still receiving first-line therapy. The different disease subtypes were defined according to the treatment-free interval between the end of first-line chemotherapy and the start of second-line therapy due to disease progression. The three different stratifications were defined as:

- Refractory disease: patients who do not respond or whose disease progresses on first-line platinum-based chemotherapy.
- Resistant disease: patients who respond to first-line platinum-based chemotherapy but relapse within 6 months.
- Platinum-sensitive disease: patients who respond to first line platinum-based chemotherapy but relapse after 6 months.

Study design

Randomised controlled trials (RCTs) that compared topotecan monotherapy, PLDH monotherapy or paclitaxel alone or in combination with a platinum-based compound with any other second-line treatment including best supportive care were considered.

For the assessment of cost-effectiveness, a broader range of studies were considered, including economic evaluations conducted alongside trials, modelling studies and analysis of administrative databases. Only full economic evaluations that compared two or more options and considered both costs and consequences (including cost-effectiveness, cost–utility and cost–benefit analysis) were included.

Outcomes

Data on the following outcomes were included:

- overall survival
- progression-free survival
- response (including complete and partial response)
- quality of life
- adverse effects of treatment (haematological toxicity), including neutropenia, thrombocytopenia, leucopenia and anaemia and non-haematological toxicity, including PPE, nausea, vomiting, diarrhoea, constipation, stomatitis, abdominal pain, mucositis, rash, fatigue, asthenia, alopecia, anorexia and any other adverse events judged to be appropriate, such as infusion associated reactions
- costs from all reported perspectives.

Where the evidence allowed, the use of the interventions in the subgroup of women with relapsed ovarian cancer that is potentially platinum sensitive was considered separately from that of women who are platinum resistant or refractory.

Publication

A full English language paper copy or trial report of the study had to be available for it to be included in the review. Studies which were reported in abstract form only, and where no further information was available, were excluded. Foreign language papers were also excluded.

Data extraction strategy

Data relating to both study design and quality were extracted by one reviewer and independently checked for accuracy by a second. Disagreements were resolved through consensus and if necessary a third reviewer was consulted. Where multiple publications of the same study were identified, data were extracted and reported as a single study.

Quality assessment strategy

The quality of the individual studies was assessed by one reviewer and independently checked for agreement by a second. Disagreements were resolved through consensus, and if necessary a third reviewer was consulted. The quality of the clinical effectiveness studies was assessed according to criteria based on CRD Report No. 4.[20] The quality of the cost-effectiveness studies was assessed according to a checklist updated from that developed by Drummond and colleagues.[21] This checklist reflects the criteria for economic evaluation detailed in the methodological guidance developed by the NICE. Full details of the quality assessment strategy are reported in Appendix 5.

Methods of analysis/synthesis

Clinical effectiveness

Details of the extracted data and quality assessment for each individual study of clinical effectiveness were presented in structured tables and as a narrative description. The possible effects of study quality on the effectiveness data and review findings were discussed. Data were reported separately for each outcome measure. Where sufficient data were available, treatment effects were presented in the form of relative risks (RRs) or hazard ratios (HRs) as appropriate. Ideally, survival data were presented as hazard ratios or median times based on Kaplan–Meier survival curves. However, this was not always possible owing to a lack of appropriate data. Where data were not available, risk ratios and p-values were presented.

Where RR estimates were not presented in the original trial report, they were calculated if sufficient data were available. In some cases the data were also presented in the form of Forest plots, but without pooled estimates.

Owing to the heterogeneity between the studies in terms of comparators, statistical pooling was not performed. Consequently, statistical χ^2 tests of heterogeneity were not performed. The small number of studies also prevented the assessment of publication bias using funnel plots or the Egger test. However, the risk is likely to be low, considering the attempts to locate unpublished data and the fact that unpublished studies in the form of industry submissions were included in the review.

Cost-effectiveness

For the cost-effectiveness section of the report, details of each identified published economic evaluation, together with a critical appraisal of its quality, were presented in structured tables. This included studies based on patient-level data and decision models and included any studies provided by the manufacturers.

For analysis based on patient-level data, the validity of the studies was assessed for the sources of resource use and effectiveness data, the valuation methods used to cost the resource use and value patient benefits, the methods of analysis and generalisability of results. For analysis based on decision models, the critical appraisal was based on a range of questions including:

- structure of model
- time horizon
- details of key input parameters and their sources
- methods of analysis (e.g. handling uncertainty).

Handling the company submissions

All the clinical effectiveness data included in the three company submissions were assessed. Where these met the inclusion criteria, they were included in the clinical effectiveness review. All economic evaluations (including accompanying models) included in the company submissions were critically appraised using the same checklist applied to the published studies. In addition, a detailed analysis was undertaken to explore the cost-effectiveness more fully. This included a rigorous assessment of the assumptions underlying the submitted economic analyses and additional sensitivity analysis to determine the robustness of these findings. Following this analysis, a new model was developed to estimate costs from the perspective of the NHS, and health outcomes in terms of life-years and quality-adjusted life-years (QALYs) for the full range of relevant treatment strategies. The impact of patient heterogeneity (e.g. platinum-sensitive and platinum-resistant/refractory patients) on the cost-effectiveness results was explored in a series of separate analyses.

Chapter 4

Results

Quantity and quality of research available

A total of 2542 titles and abstracts were screened for inclusion in the review of clinical and cost-effectiveness. Of the titles and abstracts screened, 194 studies were ordered as full papers and assessed in detail. Five studies were not received or were unavailable at the time of the assessment. The process of study selection is shown in *Figure 1*.

For the assessment of the clinical effectiveness of topotecan monotherapy, PLDH monotherapy and paclitaxel administered alone or in combination with a platinum-based agent for the second-line or subsequent treatment of advanced ovarian cancer, nine RCTs were identified.

Five of these nine trials assessed comparators that were both used within their licensed indications. These trials were:

- PLDH versus topotecan for the treatment of recurrent epithelial ovarian carcinoma[22,23]
- topotecan versus paclitaxel for the treatment of recurrent epithelial ovarian cancer[24–26]
- PLDH versus paclitaxel for the treatment of epithelial ovarian carcinoma[27]

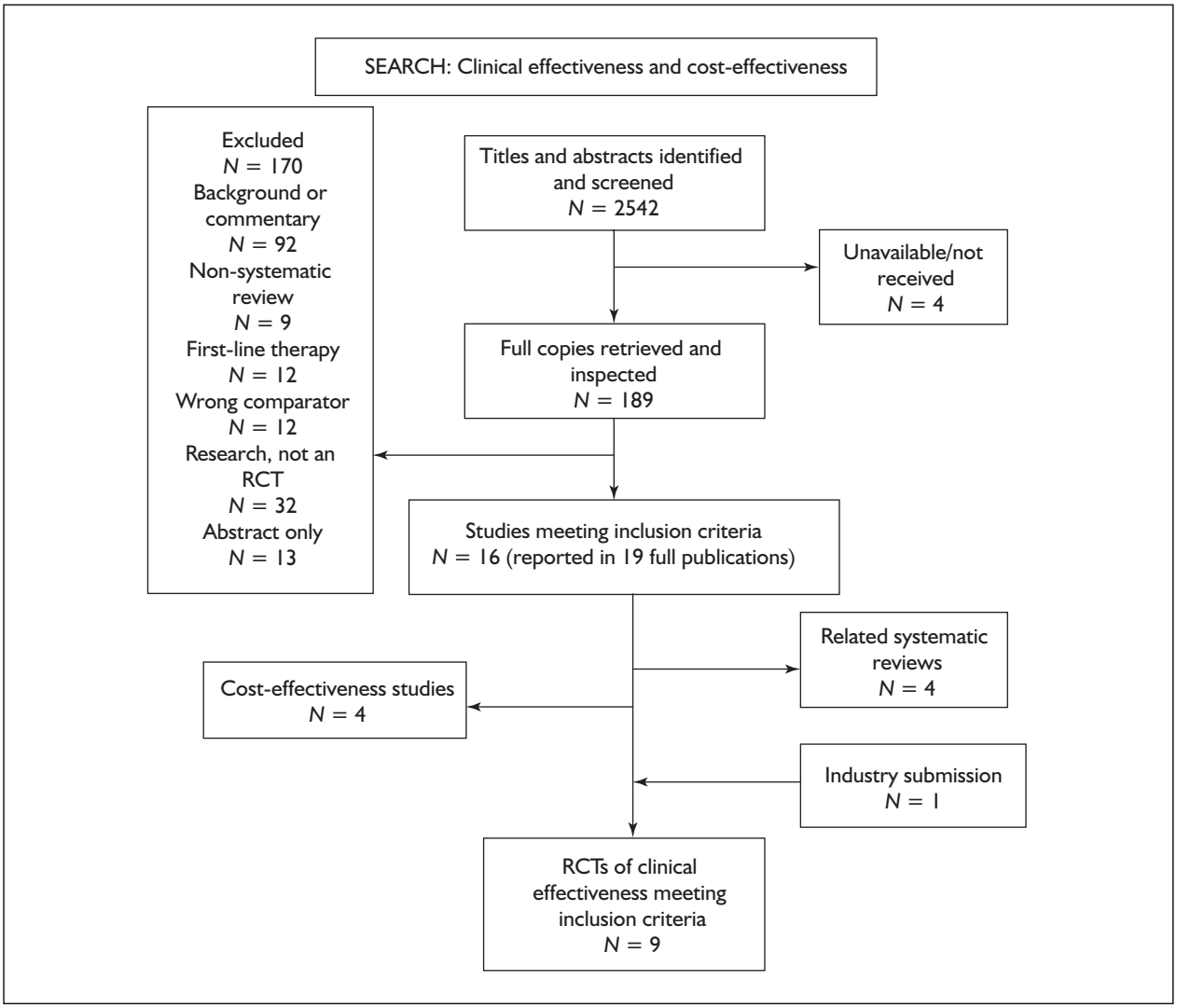

FIGURE 1 *Process of study selection for clinical effectiveness and cost-effectiveness*

- single-agent paclitaxel versus cyclophosphamide, doxorubicin and cisplatin in patients with recurrent ovarian cancer who responded to a first-line platinum-based regimen[28]
- paclitaxel plus platinum-based chemotherapy versus conventional platinum-based chemotherapy in women with relapsed ovarian cancer.[29]

In the four further trials identified, one of the comparators under investigation was used outside the licensed parameters either in terms of indication, dosage, route of administration or length of the chemotherapy cycle. These trials were:

- oxaliplatin versus paclitaxel in patients with platinum pretreated advanced ovarian cancer.[30]
- Single-agent paclitaxel given weekly versus every 3 weeks (and with oral versus intravenous steroid premedication) for patients with ovarian cancer previously treated with platinum[31]
- paclitaxel at two dose levels, the higher dose accompanied by filgrastim at two dose levels, in platinum-pretreated epithelial ovarian cancer[32]
- oral versus intravenous topotecan in patients with relapsed epithelial ovarian cancer.[33]

A full summary of the nine included RCTs is presented in *Table 1* and full data extraction tables are presented in Appendix 6. In addition, a summary of the comparators included in the review is presented in *Table 2*.

Relevant studies reported in abstract form only

In addition to the nine included trials for which there was either a full publication or a trial report available, a further four RCTs were identified that were reported in abstract form only. No further details of the studies were obtainable from the trialists and therefore the trials were excluded from inclusion in the review. The interventions that were assessed in these trials were as follows:

- topotecan versus oxaliplatin: Vermorken and colleagues (2001)[34]
- paclitaxel in combination with doxorubicin versus paclitaxel alone: Torri and colleagues (2000)[35]
- topotecan versus treosulfan: Loibl and colleagues (2003)[36]
- paclitaxel in combination with carboplatin versus carboplatin alone: Gonzalez Martin and colleagues (2003).[37]

Full copies of the abstracts are reproduced in Appendix 7.

Systematic reviews/meta-analysis

In addition to the primary studies, we identified four systematic reviews and/or meta-analyses that included evaluations of PLDH, topotecan and/or paclitaxel for second-line or subsequent therapy in advanced ovarian cancer. These included the two previous HTA reports that this review updates.[38,39] One of the previous reports was on the use of PLDH[38] and the other on the use of topotecan.[39] Of the other two identified reviews, one investigated topotecan[40] and the other assessed all three comparators under consideration in the present report.[41]

Excluded studies

A total of 164 studies were excluded. Of these, 23 were used as background articles for the review. The majority of the other excluded studies were non-randomised studies, contained the wrong comparators or were in first-line therapy. A full list of the excluded studies with the reasons for exclusion is presented in Appendix 4.

Description of included studies

This section of the report provides a summary of the nine included RCTs. For each included study a summary of the trial has been provided followed by a description of the trial quality. The trials have been grouped, first according to whether both the comparators that were evaluated within the trial were used within their licensed indications and second, by whether the trial assessed both participants with platinum-sensitive and platinum-resistant disease, or platinum-sensitive participants only.

PLDH versus topotecan (trial 30-49)

One RCT was identified which compared the efficacy and safety of PLDH to topotecan. The trial had been reported in two abstracts[42,43] and a full publication.[22] In addition, a further three reports were obtained from Schering-Plough as part of the industry submission.[23,44,45]

Description of the trial comparing PLDH and topotecan

Trial 30-49 by Gordon[22] evaluated the efficacy and safety of PLDH compared with topotecan in women with epithelial ovarian carcinoma whose disease did not respond to, or recurred after, treatment with first-line platinum-based chemotherapy. Entry into the trial was based on (1) histologically proven epithelial ovarian carcinoma, (2) measurable or measurable and

TABLE 1 *Summary of included RCTs*

Study	Study design	Participants	Intervention
Trial 30-49 (Schering-Plough) Gordon *et al.*, 2001[22] Schering-Plough, 2004[23]	Phase III, multi-centre, stratified open-label RCT	474 participants with disease that recurred after or failed first-line platinum-based chemotherapy. First-line therapy could include a platinum–taxane combination	PLDH (50 mg m^2/day every 28 days) versus topotecan (1.5 mg m^2/day for 5 days every 21 days)
Trial 039 (GlaxoSmithKline) ten Bokkel Huinink *et al.*, 1997[24] ten Bokkel Huinink *et al.*, 2004[25] Gore *et al.*, 2001[26]	Phase III, multi-centre, stratified open-label RCT	235 participants with disease that recurred after or who failed one platinum-based first-line regimen. All participants were taxane naïve	Topotecan (1.5 mg m^2/day for 5 days every 21 days) versus paclitaxel (175 mg/m^2/day every 21 days)
Trial 30-57 (Schering-Plough) Johnson & Johnson Pharmaceutical Research and Development, 2004[27]	Phase III, multi-centre, stratified open-label RCT. Study terminated after ~50% of the planned participants had been entered owing to poor participant accrual rates	216 participants with disease that recurred after or who failed one platinum-based first-line regimen. All participants were taxane naïve	PLDH (50 mg/m^2/day every 28 days) versus paclitaxel (175 mg/m^2/day every 21 days)
Cantu et al., 2002[28]	Phase II, randomised pilot study	97 participants with disease that recurred or progressed after 12 months had elapsed since the end of first-line platinum-based therapy. All participants were taxane naïve, and had received 2 or 3 prior chemotherapy regimens	Paclitaxel (175 mg/m^2 every 21 days) versus cyclophosphamide (500 mg/m^2), doxorubicin (50 mg/m^2) and cisplatin (50 mg/m^2) (CAP)
The ICON and AGO Collaborators 2003[29]	Phase III, parallel multi-centre RCT	802 participants with disease that recurred after 6 months had elapsed since the end of first-line platinum-based therapy. Participants had received ≥ 1 prior chemotherapy lines that could have included a platinum–taxane combination	Paclitaxel in combination with carboplatin or cisplatin versus carboplatin or cisplatin monotherapy
Piccart *et al.*, 2000[30]	Phase II, multi-centre stratified, open-label trial	86 participants with disease that had recurred or progressed within 12 months of first-line platinum-based therapy. Participants had received either 1 or 2 prior chemotherapy lines. All participants were taxane naïve	Paclitaxel (175 mg/m^2 every 21 days) versus oxaliplatin (130 mg/m^2 every 21 days) (oxaliplatin is not licensed for use in advanced ovarian cancer)

continued

TABLE 1 *Summary of included RCTs (cont'd)*

Study	Study design	Participants	Intervention
Rosenberg *et al.*, 2002[31]	Multi-centre, bi-factorial, stratified RCT	208 participants with disease that recurred or progressed after first-line platinum based therapy. Participants were all taxane naïve and had received only 1 prior chemotherapy line	Paclitaxel weekly (67 mg^2/week) versus paclitaxel every 3 weeks (200 mg/m^2 every 21 days) Participants in both groups were also randomised to either oral steroids 12 and 6 hours before paclitaxel or parenteral steroids 30 minutes before paclitaxel. (paclitaxel is licensed for use on a 3-week cycle)
Omura *et al.*, 2003[32]	Phase III, multi-centre, stratified RCT	449 participants with disease that recurred after or who failed one platinum-based first-line therapy. All participants were taxane naïve	Low dose paclitaxel (135 mg/m^2 every 21 days) versus medium dose paclitaxel (175 mg/m^2 every 21 days) versus high dose paclitaxel (250 mg/m^2 every 21 days) (paclitaxel is licensed for use at a dosage of 175 mg/m^2)
Gore *et al.*, 2002[33]	Multi-centre, stratified, open-label RCT	266 participants with disease that recurred after or who failed one platinum based first-line regimen. First-line therapy could include a platinum-taxane combination	i.v. topotecan (1.5 mg/m^2/day for 5 days every 21 days) versus oral topotecan (2.3 mg/m^2/day for 5 days every 21 days) (topotecan is licensed for use as an i.v. infusion)

TABLE 2 *Summary of the comparators included in the review of clinical effectiveness*

Trial	Paclitaxel	Topotecan (i.v)	PLDH	Paclitaxel combination	Platinum	CAP	Oxaliplatin	Oral topotecan
Overall patient population								
Trial 30-49[22]		✓	✓					
Trial 039[24]	✓	✓						
Trial 30-57[27]	✓		✓					
Platinum-sensitive patients								
Cantu *et al.*[28]	✓					✓		
ICON 4/AGO-OVAR 2.2[29]				✓	✓			
Unlicensed comparator								
Piccart *et al.*[30]	✓						✓	
Rosenberg *et al.*[31]	✓✓							
Omura *et al.*[32]	✓✓							
Gore *et al.*[33]		✓						✓

evaluable disease, (3) recurrence of disease or disease progression indicative of failure of first-line, platinum-based chemotherapy and (4) Karnofsky performance status (KPS) ≤ 60%. Eligible participants underwent radiological imaging [X-ray, computed tomography (CT) scan, magnetic resonance imaging (MRI)] to document baseline disease within 30 days prior to the first dose of the study drug. Participants were randomised to treatment in a 1:1 ratio stratified by platinum sensitivity and the presence or absence of bulky disease (tumour mass >5 cm). Platinum-sensitive disease was defined as a response to initial platinum-based therapy followed by a progression-free interval of >6 months. Platinum-refractory disease was defined as progression or stable disease during the initial platinum-based therapy or relapse within 6 months after completion of therapy. The study included 481 participants: 239 received a 1-hour intravenous infusion of PLDH 50 mg/m^2 every 28 days and 235 received topotecan 1.5 mg/m^2 per day as a 30-minute intravenous infusion for five consecutive days, repeated every 21 days. The majority of participants in both treatment arms received 4–5 chemotherapy cycles. At baseline the two treatment groups were well matched in terms of treatment-free interval, disease bulk, the number of previous chemotherapy regimens, the type of previous chemotherapy agents received, histology and performance status.

The trial was designed as a non-inferiority study with respect to time to progression. The efficacy evaluation of disease status was assessed by radiological imaging every 8 weeks, with participants who achieved a complete or partial response having their radiological imaging repeated at least 4 weeks later to confirm the initial observation of response. Haematological toxicity status was assessed on a weekly basis. In the long-term follow-up of participants reported by Schering-Plough[44] in which the analysis was conducted when 87% of patients had died and 13% of the observations were censored (patients either alive or lost to follow-up), the primary efficacy outcome was overall survival.

Quality of the trial comparing PLDH and topotecan

Trial 30-49 was a reasonably good-quality randomised open-label comparative trial. The only slight issue for concern in the trial was the failure to conduct a true intention-to-treat (ITT) analysis. The analysis of the trial was based on the data from participants who received at least a partial dose of the study drug. However, as this was a non-inferiority trial, the analysis presented may be more conservative than a true ITT analysis. Also, a further submission by Schering-Plough[23] as part of the industry submission, did include a true ITT analysis for the primary efficacy outcome of overall survival. The results of this analysis indicated that there was no significant difference between the results for this outcome when the data were analysed on an ITT basis. The evaluation of trial 30-49 in relation to study quality is shown in *Table 3*. Full details of the quality checklist are available in Appendix 5.

Topotecan versus paclitaxel (trial 039)

One RCT was identified which compared the efficacy and safety of topotecan versus paclitaxel. The trial had been reported in one abstract[46] and three full publications.[24–26] The first publication by ten Bokkel Huinink and colleagues in 1997[24] was a full trial publication that reported on all the efficacy and safety parameters evaluated in the trial. The later report by ten Bokkel Huinink and colleagues in 2004[25] reported the overall survival rates at longer term follow-up of the participants. A further publication by Gore and colleagues in 2001[26] reported the results from third-line therapy, when participants received crossover therapy with the alternative chemotherapy regimen.

Description of the trial comparing topotecan and paclitaxel

The aim of the trial was to compare the efficacy and toxicity of topotecan and paclitaxel in patients with advanced epithelial ovarian cancer who had progressed either while on first-line platinum-based therapy or after one cycle of platinum-based therapy.

The eligibility criteria for entry into the trial were based on a histologically proven diagnosis of measurable disease and a European Cooperative Oncology Group (ECOG) performance status of ≤2. All participants had previously received one platinum-based chemotherapy regimen without a taxane.

A total of 235 eligible participants were randomised into the trial, with stratification based on age, ascites and response to prior platinum chemotherapy (resistant, early, interim or late relapse). Resistant disease was defined as not having a response to initial chemotherapy or having an initial response but then progressing while still on therapy. Relapsed participants were those who had an initial response (complete or partial) and then relapsed within 3 months (early),

TABLE 3 *Quality checklist for included trials*

Quality criteria	Trial 30-49	Trial 039	Trial 30-57	Cantu *et al.*	ICON 4	Piccart et al.	Rosenberg *et al.*	Omura *et al.*	Gore *et al.*
Was the method used to assign participants to the treatment groups really random?	Yes	Yes	Yes	?	Yes	Yes	Yes	Yes	Yes
Was the allocation of treatment concealed?	Yes	Yes	Yes	?	Yes	Yes	Yes	?	Yes
Were details of baseline comparability presented in terms of treatment-free interval, disease bulk, number of previous regiments, age, histology and performance status?	Yes	Yes	Yes	Yes	Partial	Yes	Yes	Partial	Partial
Was baseline comparability achieved for treatment-free interval, disease bulk, number of previous regiments, age, histology and performance status?	Yes	Yes	Yes	Partial	Yes	Partial	Yes	Yes	Yes
Were the eligibility criteria for study entry specified?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Partial	Yes
Were any co-interventions identified that may influence the outcomes for each group?	No	No	No	No	No	No	No	No	No
Were the outcome assessors blinded to treatment allocation?	No	Yes	No	?	?	?	?	?	Yes
Were the individuals who administered the intervention blinded to the treatment allocation?	No	No	No	No	?	No	No	?	No
Were the participants who received the intervention blinded to the treatment allocation?	No	No	No	No	?	No	No	No	No
Was the success of the blinding procedure assessed?	NA	?	N/A	?	?	?	NA	?	?
Were at least 80% of the participants originally included in the randomisation process, followed up in the final analysis?	Yes	Yes	No[2]	Yes	Yes	Yes	Yes	Partial	Yes
Were the reasons for any withdrawals stated?	Yes	Yes	Yes	No	Yes	Yes	Partial	No[d]	Yes
Was an ITT analysis included?	Partial[a]	No	Yes	No	Yes[c]	Yes	Yes	No	Yes

Yes, item adequately addressed; No, item not adequately addressed; Partial, item partially addressed; ?, unclear or not enough information; NA, not applicable.

[a] The published study report is not based on a true ITT analysis in which all of the participants randomised to take part in the trial are included in the analysis. The manufacturer's submission which includes an analysis of the long term follow-up data does include an ITT analysis.

[b] Trial was terminated owing to lack of patient accrual.

[c] Except for toxic effects.

[d] Only ineligible participants described.

3–6 months (interim) or more than 6 months after chemotherapy was stopped (late). A total of 117 participants were randomised to receive 1.5 mg/m^2 topotecan as a 30-minute infusion on five consecutive days every 21 days and 118 to receive 175 mg/m^2 paclitaxel over 3 hours every 21 days. Nine participants did not receive any treatment (five randomised to topotecan and four to paclitaxel) and were not included in the analysis. A further 24 participants (16 in the topotecan arm and eight in the paclitaxel arm) were not evaluated for response, although these participants were included in the denominator when response rates were calculated. The most common reason why participants were not evaluated was adverse events. On the topotecan arm, two participants had no measurable disease and two did not have all their lesions undergo follow-up evaluation; therefore, no evaluation of response was possible. In addition, two of the topotecan group participants had evidence of response, but the response was not allowed because a confirming scan was not performed. There were no paclitaxel group participants not evaluated for these reasons. Duration of treatment was dependent on response. The median number of treatment cycles in both the treatment arms was five, range 1–17 in the topotecan group and 1–12 in the paclitaxel group. Participants whose best response was stable disease after six courses of one regimen could be removed from the study or switched to the alternate treatment regimen.

At baseline, the two treatment arms were well matched in terms of age, performance status, tumour diameter, tumour histology, histological grade, weight and platinum sensitivity. Some 54% of topotecan-treated participants and 52% of paclitaxel-treated participants had not responded or had relapsed within 6 months of completing first-line therapy.

Tumours were evaluated by CT, MRI scan, ultrasound or physical examination at baseline. All claimed responses were subjected to independent radiological review. However, non-responses were not subjected to independent review.

The primary efficacy parameters were response rate, duration of response and time to progression. The secondary criteria for efficacy were time to response and survival. Time to response, time to progression and survival were all measured from the time of the first dose of the study drug. Response duration was measured from the time of the first documented complete or partial response to the first sign of disease progression. Health-related quality of life (QoL) was also assessed in the trial using the European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire C-30 (QLQ-C30)

A total of 110 participants received crossover therapy as third-line treatment. Sixty-one participants crossed over from paclitaxel to topotecan and 49 crossed over from topotecan to paclitaxel. The results from third-line therapy are reported separately.

Quality of the trial comparing topotecan and paclitaxel

This trial was a good-quality randomised open-label comparative trial. The only issue for concern in relation to quality was the failure to conduct an ITT analysis, as only participants who received at least one dose of study drug were actually included in the final analysis. The overall survival data reported in the trial are also difficult to interpret owing to the switch to alternative therapy allowed in the design of the study. An evaluation of the trial in relation to study quality is shown in *Table 3*.

PLDH versus paclitaxel

One RCT was included that compared the efficacy and safety of PLDH with paclitaxel. The trial had been reported in one abstract[47] and in addition a full trial report was obtained from Schering-Plough as part of the industry submission.[27]

Description of the trial comparing PLDH and paclitaxel

The trial by Schering-Plough[27] was a Phase III randomised open-label comparative trial that evaluated the efficacy and safety of PLDH compared with paclitaxel in women with epithelial ovarian carcinoma following failure of first-line platinum-based chemotherapy. Protocol-eligible participants were women with measurable disease, who had received one prior platinum-based regimen without a taxane. The planned enrolment was for 438 participants, but only 216 were ultimately randomised (108 in each treatment arm).

Participants entering the trial were stratified by platinum-sensitivity and bulky disease and randomised in a 1:1 ratio within each stratum to receive either a 1-hour i.v. infusion of PLDH 50 mg/m^2 every 28 days or paclitaxel 175 mg/m^2 as a 3-hour infusion every 21 days. All randomised participants underwent radiological imaging (X-ray, CT scan, MRI) to document baseline

disease within 30 days prior to the first dose of the study drug. Participants were followed weekly to assess haematological toxicities, and radiologic imaging was repeated every 7–8 weeks to assess disease status. Participants who achieved a complete or partial response were re-evaluated 4 weeks later to confirm the initial observation of response.

At baseline, the two treatment groups were well matched 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. All participants were to have been followed for a minimum of 1 year for survival and disease progression. However, the study was terminated after approximately 50% of the planned participants had been entered into the trial owing to poor participant accrual. This was related to Taxol being approved 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.

The efficacy and safety analysis was therefore limited to overall survival only, and an examination of adverse events.

Quality of the trial comparing PLDH and paclitaxel

The study was a reasonably good-quality randomised open-label comparative trial. However, owing to its early termination only 216 participants were randomised, 108 into each treatment arm. The planned enrolment had been for 438 participants. It is therefore likely that the trial is significantly under-powered to detect any difference in treatment effect between the two treatment groups. Furthermore, owing to its early termination, 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. Owing to these caveats, the results of the trial should be interpreted with caution. The evaluation of trial 30–57 in relation to study quality is shown in *Table 3*. Full details of the quality checklist are available in Appendix 5.

Paclitaxel versus combination cyclophosphamide, doxorubicin and cisplatin (Cantu et *al.*[28])

One publication of a single RCT that compared single-agent paclitaxel and a platinum-containing regimen in previously treated patients with recurrent ovarian cancer was identified.[28]

Description of the trial comparing paclitaxel and CAP

The aim of the randomised pilot study by Cantu and colleagues[28] was to assess the activity, efficacy and tolerability of single-agent paclitaxel and a platinum-containing regimen in previously treated patients with recurrent ovarian cancer. The eligibility criteria for entry into the trial were based on a histologically proven diagnosis of measurable disease, that recurred or progressed after 12 months had elapsed since the end of first-line therapy that had included cisplatin or carboplatin, and a WHO performance status ≤ 2. Ninety-seven eligible participants were randomised to either single-agent paclitaxel 175 mg/m^2 infused over 3 hours or a combination of cyclophosphamide 500 mg/m^2, doxorubicin 50 mg/m^2, and cisplatin 50 mg/m^2 (CAP). Both of these regimens were administered intravenously at 3-week intervals. The median number of cycles on each arm was six.

Forty-seven participants were randomised to the CAP regimen and 50 were allocated paclitaxel. However, three participants in the paclitaxel arm were lost to follow-up just after randomisation. The analysis is therefore based on 94 participants (47 in each group). At baseline, the two treatment groups were reasonably well matched in terms of age, histology, disease site, prior chemotherapy regimens and treatment-free interval. There were, however, more participants with bulky disease at the time of first diagnosis in the paclitaxel treatment group (57%) than in the CAP arm (34%). All the participants had previously been treated with two or three chemotherapy regimens that did not include a taxane. The median treatment-free interval was 30.2 months in the paclitaxel arm and 38.8 months among participants receiving CAP. Although it was not prespecified in the trial protocol, participants who failed to respond to either CAP or paclitaxel as second-line therapy were crossed over to received the alternative regimen as third-line therapy. In total 23 participants who did not respond to CAP were crossed over to the paclitaxel regimen and 30 were crossed over from paclitaxel to CAP.

The primary outcome of the trial was overall survival. The secondary objectives were to determine progression-free intervals and the overall response to therapy.

Quality of the trial comparing paclitaxel and CAP

An evaluation of Cantu and colleagues' trial[28] in relation to study quality is displayed in *Table 3*. Overall, owing to the level of reporting in the trial

publication, it was not possible to evaluate a number of the methodological aspects of the trial. The authors did state that the trial was a randomised pilot study, but the method of randomisation was not reported. It can be suggested that, owing to the imbalance between the two treatment arms at baseline on one important prognostic factor, a simple randomisation without stratification had been used. However, as this was not reported it was also impossible to assess the degree to which allocation concealment had been attained. It was also not possible to assess whether the outcome assessors were blinded to treatment allocation. The trial was also not analysed on an ITT basis as reported in the paper, as the three participants lost to follow-up were not included in the final analyses. Furthermore, the addition of crossover between the two regimens at third-line therapy makes the analysis of overall survival data difficult. Full details of the quality checklist are available in Appendix 5.

Paclitaxel–platinum combination therapy versus platinum therapy alone (The ICON and AGO Collaborators[29])

One RCT was included which investigated the use of paclitaxel in combination with platinum-based chemotherapy in patients with epithelial ovarian carcinoma who had relapsed after 6 months, following first-line platinum-based chemotherapy. The trial had been reported in one abstract[48] and a full publication.[29]

Description of the trial comparing paclitaxel–platinum combination with platinum alone

The ICON4/AGO-OVAR-2.2 trial[29] was a multi-centre trial which was run in parallel, with ICON4 being coordinated by the Instituto Mario Negri, Italy (IRFMN) and the Medical Research Council Clinical Trials Unit, UK (MRC CTU), and AGO-OVAR-2.2 being coordinated by AGO, Germany. The trial compared the efficacy and safety of paclitaxel in combination with platinum-based chemotherapy to platinum-based chemotherapy alone in women with epithelial ovarian carcinoma who had relapsed after 6 months, following first-line platinum-based chemotherapy. The eligibility criteria for the trial differed slightly across the three protocols. Patients in the MRC CTU protocol were permitted to have received more than one line of previous chemotherapy; participants in the IRFMN protocol were required to have been treatment free for a period >12 months and to have measurable disease; participants randomised into the AGO protocol must have previously received paclitaxel in combination with platinum-based therapy (cisplatin or carboplatin), and those randomised into the ICON4 (IRFMN and MRC CTU) protocol were required to have received platinum-based chemotherapy, with or without paclitaxel.

Eligible participants were randomised to treatment in a 1:1 ratio. In the ICON4 protocol, stratification was done by centre, age, last chemotherapy received, time since completion of last chemotherapy and intended platinum treatment. In the AGO protocol, stratification was based on time since completion of last chemotherapy and whether the participant had undergone secondary debulking surgery. In total 802 participants were randomised; 392 were assigned paclitaxel plus platinum-based chemotherapy and 410 were assigned conventional platinum-based therapy alone. When the planned treatment doses for carboplatin were determined by the area-under-the-curve (AUC) method of Calvert and colleagues,[49] the minimum dose was 5[glomerular filtration rate (GFR) + 25] mg, and when it was determined by the Cockcroft equation, the dose was a minimum of 6(GFR + 25) mg. The planned minimum dose of cisplatin (ICON4 protocol only) was 75 mg/m^2 if given as one agent and 50 mg/m^2 if given in combination with other drugs. Participants in the ICON4 protocol assigned paclitaxel plus platinum in combination were to receive 175 mg/m^2 paclitaxel given as a 3-hour intravenous infusion, followed by either carboplatin or cisplatin at the same dose as set out above. Participants in the AGO protocol assigned paclitaxel plus carboplatin were to receive 185 mg/m^2 paclitaxel given in a 3-hour infusion, followed by carboplatin at the same dose as set out above. All drugs were to be given on day 1 of each cycle.

Treatment data were collected at each cycle of treatment, with further follow-up data collected every 3 months for the first 2 years, and 6 monthly from then on. QoL data were collected for all patients in the MRC CTU and AGO protocols, using the EORTC QLQ-C30. At baseline the two treatment groups were well matched in terms of age, WHO performance status, the type of last chemotherapy regimen received, the number of previous chemotherapy lines and the treatment-free interval, with 75% of the participants having experienced a treatment-free interval of ≤ 12 months and the remaining 25% a treatment free interval of >12 months.

The primary outcome measure of the trial was overall survival and the secondary outcomes were progression-free survival and QoL.

Quality of the trial comparing paclitaxel–platinum combination with platinum alone

ICON4/AGO-OVAR-2.2 was a good-quality randomised multi-centre parallel trial. The evaluation of the ICON4/AGO-OVAR-2.2 trial in relation to study quality is shown in *Table 3*. Full details of the quality checklist are available in Appendix 5.

Trials in which one of the comparators was used outside its licensed indication

Single-agent paclitaxel versus oxaliplatin (Piccart and colleagues[30])

One randomised Phase II study by Piccart and colleagues[30] was identified that investigated the efficacy of single-agent paclitaxel compared with oxaliplatin.

Description of the trial comparing paclitaxel with oxaliplatin

The aim of this multi-centre open-label, randomised Phase II study was to evaluate the efficacy of oxaliplatin compared with single-agent paclitaxel in a relapsing progressive ovarian cancer patient population. Entry into the trial was based on a histologically proven diagnosis of epithelial ovarian carcinoma in patients who had progressed or stabilised after prior treatment. Participants were required to have received at least one but no more than two prior platinum-based chemotherapy regimens and to have relapsed within 1 year of the end of treatment. All participants were also required to have a WHO performance status of 0–2.

Eligible participants were stratified by centre, performance status (0 or 1 versus 2), platinum-free interval (0–6 months versus 6–12 months) and the number of prior platinum-based regimens (one versus two). Out of the 86 participants randomised, 41 received paclitaxel 175 mg/m^2 administered as a 3-hour intravenous infusion every 21 days and 45 received oxaliplatin 130 mg/m^2 as a 2-hour intravenous infusion every 21 days. The median number of cycles administered per patient was six in the paclitaxel arm and four in the oxaliplatin arm (range: 1–8 in both treatment arms).

Participants underwent complete examination (clinical, gynaecological, histological and haematological) at baseline and then before each treatment cycle. Antitumoural activity was assessed by MRI or CT scan every two cycles.

At baseline, participants were reasonably balanced between the treatment arms in terms of age, disease stage and number of sites involved and the number and type of prior chemotherapy regimens. However, an imbalance was found in the histological distribution, with 17 patients (41%) of participants in the paclitaxel arm and 33 (73%) in the oxaliplatin arm having a serous tumour type. Thirty-one participants (76%) in the paclitaxel arm and 32 (71%) in the oxaliplatin arm were classified at baseline as being platinum resistant.

The primary efficacy end-point in the trial was the objective confirmed response rate. The secondary efficacy outcomes were time to progression (TTP), time to treatment failure and overall survival. QoL as measured by the EORTC QLQ-C30 was also assessed as a further outcome.

Quality of trial comparing paclitaxel to oxaliplatin

The trial conducted by Piccart and colleagues[30] was a good-quality randomised phase II study. The evaluation of the trial in relation to study quality is shown in *Table 3*. Full details of the quality checklist are available in Appendix 5.

Paclitaxel weekly versus every 3 weeks (Rosenberg and colleagues[31])

One report of an RCT by Rosenberg and colleagues[31] that evaluated single-agent paclitaxel given weekly versus every 3 weeks and with oral versus intravenous steroid premedication met the inclusion criteria.

Description of the trial comparing paclitaxel weekly with every 3 weeks

The aim of this randomised bifactorial trial was to evaluate the efficacy and toxicity of paclitaxel given at the same dose intensity and administered weekly or every 3 weeks, and to assess the safety of intravenous steroids versus standard oral premedication. The participants who were eligible to enter the trial needed to have a histologically proven diagnosis, measurable disease, a KPS ≤ 60% and to have had no more than one prior platinum-containing chemotherapy regimen. All the participants were taxane naïve.

Prior to study entry, participants were stratified according to platinum sensitivity, before being randomised according to a bifactorial design to receive either paclitaxel 67mg/m^2/week over a period of 3 hours (one course was defined as 3 weeks of therapy) or 200 mg/m^2 every 3 weeks over a 3-hour period. In addition, according to the bifactorial design, participants were also randomised to receive either oral or intravenous steroid premedication. The premedication

consisted of oral dexamethasone 20 mg administered 12 and 6 hours before paclitaxel or dexamethasone 20 mg given intravenously 30 minutes prior to paclitaxel.

Appropriate radiological examinations were performed at baseline and then every 6 weeks during the treatment period. Haematological evaluation was undertaken on a weekly basis.

At baseline, the two treatment groups were well matched and there were no significant differences between the groups in terms of age, WHO performance status, the treatment-free interval, tumour size or paresthesia at inclusion.

The primary efficacy end-point of interest was the response rate. The secondary efficacy end-points were response duration, progression-free and overall survival and, in addition, adverse reactions were also studied. The efficacy analysis was undertaken on an ITT basis, and the safety evaluation included all the participants who actually received paclitaxel.

Quality of the trial assessing two different paclitaxel regimens

The randomised bifactorial trial by Rosenberg and colleagues[31] was a reasonably good-quality trial. However, according to the sample size estimation published in the paper, the trial as it was conducted may not have been adequately powered to detect a difference between the two treatment groups on the primary outcome measure of response rate. It is stated in the report that 318 participants were needed to detect a relative difference of $\geqslant$54% with 80% power. However, only 208 participants were actually enrolled into the trial. *Table 3* shows an evaluation of the trial in relation to study quality. Full details of the quality checklist are also available in Appendix 5.

Paclitaxel at doses of 175 and 250 mg/m^2 (Omura and colleagues[32])

One RCT by Omura and colleagues[32] that evaluated single-agent paclitaxel at two different dose levels was identified and included in the review.

Description of the trial comparing paclitaxel at different dose intensities

The purpose of the Phase III multi-centre trial by Omura and colleagues[32] was to determine whether increasing the dose of paclitaxel increases the probability of clinical response, progression-free survival or overall survival in women who have persistent or recurrent ovarian cancer, and whether doubling the dose of prophylactic filgrastim accompanying the higher paclitaxel dose decreases the frequency of neutropenic fever. The eligibility criteria for the trial were based upon participants having histologically confirmed epithelial ovarian cancer, a Gynaecologic Oncology Group performance status of 0, 1 or 2 and having received no more than one prior platinum-based chemotherapy regimen and no prior taxane. In the original study protocol, participants had to have platinum-resistant clinically measurable disease, defined as progression during first-line therapy or within 6 months of completing therapy, a best response of stable disease after six courses of platinum therapy or stable disease with rising CA-125 levels while on platinum. However, after the study had begun, the eligibility criteria were expanded, owing to declining enrolment, to include participants with platinum-sensitive disease and participants without clinically measurable disease. Platinum-sensitive participants were defined as those who had an initial response to platinum therapy lasting at least 6 months, followed by progression or recurrence.

At the initiation of the trial, the study regimens included paclitaxel administered at 135, 175 or 250 mg/m^2 by 24-hour intravenous infusion every 21 days. Participants were randomly assigned to treatment, stratified upon clinically measurable disease, platinum sensitivity and cooperative trial group. A total of 449 participants were enrolled in the study. Out of these, 77 were assigned to the lowest dose regimen before the arm was closed owing to poor participant accrual. There were 184 participants assigned to the 175 mg/m^2 dose of paclitaxel without filgrastim, of whom 164 (89%) were deemed eligible, and 188 participants assigned to the 250 mg/m^2 dose of paclitaxel with filgrastim, of whom 166 (88%) were eligible. Within the high-dose paclitaxel group, participants were also randomised to receive either 5 or 10 μg/kg filgrastim per day subcutaneously. The 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).

At baseline, the two treatment arms were reasonably well matched in terms of the prognostic factors of age, performance status, measurable disease status and platinum sensitivity.

In the 175 mg/m^2 arm 76% (125/184) of the participants were categorised as having platinum-resistant disease and 24% (39/184) as being platinum sensitive. In the 250 mg/m^2 treatment arm 79% (132/188) of participants were platinum resistant and 21% (34/188) had platinum-sensitive disease. However, there were slightly more participants with mucinous and clear-cell type histology randomised to the higher dose regimen.

Overall in the trial, there were no significant differences between the two groups in the number of treatment cycles administered. Some 58% of the participants in the paclitaxel 175 mg/m^2 arm and 55% of participants in the 250 mg/m^2 arm received six or more cycles of therapy. Over these first six courses of treatment, approximately 76% and approximately 70% of the planned ideal dose was delivered to participants on the 175 and 250 mg/m^2 regimen, respectively. Although dose reductions occurred in both treatment arms, a difference in total dose and dose intensity was maintained during the first six courses of treatment.

Response was assessed throughout the trial before every other cycle of therapy. The primary treatment outcomes assessed were progression free and overall survival. These analyses were based on all participants deemed eligible for inclusion in the trial. All analysis of response rate was based on participants with measurable disease at baseline, whereas analyses of adverse events were based on all participants who received any study treatment. No results were reported for the 77 participants who were assigned to the lowest dose paclitaxel regimen of 135 mg/m^2.

Quality of the trial assessing paclitaxel at different dose intensities

An evaluation of the trial of Omura and colleagues[32] in relation to study quality is displayed in *Table 3*. Overall, owing to the level of reporting in the trial publication, it was not possible to evaluate a number of the methodological aspects of the trial. Of particular note in relation to the trial quality, there are two important aspects, first the sample size on which the reported results are based and second the related aspect of the protocol amendment to expand the eligibility criteria. The publication states that the planned sample size for the trial was 540 participants; however the reported results are based on only 265 participants. It is therefore likely that the trial may be significantly underpowered to detect any difference in treatment effect between the two treatment arms for which results are reported. This may be related to the change in the protocol, which allowed for an expansion in the eligibility criteria for participant entry. A number of participants were enrolled into the trial who were later deemed to be ineligible for participation. These participants were not included in the analysis. The trial results are therefore not based on an ITT analysis, and no description of the number or reasons for withdrawal from the trial is reported.

Oral versus intravenous topotecan (Gore and colleagues[33])

One publication of a single RCT that compared oral versus intravenous topotecan in patients with relapsed epithelial ovarian cancer met the inclusion criteria.[33]

Description of the trial comparing oral and intravenous topotecan

The aim of this open-label, multi-centre RCT was to compare the efficacy, safety and tolerability of oral topotecan versus standard intravenous topotecan in participants with relapsed epithelial ovarian cancer. The eligibility criteria for entry into the trial were based on a histologically proven diagnosis of measurable disease, that was originally FIGO Stage III or IV, and an ECOG performance status ≤ 2. All participants had progressed on first-line therapy or had relapsed within 12 months of completing initial treatment. Initial treatment must have included a platinum-based therapy, which could have been administered in combination with a taxane. Only one previous chemotherapy regimen was allowed.

A total of 266 eligible participants were randomised, with stratification based on response to prior platinum chemotherapy, tumour size and whether or not the previous regimen had included a taxane. A total of 135 participants were randomised to receive oral topotecan at a dose of 2.3 mg/m^2/day for 5 days and 131 to receive intravenous topotecan at a dose of 1.5 mg/m^2/day for 5 days. The treatment cycle was 21 days in both arms. The median number of treatment cycles was 4 (range: 1–23) in the oral topotecan treatment group and six (range: 1–26) in the intravenous topotecan group.

At baseline, the two treatment arms were well matched in terms of age, initial FIGO disease stage, performance status, tumour size and platinum sensitivity. In each group, 30% of the participants were platinum refractory and 70% were either platinum resistant or platinum sensitive.

Tumours were evaluated by CT, MRI scan, chest X-ray or photography at baseline. Lesions evaluated at baseline by CT or MRI scan were then reassessed at the end of every second treatment cycle and those evaluated by chest X-ray or photography were reassessed at the end of every treatment course throughout the trial. All claimed complete or partial responses were reassessed at a further 4 weeks and were subjected to independent radiological review. All adverse events were collected throughout the trial.

Time to response, time to progression and survival were all measured from the time of the first dose of topotecan. Response duration was measured from the time of the first documented complete or partial response to the first sign of disease progression. The response rate was also evaluated by serial measurement of CA-125 values. Response was defined as a 50% decrease in the two samples, confirmed by a further sample, or a serial decrease over three samples of >75%. The final sample analysed had to be at an interval of at least 28 days after the previous sample.

Quality of the trial assessing oral and intravenous topotecan

The trial by Gore and colleagues[33] was a good-quality randomised multi-centre open-label trial. The trial was also well reported within the publication. An evaluation of the trial of oral versus intravenous topotecan in relation to study quality is shown in *Table 3* and full details of the quality assessment checklist are available in Appendix 5.

Assessment of clinical effectiveness

Effectiveness of PLDH versus topotecan

This section of the report summarises the results reported for the long-term follow-up of trial 30-49 requested from Schering-Plough.[44] The objective of the study was to compare the efficacy of PLDH with that of topotecan in terms of survival and progression-free survival when 90% of participants had died or were lost to follow-up.

Overall survival

Overall survival was defined in the protocol as the time from the start of study drug administration to death. There was a statistically significant benefit in terms of overall survival observed for the PLDH-treated arm compared with the topotecan-treated group, HR = 1.216 (95% CI: 1.00 to 1.48). The reduction in the risk of death for participants treated with PLDH compared with those treated with topotecan was 18%. The median overall survival was 62.7 weeks (range: 1.7–258.3 weeks) for the PLDH group compared with 59.7 weeks (range: 1.6–247.1 weeks) for the topotecan arm. The 1-, 2- and 3-year survival rates for participants treated with PLDH were 56.3% (95% CI: 50.0 to 62.6%), 34.7% (95% CI: 28.6 to 40.8%) and 20.2% (95% CI: 14.9 to 15.5%), respectively, and 54.0% (95% CI: 47.6 to 60.3%), 23.6% (95% CI: 18.1 to 29.2%) and 13.2% (95% CI: 8.8 to 17.7%), respectively, for the topotecan-treated arm. A summary of the overall survival data is given in *Table 4* and the corresponding Kaplan–Meier survival curves are displayed in *Figure 2*.

A further analysis of the results for overall survival by the subgroups of patients with platinum-sensitive or platinum-resistant disease indicated that for participants with platinum-sensitive disease (46% of the study population) there was a pronounced overall survival benefit for participants treated with PLDH compared with those treated with topotecan; HR = 1.432 (95% CI: 1.066 to 1.923); $p = 0.017$. This corresponded to a 30% reduction in the risk of death in participants treated with PLDH. The median survival was 107.9 weeks (range: 6.9–258.3 weeks) for PLDH-treated participants compared with 70.1 weeks (range: 1.6–258.3 weeks) for the topotecan-treated participants. The 1-, 2- and 3-year survival rates for participants with platinum-sensitive disease were 74.1% (95% CI: 65.8 to 82.4%), 51.2% (95% CI: 41.6 to 60.7%) and 28.4% (95% CI: 19.6 to 37.1%), respectively, for participants treated with PLDH compared with 66.2% (95% CI: 57.4 to 75.1%), 31.0% (95% CI: 22.2 to 39.7%) and 17.5% (95% CI: 10.2 to 24.7%), respectively, for participants treated with topotecan. A summary of the overall survival in the platinum-sensitive disease subgroup is given in *Table 5* and the corresponding Kaplan–Meier survival curves are displayed in *Figure 3*.

The results of the analysis for the subgroup of patients with platinum-resistant disease (54% of the study population) showed that there was no statistically significant difference in survival between the two treatment groups: HR = 1.069 (95% CI: 0.823 to 1.387); $p = 0.618$. The median overall survival was 38.3 weeks (range: 1.7–253.9 weeks) for the PLDH-treated participants and 42.1 weeks (range: 1.6–239.3 weeks) for the topotecan-treated participants. The 1-, 2- and 3-year survival rates for the participants with platinum-resistant disease

TABLE 4 *Summary of overall survival data based on long-term follow-up for PLDH versus topotecan*

Intervention	*N*	Censored (%)	Median[a] (weeks)	Range[b] (weeks)	*p*-Value	HR[c]	95% CI for HR
PLDH	239	16.7	62.7	1.7–258.3	0.050	1.216	1.00 to 1.48
Topotecan	235	8.9	59.7	1.6–247.1[d]			

[a] Kaplan–Meier estimates.
[b] Stratified log-rank test.
[c] An HR >1 indicates an advantage for PLDH.
[d] A censored observation.

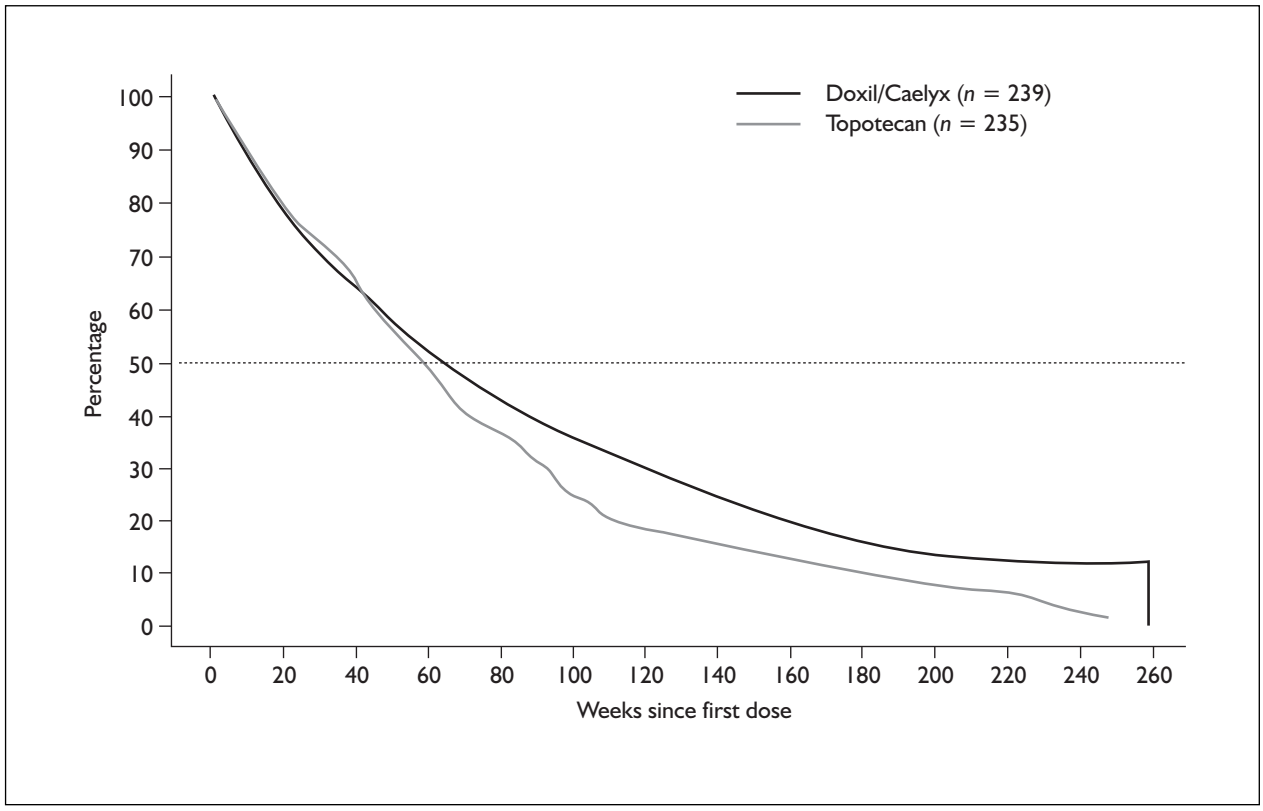

FIGURE 2 *Kaplan–Meier overall survival curves for PLDH versus topotecan. Reproduced with permission from Schering-Plough.*[44]

TABLE 5 *Summary of overall survival data based on long-term follow-up for PLDH versus topotecan: platinum-sensitive disease subgroup*

Intervention	*N*	Censored (%)	Median (weeks)[a]	Range (weeks)[b]	*p*-Value	HR[c]	95% CI for HR
PLDH	109	22.0	107.9	6.9 – 258.3	0.017	1.432	1.066 to 1.923
Topotecan	110	10.9	70.1	1.6 – 247.1[d]			

[a] Kaplan–Meier estimates.
[b] Stratified log-rank test.
[c] HR > 1 indicates an advantage for PLDH.
[d] A censored observation.

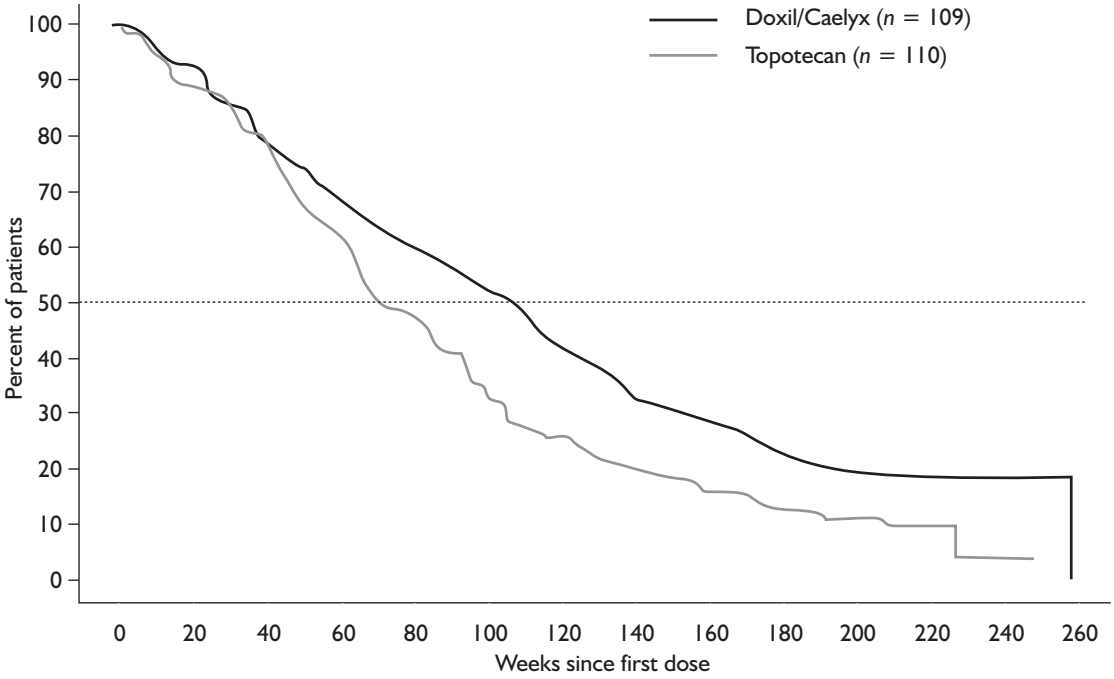

FIGURE 3 *Kaplan–Meier survival curves for PLDH versus topotecan: platinum-sensitive disease subgroup. Reproduced with permission from Schering-Plough.*[44]

TABLE 6 *Summary of overall survival data based on long-term follow-up for PLDH versus topotecan: platinum-refractory disease subgroup*

Intervention	*N*	Censored (%)	Median (weeks)[a]	Range (weeks)[b]	*p*-Value	HR[c]	95% CI for HR
PLDH	130	12.3	38.3	1.7–253.9[d]	0.618	1.069	0.82 to 1.387
Topotecan	125	7.2	42.1	1.6–239.3			

[a] Kaplan–Meier estimates.
[b] Stratified log-rank test.
[c] An HR >1 indicates an advantage for PLDH.
[d] A censored observation.

treated with PLDH were 41.5% (95% CI: 32.8 to 50.1%), 21.1% (95% CI: 14.1 to 28.2%) and 13.8% (95% CI: 7.6 to 20.0%), respectively, compared with 43.2% (95% CI: 34.5 to 51.9%), 17.2% (95% CI: 10.5 to 23.8%) and 9.5% (95% CI: 4.2 to 14.7%), respectively, for the topotecan-treated group. *Table 6* summarises the long-term survival data for the participants with platinum-refractory disease and the corresponding Kaplan–Meier survival curves are displayed in *Figure 4*.

A multivariate Cox regression analysis was performed to assess the influence of possible prognostic factors on the treatment effect for overall survival. The results of this analysis for subgroups according to baseline disease characteristics are displayed in *Table 7*. The variables included in the regression model were treatment, platinum sensitivity (sensitive or resistant), bulky disease (yes/no), baseline KPS (<80, ≥ 80), treatment-free interval after last dose of first-line therapy and the presence or absence of ascites at baseline.

The results of the subgroup analysis for overall survival by potential prognostic baseline variables indicated that age <65 years, platinum-sensitive disease and the absence of ascites are disease characteristics associated with improved survival. None of the other potential baseline variables

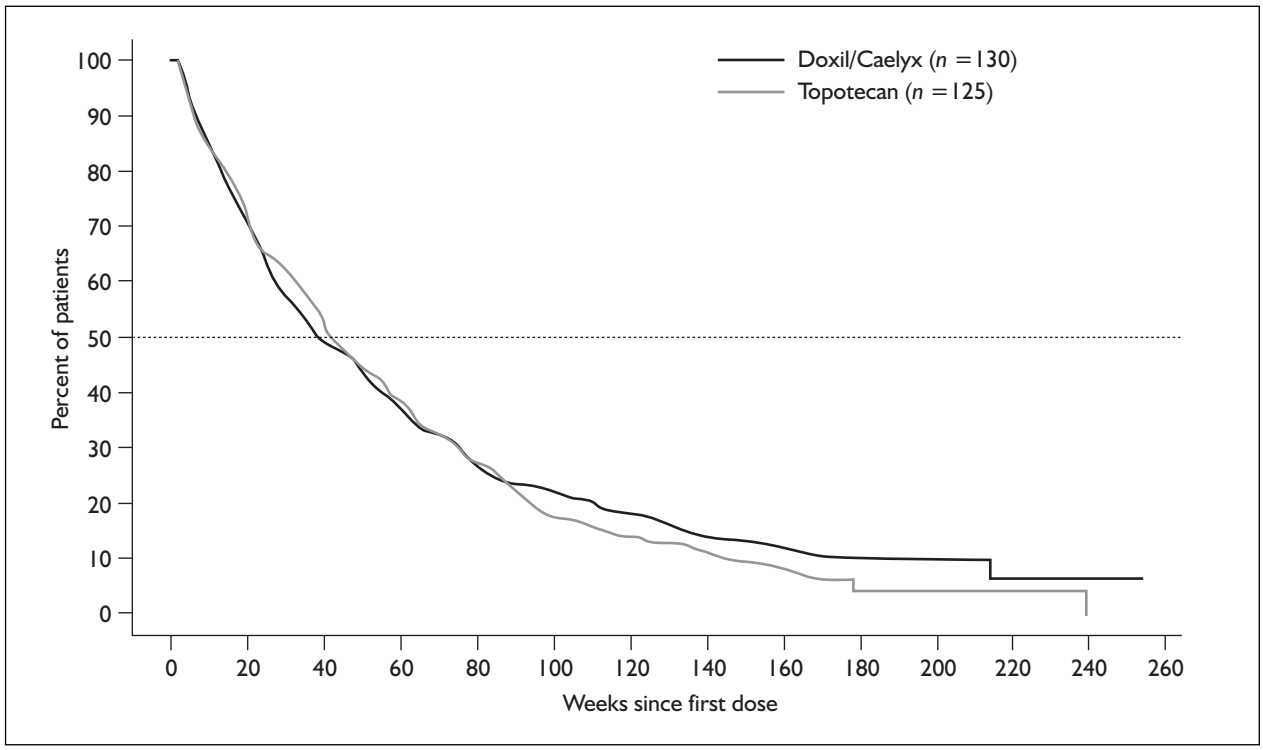

FIGURE 4 *Kaplan–Meier survival curves for PLDH versus topotecan: platinum-refractory disease subgroup. Reproduced with permission from Schering-Plough.*[44]

TABLE 7 *Overall survival for subgroups according to baseline disease characteristics (multivariate Cox regression analysis)*

Variable	Group	*N*	HR[a]	95% CI for HR
	ITT	474	1.216	1.00 to 1.478
Age (years)	<65	294	1.322	1.022 to 1.710
	≥ 65	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 (months)	≤ 6	211	1.103	0.826 to 1.474
	>6 to 18	201	1.284	0.945 to 1.744
	>18	62	1.191	0.633 to 2.137
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] Hazard ratios are for the comparison of treatment groups within the subgroup. An HR >1 indicates an advantage for PLDH

were significantly associated with an improvement in overall survival for PLDH in comparison with topotecan.

Progression-free survival (PFS)

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 participant was on the study drug or during the long-term follow-up period.

There were no statistically significant differences between the PLDH-treated participants and the topotecan-treated participants in terms of PFS. The median PFS was 16.1 weeks (range: 1.3–162.4 weeks) for the PLDH group and

TABLE 8 *Summary of progression-free survival data based on long-term follow-up for PLDH versus topotecan*

Intervention	*N*	Censored (%)	Median[a] (weeks)	Range[b] (weeks)	*p*-Value	HR[c]	95% CI for HR
PLDH	239	16.1	16.1	1.3–162.4[d]	0.241	1.118	0.93 to 1.35
Topotecan	235	16.9	16.9	0.4–178.6			

[a] Kaplan–Meier estimates.
[b] Stratified log-rank test.
[c] An HR >1 indicates an advantage for PLDH.
[d] A censored observation.

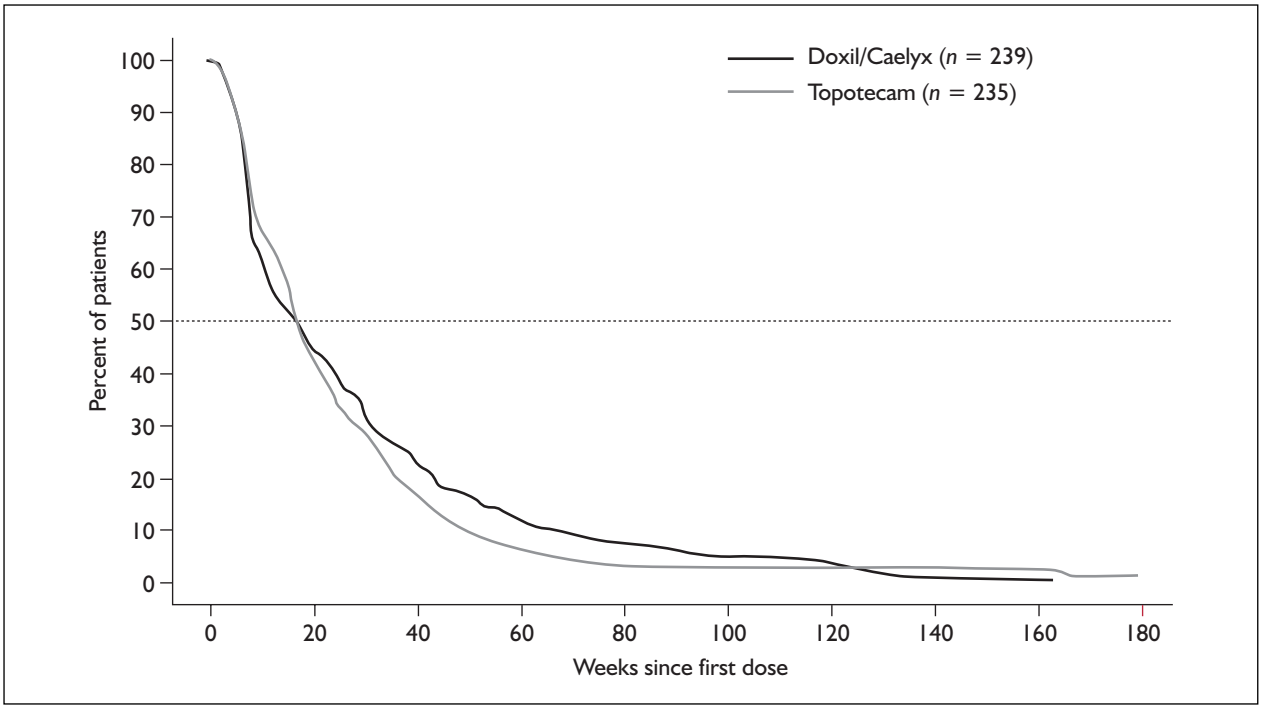

FIGURE 5 *Kaplan–Meier progression-free survival curves for PLDH versus topotecan. Reproduced with permission from Schering-Plough.*[44]

16.9 weeks (range: 0.4–178.6 weeks) for the topotecan-treated participants. The corresponding HR = 1.118 (95% CI: 0.93 to 1.35). *Table 8* provides a summary of the PFS data for both groups of participants and *Figure 5* shows the corresponding Kaplan–Meier survival curves.

A further analysis of the results for PFS by the subgroups of patients with platinum-sensitive or platinum-resistant disease was undertaken. The results of the analysis for patients with platinum-sensitive disease showed a median PFS of 27.3 weeks (range: 2.4–151.9 weeks) for the PLDH-treated participants and 22.7 weeks (range: 0.4–155.9 weeks) for the topotecan-treated group. The HR of 1.287 (95% CI: 0.98 to 1.69) indicated that there were no statistically significant differences between the two treatment groups in this subgroup of platinum-sensitive patients on this outcome measure.

No further significant differences were observed between the two treatment groups in the platinum-resistant subgroup of participants. The median PFS was 9.1 weeks (range: 1.3–162.4 weeks) in the PLDH-treated group compared with 13.6 weeks (range: 1.4–178.6 weeks) in the topotecan-treated participants; HR = 0.99 (95% CI: 0.77 to 1.28).

A further multivariate Cox regression analysis was performed to assess the influence of possible prognostic factors on the treatment effect for PFS. Again, the variables included in the regression model were treatment, platinum sensitivity (sensitive or refractory), bulky disease (yes/no),

TABLE 9 *Summary of objective response rates based on long-term follow-up for PLDH versus topotecan*

Overall response	PLDH (n = 239)		Topotecan (n = 235)	
	Response rate % (n)	95% CI for response rate	Response rate % (n)	95% CI for response rate
Total[a]	19.7 (47)	14.6 to 24.7%	17.0 (40)	12.2 to 21.8%
Complete	3.8 (9)		4.7 (11)	
Partial	15.9 (38)		12.3 (29)	

[a] Numbers are those originally determined by investigators; independent radiologic assessment differed in some instances.

baseline KPS (<80, ≥ 80), treatment-free interval after last dose of first-line therapy and the presence or absence of ascites at baseline.

The results of this regression analysis indicated that there were no statistically significant differences between the treatment groups in relation to the effect of any of the potentially prognostic variables on PFS.

Response

A responder was defined as a participant with at least a durable (complete or partial) response. A durable response was the participant's maximum confirmed response. A complete response (CR) was defined as the complete disappearance of all known measurable and assessable disease on two separate measurements at least 4 weeks apart. A partial response (PR) was defined as a 50% reduction in the sum of products of the perpendicular diameters of all measurable lesions for at least 4 weeks. Total response data included both complete and partial responses.

The total response rate was similar for the two treatment groups. Forty-seven (19.7%; 95% CI: 14.6 to 24.7%) of the participants in the PLDH-treated group and 40 (17%; 95% CI: 12.2 to 21.8%) of the topotecan-treated participants had either a PR or CR as their best confirmed response. Seventy-seven (32.2%) of the PLDH treated group and 95 (40.4%) of the topotecan-treated participants had stable disease as their best response. A summary of the objective response data is given in *Table 9*.

The response rates were also analysed according to the subgroups of platinum-sensitive and platinum-resistant participants. For participants with platinum-sensitive disease, 32 (29.4%; 95% CI: 20.8 to 37.9%) of the 109 participants treated with PLDH and 31 (28.2%; 95% CI: 19.8 to 36.6%) of the 110 participants in the topotecan-treated group had confirmed PR or CR as their best response. Forty (36.7%) of the PLDH-treated participants and 42 (38.2%) of the topotecan-treated participants had stable disease as their best response. For participants with platinum-resistant disease, 15 (11.5%; 95% CI: 6.0 to 17.0%) of the 130 participants in the PLDH group and nine (7.2%; 95% CI: 2.7 to 11.7%) of the 125 topotecan-treated participants had confirmed objective PR or CR as their best response. Thirty-seven (28.5%) of the PLDH-treated group and 53 (42.2%) of the topotecan-treated group had stable disease as their best response. *Figure 6* shows the data relating to the incidence of complete, partial, total and stable responses. It can clearly be seen that there were no statistically significant differences between the PLDH and topotecan arms in terms of response rates (complete, partial, total or stable) for any participants in the trial.

Quality of life

QoL was assessed in the trial using the EORTC QLQ-C30. The questionnaire consists of nine subscales – one global QoL scale, five function scales (physical, role, emotional, cognitive and social) and three symptom scales (fatigue, pain and nausea/vomiting), in addition to six questions on single items that cover dyspnoea, sleep disturbance, appetite loss, constipation, diarrhoea and financial impact. Higher scores on the function scales indicate better functioning and QoL, whereas higher scores on the symptoms scales indicate the increased presence of symptoms.

Assessments were made at baseline and at the start of each treatment cycle until 24 weeks follow-up. Owing to the difference in the cycle length of the two treatment regimens, the first time point at which data could be collected from the two study groups was at week 12. At baseline, the questionnaire was completed by 82% of participants, but <50% of participants in either treatment arm completed the questionnaire at 12 weeks.

At baseline, the function and symptom scale scores were similar for the two treatment groups. At 12 weeks follow-up, 28.5% (68/239) of the

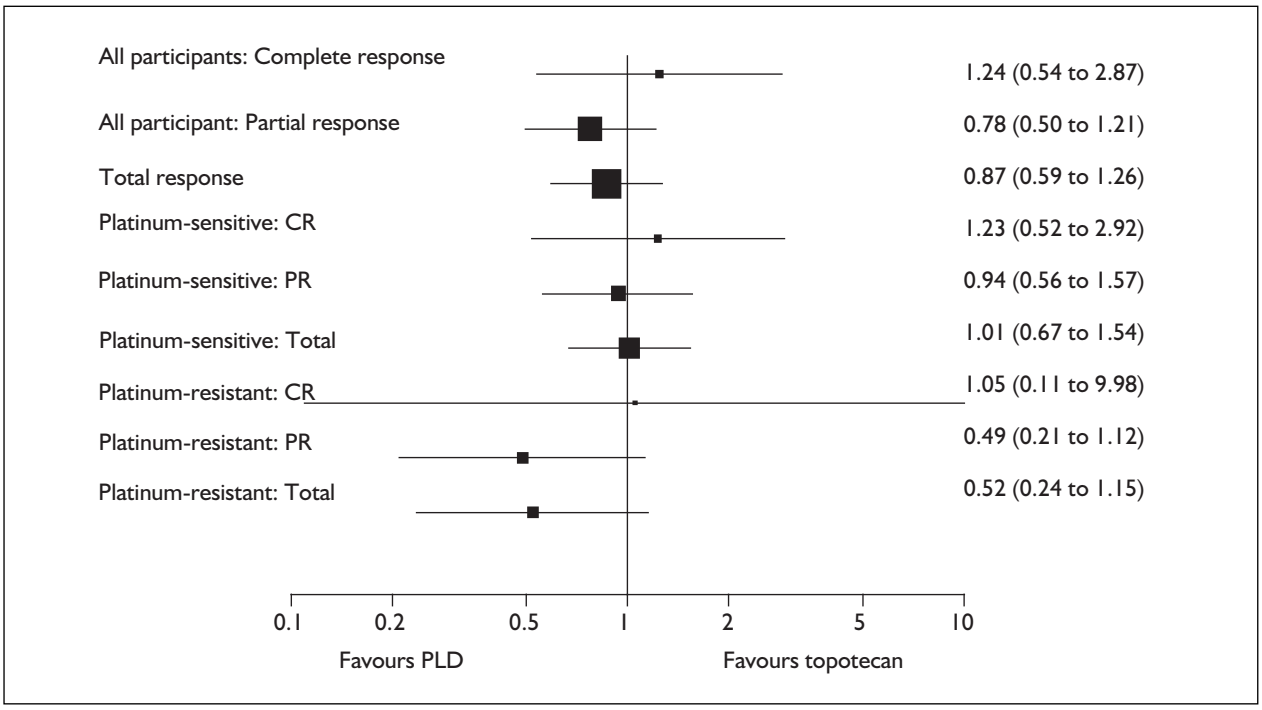

FIGURE 6 *Relative risks for response rates for PLDH versus topotecan sub-group analysis stratified by platinum sensitivity*

TABLE 10 *Percentage of patients with a maintained or improved QoL score at 12 weeks follow-up for PLDH versus topotecan.*

QoL subscale	PLDH	Topotecan
Physical functioning	56 (66/118)	56 (61/107)
Role functioning	65 (77/118)	58 (63/109)
Emotional functioning	67 (80/119)	74 (80/108)
Cognitive functioning	73 (87/119)	73 (79/108)
Social functioning	69 (82/119)	64 (69/108)
Global QoL	58 (68/117)	52 (54/104)
Fatigue	57 (67/118)	56 (61/109)
Nausea/vomiting	72 (86/119)	71 (77/109)
Pain	64 (76/119)	81 (88/109)

participants in the PLDH-treated group and 23.4% (55/235) of the participants in the topotecan-treated group had improved or stable global QoL scores; RR=0.82 (95% CI: 0.61 to 1.12). In the PLDH-treatment group, 20.5% (49/239) had a worsened global QoL score compared with 20.4% (48/235) of participants in the topotecan treatment group; RR=0.97 (95% CI: 0.70 to 1.42). Neither of these observations was statistically significant.

The numbers of patients with a maintained or improved score at 12 weeks for each of the subscales is shown in *Table 10*. The corresponding RRs were calculated and are presented in *Figure 7*. The number of patients with a maintained or improved pain subscale score showed a statistically significant difference between the PLDH-treated participants and the topotecan-treated group, in favour of topotecan; RR=1.26 (95% CI: 1.08 to 1.50). However, there were no other statistically significant differences between the two groups observed on any of the other subscale scores.

Quality-adjusted survival analysis

Interventions may vary not only in terms of their effect on disease status, but also in terms of their effect on QoL. Quality-adjusted survival analysis is an approach that compares treatments, taking into account both the quality and quantity of the life of a patient, and such an analysis was undertaken to compare PLDH versus topotecan.

The time without symptoms or toxicity (TwiST) is the period of time during which the average patient experiences no symptoms or toxicity, and a

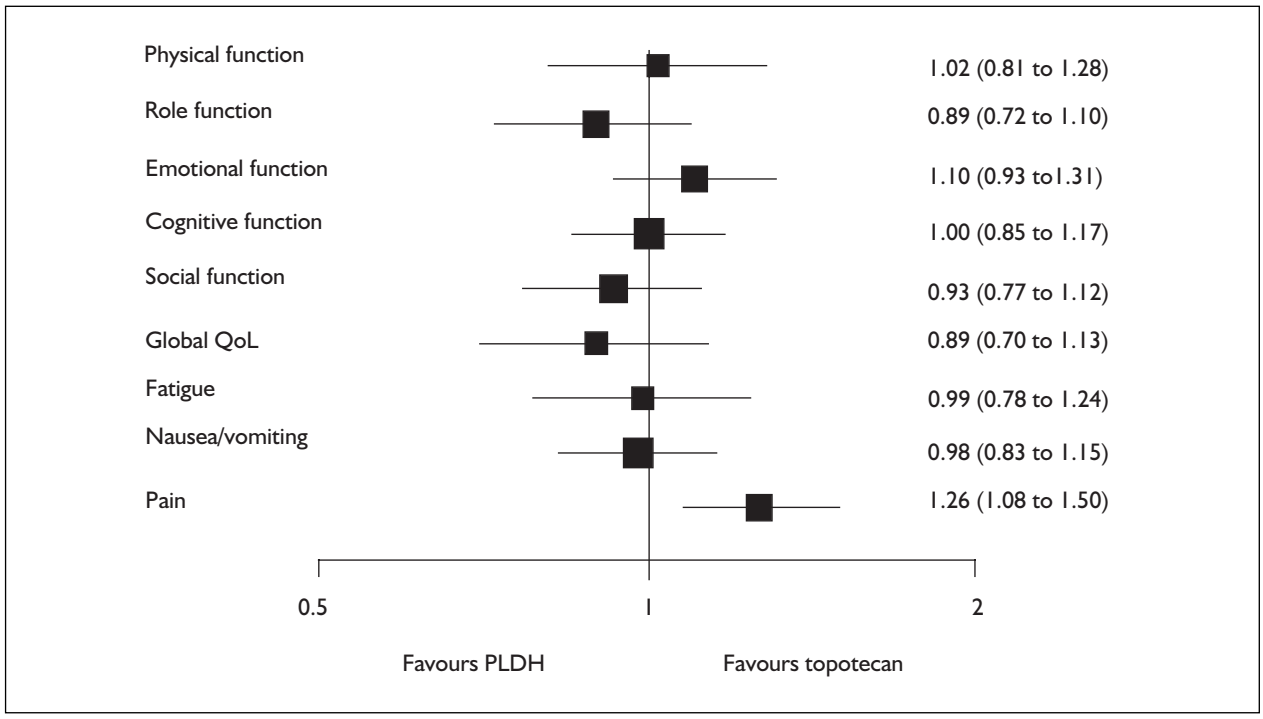

FIGURE 7 *Relative risk of number of patients with a maintained or improved QoL score at 12 weeks follow-up for PLDH versus topotecan*

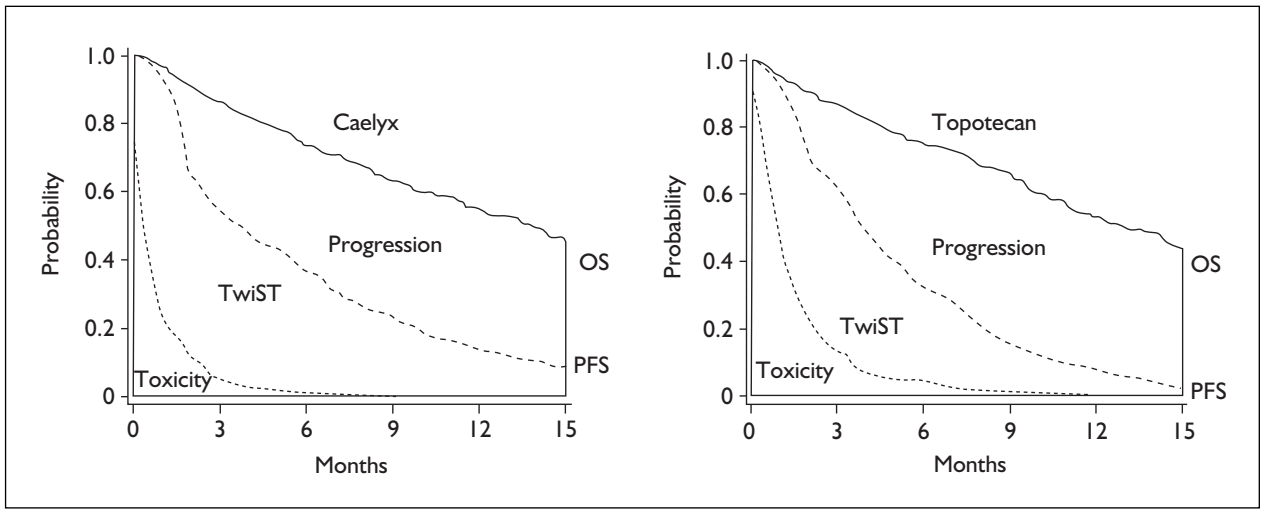

FIGURE 8 *Q-TwiST survival analysis: partitioned survival curves. Reproduced with permission from Schering-Plough.*[45]

higher TwiST is desirable. *Figure 8* shows the overall survival curve for each treatment group partitioned into the three health states: TOX (time a participant reported a grade 3 or higher toxicity); PROG (time from relapse until death or until 15 months following randomisation, which ever occurred first); and TwiST (time a patient was not in progression or toxicity). The areas between the consecutive curves represent the average time participants spent in each particular health state.

The average times spent in the three health states TOX, PROG and TwiST for the two treatment arms and their differences are presented in *Table 11*.

Compared with topotecan, PLDH had a smaller TOX value (–0.70) and PROG value (–0.46) whereas the time spent in TwiST was higher (+1.14). This indicates that the participants in the PLDH treatment group spent more time in the

TABLE 11 *Time (months) spent in the three health states and their differences*

Health states	PLDH	Topotecan	Differences (95% CI)
TOX	0.84	1.54	–0.70 (–1.04 to –0.36)
TwiST	4.65	3.51	1.14 (0.46 to 1.82)
PROG	5.07	5.53	–0.46 (–1.31 to 0.39)

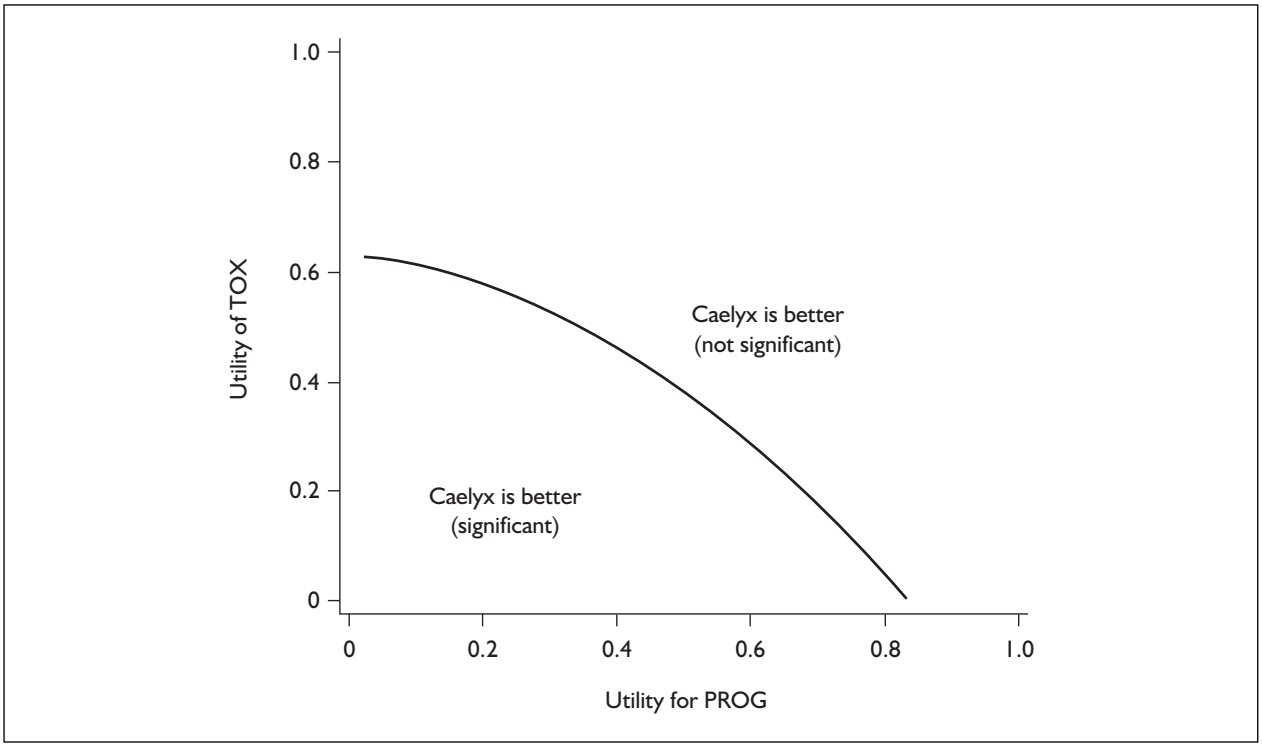

FIGURE 9 *Q-TwiST threshold utility analysis for PLDH versus topotecan. Reproduced with permission from Schering-Plough,*[45]

good health state of TwiST and less time in the poor health states of TOX and PROG relative to the topotecan treatment group.

Ultimately, quality-adjusted TwiST (Q-TwiST) combines the states of TOX, TwiST and PROG into a single measure by summing the time spent in these three health states weighted by their relative utilities. The utility values vary between 0 and 1, where 1 represents perfect health and 0 denotes a state as bad as death. The utility for TwiST is always taken to be 1. Utility values <1 for the health states TOX and PROG penalise treatments for toxicity and disease progression periods.

Figure 9 shows that for all combinations of the utility values, Q-TwiST would always favour PLDH relative to topotecan, with this difference being statistically significant for the AUC. This suggests that PLDH provided both lower treatment toxicity and better treatment effect than topotecan, and thus improved the Q-TwiST.

The Q-TwiST analysis suggests that even though there is only a marginally significant difference observed in overall survival in favour of PLDH, when QoL outcomes such as toxicity and progression are also taken into account, PLDH has further advantages over topotecan. However, Q-TwiST analysis is a simplistic model that is largely based on the assumption that a day with any toxicity is valued the same (awarded the same utility value) regardless of the type of adverse event experienced. A full analysis of quality-adjusted survival should weight patients' QoL according to the actual health states and toxicities they experience, including the period without either toxicity or progression.

TABLE 12 *Treatment-emergent adverse events in at least 10% of participants by preferred term: all grades, Grade 3 and Grade 4*

Body system and adverse event[a]	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) 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)
Leucopenia	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
Dyspnoea	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)	0
Alopecia	46 (19.2)	3 (1.3)	0	123 (52.3)	15 (6.4)	0

[a] At each level of summarisation, body system and COSTART preferred term, a participant is counted once for one or more adverse events at that level.
[b] Investigators reported grade 3 alopecia even though the National Cancer Institute Common Toxicity Criteria (NCI CTC) lists criteria only for grade 2.

Adverse events

Extensive data on adverse events were reported in the submission from Schering-Plough.[44] However, only the data on treatment-related effects experienced by at least 10% of participants will be reported and discussed in this section.

Overall in this trial, 18% (43/239) of the PLDH-treated participants and 16% (37/235) of the participants in the topotecan group discontinued treatment owing to adverse events. In addition, three participants treated with topotecan died as a result of treatment-related adverse events in the form of neutropenia and sepsis. No treatment-related deaths were recorded in the participants treated with PLDH. *Table 12* and *Figures 10* and *11* provide further details of the adverse events experienced in the two treatment groups.

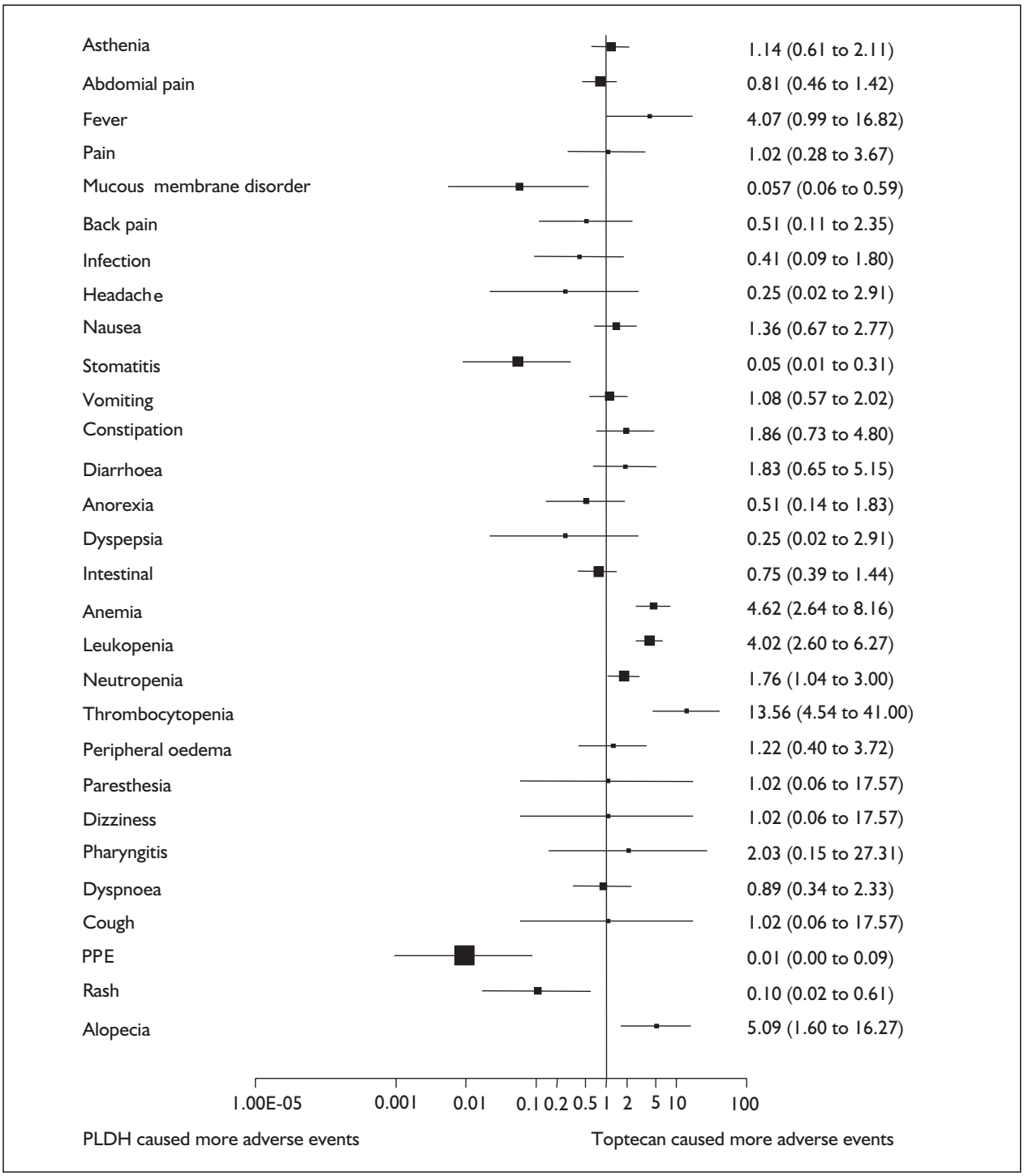

FIGURE 10 *Relative risks of grade 3 treatment-related adverse events for PLDH versus topotecan*

Treatment-related adverse events occurred in 92.9% (222/239) of the PLDH-treated participants and 98.7% (232/235) of the topotecan-treated group.

The most common treatment-related adverse events for the PLDH-treated participants were PPE (50.6%), stomatitis (40.6%), nausea (36.8%), leucopenia (36.4%), anaemia (36.0%), neutropenia (35.1%) and asthenia (32.6%). In addition, more than 75% of the total instances of the following adverse events were considered by the investigators to be related to treatment with PLDH: mucous membrane disorder, thrombocytopenia, paresthesia, rash and alopecia.

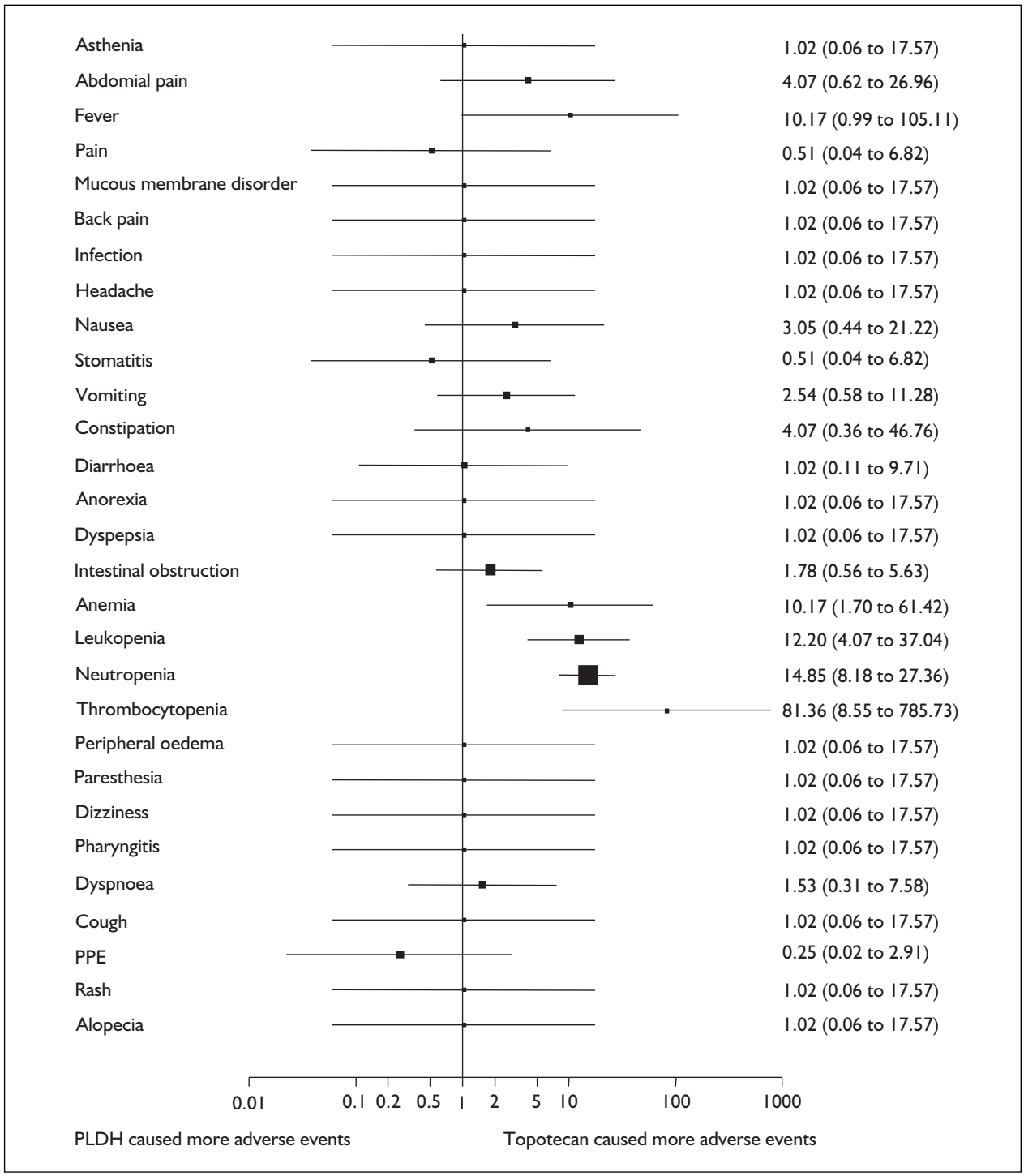

FIGURE 11 *Relative risks of grade 4 treatment-related adverse events for PLDH versus topotecan*

The most common treatment-related adverse events for the topotecan-treated participants were neutropenia (81.3%), anaemia (71.9%), thrombocytopenia (64.7%), leucopenia (63.4%), nausea (54.9%), alopecia (52.3%), asthenia (44.3%) and vomiting (34.9%). More than 75% of the total instances of the following adverse events were considered by the investigators to be related to treatment with topotecan: mucous membrane disorder, stomatitis, PPE and alopecia.

Grade 3 adverse events

The incidence of adverse events was different,

both in type and severity, between the two treatment arms.

The incidence of the following type of grade 3 events was significantly higher in the PLDH-treated arm compared with the topotecan-treated group:

- mucous membrane disorder (3.8% versus 0%), RR = 0.05 (95% CI: 0.006 to 0.56)
- stomatitis (7.9% versus 0.4%), RR = 0.056 (95% CI: 0.01 to 0.31)
- PPE (23% versus 0%), RR = 0.009 (95% CI: 0.001 to 0.087)
- rash (4.2% versus 0.4%), RR = 0.11 (95% CI: 0.017 to 0.61).

Conversely, the incidence of the following events was significantly higher in the topotecan-treated group than the PLDH-treated group:

- fever (3.4% versus 0.8%), RR = 4.07 (95% CI: 1.00 to 16.82)
- anaemia (25.1% versus 5.4%), RR = 4.62 (95% CI: 2.64 to 8.16)
- leucopenia (35.3% versus 8.8%), RR 4.02 (95% CI: 2.6 to 6.27)
- neutropenia (14.0% versus 7.9%), RR = 1.7 (95% CI: 1.04 to 3.00)
- thrombocytopenia (17.0% versus 1.3%), RR = 13.56 (95% CI: 4.54 to 40.99)
- alopecia (6.4% versus 1.3%), RR = 5.09 (95% CI: 1.60 to 16.27).

There were no statistically significant differences in the number of grade 4 adverse events reported in the PLDH group compared with the topotecan treatment arm. However, the incidence of reports of pain, stomatitis and PPE did remain higher in the PLDH group, although these failed to reach statistical significance. There were, however, significant differences in the number of grade 4 adverse events reported in the topotecan group relative to the PLDH group, with the adverse event profile being very similar to that observed for grade 3 events. These differences were again observed for:

- fever (2.1% versus 0), RR = 10.17 (95% CI: 1.00 to 105.11)
- anaemia (4.3% versus 0.4%), RR = 10.17 (95% CI: 1.70 to 61.42)
- leucopenia (15.3% versus 8.8%), RR = 12.20 (95% CI: 4.07 to 37.04)
- neutropenia (35.3% versus 8.8%), RR = 14.85 (95% CI: 8.18 to 27.36)
- thrombocytopenia (17.0% versus 0%), RR = 13.56 (95% CI: 4.54 to 41.00).

Summary of effectiveness data for PLDH versus topotecan

One RCT was identified which investigated the efficacy and safety of PLDH compared with topotecan in women with epithelial ovarian carcinoma whose disease did not respond to or recurred after treatment with first line platinum-based chemotherapy.

Overall survival

The overall survival rates favoured PLDH compared with topotecan with median survival rates of 62.7 versus 59.7 weeks, respectively; HR = 1.216 (95% CI: 1.00 to 1.48); $p = 0.050$.

The overall survival benefit from treatment with PLDH versus topotecan was most pronounced in the platinum-sensitive subgroup of patients with median survival rates of 107.9 versus 70.1 weeks, respectively; HR = 1.432 (95% CI: 1.07 to 1.92); $p = 0.017$.

For participants with platinum-refractory disease there were no statistically significant differences in overall survival between the two treatment groups. Median survival was 38.3 weeks in the PLDH group and 42.1 weeks in the topotecan group; HR = 1.07 (95% CI: 0.82 to 1.39); $p = 0.619$.

For PFS and response, the point estimates favoured PLDH over topotecan, but as all CIs crossed unity this benefit was not significant.

Progression-free survival

There were no significant differences in PFS between the two groups. Median survival was 16.1 weeks in the PLDH group versus 16.9 weeks in the topotecan group (HR = 1.118; 95% CI 0.93 to 1.35).

Response

No significant differences were observed between the groups in terms of response rates; 19.7% of the PLDH group and 17% of the topotecan group had either a complete or partial response.

Quality of life

At 12 weeks, there were no significant differences between the groups in the number of participants who had a maintained or improved score on the EORTC QLQ-C30 overall. However, a significant difference on the pain subscale was observed in favour of topotecan, RR = 1.26 (95% CI: 1.08 to 1.50).

Adverse events

The most common adverse events for the PLDH

group were: PPE (50.6%), stomatitis (40.6%), nausea (36.8%), leucopenia (36.4%), anaemia (36.0%), neutropenia (35.1%) and asthenia (32.6%).

The most common adverse events in the topotecan group were: neutropenia (81.3%), anaemia (71.9%), thrombocytopenia (64.7%), leucopenia (63.4%), nausea (54.9%), alopecia (52.3%), asthenia (44.3%) and vomiting (34.9%).

There were no statistically significant differences in the number of grade 4 adverse events reported in the PLDH group compared with the topotecan treatment arm. However, the incidence of reports of pain, stomatitis and PPE did remain higher in this group, although these failed to reach statistical significance. There were, however, significant differences in the number of grade 4 adverse events reported in the topotecan group relative to the PLDH group, with the adverse event profile being very similar to that observed for grade 3 events. These differences were observed for:

- fever (2.1% versus 0), RR = 10.17 (95% CI: 1.00 to 105.11)
- anaemia (4.3% versus 0.4%), RR = 10.17 (95% CI: 1.70 to 61.42)
- leucopenia (15.3% versus 8.8%), RR = 12.20 (95% CI: 4.07 to 37.04)
- neutropenia (35.3% versus 8.8%), RR = 14.85 (95% CI: 8.18 to 27.36)
- thrombocytopenia (17.0% versus 0%), RR = 13.56 (95% CI: 4.54 to 41.00).

Effectiveness of topotecan versus paclitaxel

This section of the report summarises the results reported in the three publications of trial 039, which compared topotecan with paclitaxel.[24–26] Where long-term follow-up data have been reported, these have been used as opposed to data reported from an analysis at an earlier time point in the trial. The results for the effectiveness outcomes of overall survival and time to progression are therefore taken from the publication of the long-term follow-up data.[25] The results reported from further treatment after crossover to the alternative drug as third-line therapy are taken from the paper by Gore *et al.*[26] All other results are taken from the earlier full publication of the trial results.[24]

Overall survival[25] (HR < 1 favours topotecan)

There were no statistically significant differences found between the topotecan treatment arm and the paclitaxel treatment group in terms of overall survival at long-term follow-up. At this time the median follow-up time was 58.5 weeks for the topotecan group (range: 0–86 weeks) and 52.6 weeks for the paclitaxel treatment group (range: 0–117 weeks). The median survival was 63.0 weeks (95% CI: 47.0 to 71.9) (range: <1–238.4+ weeks; 20.5% censored) in the topotecan treatment arm and 53.0 weeks (95% CI: 42.3 to 68.7) (range: <1–226.3+ weeks; 12.3% censored) in the paclitaxel treatment group. The corresponding adjusted HR, after adjustment for stratification factors, was 0.914 (95% CI: 0.681 to 1.226); $p = 0.44$. *Figure 12* shows the percentage of participants receiving topotecan or paclitaxel surviving at least 4 years post-randomisation.

A further analysis of the results for overall survival by the subgroups of participants with platinum-sensitive or platinum-resistant disease was undertaken. The results indicated that within the subgroup of participants with platinum-sensitive disease (late relapse), there were no significant differences between the two treatment arms in terms of survival; unadjusted HR = 1.010 (95% CI: 0.663 to 1.541). For participants with disease classified as being platinum resistant (refractory, early and interim relapse), there were also no statistically significant differences between the two treatment arms in terms of overall survival; unadjusted HR = 0.738 (95% CI: 0.498 to 1.093).

Time to progression[25]

There were no statistically significant differences between the two treatment arms in terms of TTP. The median TTP was 18.9 weeks (95% CI: 12.1 to 23.7) (range: <1–92.6+ weeks; 25% censored) in the topotecan-treated group compared with 14.7 weeks (95% CI: 11.9, 18.3) (range: <1–137.3+ weeks; 12.3% censored) in the paclitaxel-treated group. The corresponding adjusted HR, after adjustment for stratification factors, was 0.811 (95% CI: 0.603 to 1.092); $p = 0.08$.

Further analysis of the results for TTP by the subgroups of participants with platinum-sensitive or platinum-resistant disease indicated that for both disease subgroups there were no statistically significant differences between the two treatment groups in terms of TTP. For the platinum-sensitive disease subgroup the unadjusted HR was 0.823 (95% CI: 0.538 to 1.261). The unadjusted HR for the participants with platinum-resistant disease was 0.749 (95% CI: 0.501 to 1.121).

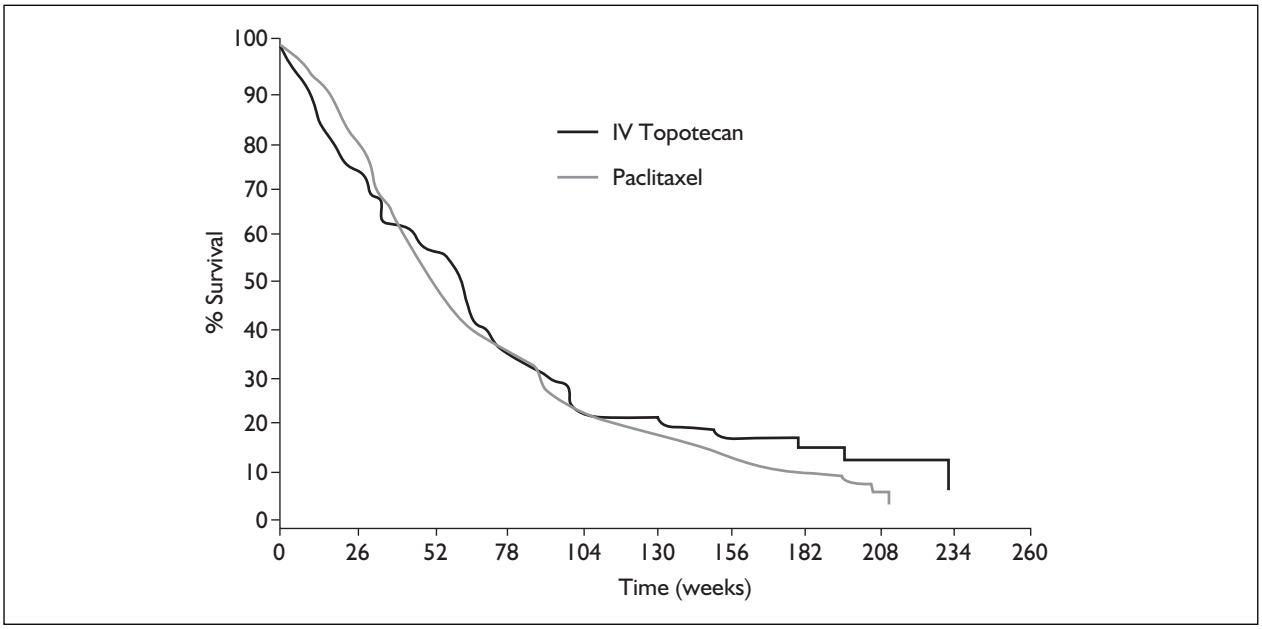

FIGURE 12 *Percentage of participants receiving topotecan or paclitaxel surviving at least 4 years postrandomisation. Reproduced from ten Bokkel Huiink W, Lane SR, Ross GA on behalf of the International Topotecan Study Group. Long term survival in a phase III, randomised study of topotecan versus paclitaxel in advance epithelial ovarian carcinoma.* Annals of Oncology *2004;**15:**100–2, with permission of Oxford University Press.*

TABLE 13 *Response rate by treatment group for topotecan versus paclitaxel*

	Topotecan (n = 112)		Paclitaxel (n = 114)		
Response to treatment	**Number**	**%**	**Number**	**%**	***p*-Value**
Responders					
CR	5	4.5	3	2.6	
PR	18	16.1	12	10.5	
Total	23	20.5	15	13.2	0.138
95% CI		13 to 28.3		7.0 to 19.4	
Non-responders					
SD	33	29.5	38	33.3	
PD	39	34.8	56	49.1	
NE	17	15.2	5	4.4	
Total	89	79.5	99	86.8	

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable.

Response[24]

Response rate

In total, 202 participants were evaluated for response, 96 in the topotecan group and 106 in the paclitaxel group. All participants who were not fully assessed for efficacy or who were not evaluated were considered to be non-responders.

There were no statistically significant differences in the response rates between the topotecan-treated group and the paclitaxel-treated group. The overall response rate was 20.5% for the participants treated with topotecan and 13.2% for participants treated with paclitaxel (p = 0.138). For the 23 participants who responded to topotecan, five (4.5%) had a complete response and 18 (16.1%) had a partial response. For the 15 participants treated with paclitaxel who had a response, three (2.6%) had a complete response and 12 (10.5%) had a partial response. *Table 13* shows the response rates by treatment group for topotecan versus paclitaxel.

The response to the two different drug regimens was further explored in relation to prior platinum sensitivity (resistant, early relapse, interim relapse

TABLE 14 *Response in relation to platinum sensitivity for topotecan versus paclitaxel*

	Resistant		Early relapse		Interim relapse		Late relapse		Total	
Platinum sensitivity	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
Topotecan	*n* = 34		*n* = 6		*n* = 20		*n* = 52		*n* = 112	
CR	0	0.0	0	0.0	1	5.0	4	7.7	5	4.5
PR	3	8.8	1	16.7	3	15.0	11	21.2	18	16.1
Total (CR + PR)	3	8.8	1	16.7	4	20.0	15	28.8	23	20.5
Paclitaxel	*n* = 33		*n* = 10		*n* = 16		*n* = 55		*n* = 114	
CR	0	0.0	0	0.0	0	0.0	3	5.5	3	5.7
PR	1	3.0	1	10.0	2	12.5	8	14.5	12	10.7
Total (CR + PR)	1	3.0	1	10.0	2	12.5	11	20.0	15	13.4

TABLE 15 *Response in relation to baseline disease status for topotecan versus 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
5–10 cm	10.9	12.5
First-line response		
Responders	15.2	10.5
Non-responders	5.4	2.6

or late relapse). The results of the analysis for response by these different subgroups is displayed in *Table 14*.

In the subgroup of participants who were classified as having platinum-resistant disease, three out of 34 (8.8%) in the topotecan treatment group had a PR, compared with one out of 33 (3%) in the paclitaxel treatment arm. The rates of response to topotecan compared with paclitaxel for early, interim or late relapse were 16.7% (1/6) versus 10.0% (1/10), 20.0% (4/20) versus 12.5% (2/16) and 28.8% (15/52) versus 20.0% (11/55), respectively.

A further analysis of response to treatment relative to baseline disease characteristics indicated that in both the treatment groups higher response rates were observed in participants without ascites at baseline, and in participants with smaller tumour burden (<5 cm), better performance status scores and those who responded to first-line therapy. *Table 15* displays the results for response to treatment in relation to baseline disease status.

Duration of response

Response duration was measured from the time of the first documented complete or partial response to the first sign of disease progression.

The median duration of response was 32.1 weeks (range: 5.4–53.1 weeks) for participants treated with topotecan who evidenced a response, compared with 19.7 weeks (range: 6.3–24.3 weeks) for participants treated with paclitaxel. These differences in the duration of response between the two groups were not statistically significant ($p = 0.221$). *Table 16* shows the duration of response for the two treatment groups.

TABLE 16 *Response duration for participants treated with topotecan or paclitaxel*

Response duration (weeks)	Topotecan *n* = 23	Paclitaxel *n* = 15
Median	32.1 weeks	19.7
Range	5.4–53.1	6.3–24.3
Risk ratio	0.416	
p-Value	0.2218	

TABLE 17 *Time to response data for participants treated with topotecan or paclitaxel*

Time to response (weeks)	Topotecan *n* = 23	Paclitaxel *n* = 15
Median	9.0	6.0
Range	3.1–19.0	2.4–12.3
Risk ratio	0.476	
p-Value	0.0409	

Time to response

There was a statistically significant difference between the topotecan and paclitaxel treatment arms in terms of time to response, in favour of paclitaxel. The median time to documented radiological response for participants in the topotecan treatment arm was 9.0 weeks (range: 3.1–19.0 weeks) compared with a median of 6 weeks (range: 2.4–12.3 weeks) for participants treated with paclitaxel. *Table 17* displays the results for the outcome of time to response.

Quality of life

QoL was assessed in the trial using the EORTC QLQ-C30. However, no results for this outcome were reported other than that the results were similar in both treatment groups.

Adverse events

Toxicity was summarised as both the worst CTC grade experienced by each patient and as the worst CTC grade experienced within each course for each participant.

Two participants in the topotecan treatment group died as a result of treatment-related toxicity. Both of these deaths were attributed to topotecan-induced sepsis. There were no deaths that were attributed to paclitaxel-induced myelosuppression. A further 7% of participants treated with topotecan and 4% of participants in the paclitaxel treatment group were withdrawn from the study owing to treatment-related toxicity. The primary reasons for withdrawal in the topotecan-treated participants were febrile neutropenia, infection and sepsis. Neurotoxicity was the primary reason for withdrawal for paclitaxel-treated participants.

Haematological toxicity

The majority of categories of reported grade 3 and 4 haematological toxicities occurred significantly more often in the topotecan group than the paclitaxel treatment arm. The only incidence of haematological toxicity that was higher in the paclitaxel group was for grade 3 neutropenia. This was observed in 30.4% of the paclitaxel treatment arm compared with 15.3% of the topotecan-treated participants, RR = 1.98 (95% CI: 1.19 to 3.34). All other haematological toxicities were higher in the topotecan treatment group, although this was not significantly higher for grade 4 anaemia. *Table 18* shows the number and percentages of participants who experienced

TABLE 18 *Number and percentage of patients and courses with haematological toxicity by worst CTC grade*

	Grade 3				Grade 4			
	Participants: *n* (%)		Course: *n* (%)		Participants: *n* (%)		Course: *n* (%)	
Toxicity	T	P	T	P	T	P	T	P
Leucopenia	56/110 (50.9)	20/112 (17.9)	234/590 (39.7)	51/585 (8.8)	38/110 (34.5)	2/112 (1.8)	57/590 (10.0)	2/586 (0.3)
Neutropenia	17/111 (15.3)	34/112 (30.4)	166/590 (28.1)	123/584 (21.1)	89/111 (80.2)	24/112 (21.4)	211/590 (35.8)	50/584 (8.6)
Thrombocytopenia	25/111 (22.5)	2/112 (1.8)	89/591 (15.1)	2/565 (0.3)	30/111 (27.0)	3/112 (2.7)	59/591 (10.0)	3/585 (0.5)
Anaemia	42/111 (37.8)	4/112 (3.6)	89/591 (15.1)	8/585 (1.4)	4/111 (3.6)	3/112 (2.7)	6/591 (1.0)	3/585 (0.5)

T, topotecan-treated groups; P, paclitaxel-treated group.

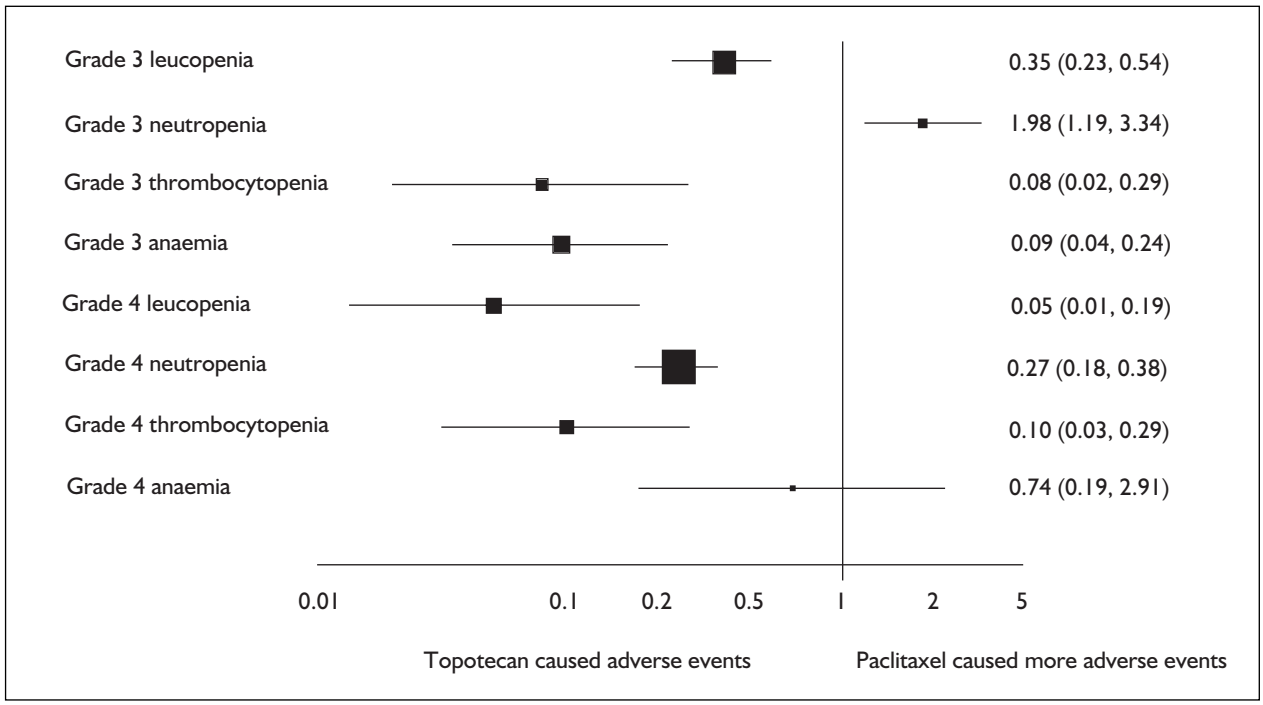

FIGURE 13 *Relative risks of grade 3 and 4 haematological toxicity for topotecan versus paclitaxel*

TABLE 19 *Related or possibly related non-haematological toxicities occurring in more than 10% of patients treated with topotecan or paclitaxel*

Adverse event	Topotecan (% patients)		Paclitaxel (% patients)	
	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4
Alopecia	75.9	0.0	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	0.0
Diarrhoea	33.9	6.3	37.8	0.9
Abdominal pain	21.5	5.4	36.0	3.5
Fever	27.7	0.9	17.7	0.0
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	0.0	25.4	2.6
Neuropathy	0.9	0.0	15.8	0.0
Skeletal pain	4.5	0.0	11.4	5.3
Flushing	4.5	0.0	14.1	0.0
Paresthesia	0.9	0.0	29.0	0.0

grade 3 and 4 haematological toxicities by participant and course for each treatment group. The RRs of experiencing a grade 3 or 4 haematological adverse event by treatment group are displayed in *Figure 13*.

Non-haematological toxicities

The majority of non-haematological adverse events were mild to moderate in severity (grade 1/2). The most frequently reported toxicities considered related or possibly related to treatment in both groups were alopecia and gastrointestinal disturbances, including nausea, vomiting, diarrhoea and constipation. The grade 3/4 adverse events reported more commonly in the topotecan group than in the paclitaxel group

TABLE 20 *Response to topotecan (third-line) treatment according to response to paclitaxel (second-line) treatment*

Response to topotecan (second-line) treatment	Patient response to paclitaxel (third-line) treatment (no.)				
	CR	PR	SD	PD	NE
PR, *n* = 7	1	0	2	4	0
SD, *n* = 27	0	2	4	10	1
PD, *n* = 22	1	1	6	10	4
NE, *n* = 3	0	0	0	1	2

TABLE 21 *Response to paclitaxel (third-line) treatment according to response to topotecan (second-line) treatment*

Response to paclitaxel (second-line) treatment	Patient response to topotecan (third-line) treatment (no.)				
	CR	PR	SD	PD	NE
PR, *n* = 2	0	0	1	1	0
SD, *n* = 17	0	4	4	10	5
PD, *n* = 35	0	3	3	24	5
NE, *n* = 1	0	1	0	0	0

were nausea (9.8 versus 1.8%), vomiting (9.9 versus 2.7%), constipation (5.4 versus 0%), abdominal pain (5.4 versus 3.5%), asthenia (5.4 versus 3.5%), fatigue (8.0 versus 6.1%) and fever/infection (0.9 versus 0%). The grade 3/4 adverse events reported more commonly in the paclitaxel treatment arm relative to the topotecan treatment arm were alopecia (0.9 versus 0%), arthralgia (2.6% versus 0.9%), myalgia (2.6 versus 0%) and skeletal pain (5.3 versus 0%). A summary of the non-haematological toxicities that occurred in more than 10% of participants in the trial is displayed in *Table 19*.

Effectiveness of third-line crossover therapy for topotecan versus paclitaxel

This section of the report is based on the publication by Gore and colleagues[26] that reports the results for response to third-line therapy for topotecan versus paclitaxel.

A total of 110 participants crossed over to the alternative drug regimen as third-line therapy within the trial owing to either failure to respond to second-line therapy, relapse after an initial response to second-line therapy or toxicity. Sixty-one participants crossed over from paclitaxel to topotecan and 49 participants crossed over from topotecan to paclitaxel.

At crossover there were no major differences in the demographic characteristics of the two groups of participants. However, there were statistically significant differences in the two groups' potential chemo-responsiveness. The topotecan group contained fewer participants who had evidenced a PR to second-line therapy compared with the paclitaxel group (3 versus 14%), and more participants in this group had progressive disease (57 versus 45%). Participants who were in the topotecan treatment group received a median of three courses of treatment (range: 1–23) and those in the paclitaxel treatment arm a median of four courses (range: 1–12). The planned dose was maintained in 95% of courses of topotecan and 94% of courses of paclitaxel.

Overall survival

There were no statistically significant differences between the topotecan and paclitaxel treatment arms in terms of overall survival on third-line therapy. The median survival time from the initiation of crossover therapy was 40 weeks (range: 1–123 weeks) for participants who received topotecan as third-line therapy compared with 48 weeks (range: 2–86 weeks) for participants who received paclitaxel.

Time to progression

There were no differences between the two treatment groups in terms of TTP. The median TTP was 9 weeks in both of the treatment arms.

Response

There were no significant differences between the participants in the two treatment groups in relation to response rate on third-line therapy. The overall response rate to topotecan was 13% (8/61; eight PR) and to paclitaxel was 10% (5/49; two CR and three PR); $p = 0.6838$. *Tables 20* and *21* show the

TABLE 22 *Haematological toxicity during cross-over (third-line) treatment with topotecan versus paclitaxel*

	Third-line treatment (% of participants)	
Toxicity	**Topotecan (*n* = 61)**	**Paclitaxel (*n* = 49)**
Neutropenia		
Grade 1	0	15
Grade 2	3	15
Grade 3	14	31
Grade 4	81	23
Thrombocytopenia		
Grade1	47	17
Grade 2	12	0
Grade 3	8	2
Grade 4	22	0
Anaemia		
Grade 1	8	52
Grade 3	62	42
Grade 3	27	2
Grade 4	2	0

responses to topotecan and paclitaxel according to participants' response to previous second-line chemotherapy. In total, seven out of the eight participants who responded to topotecan as a third-line therapy had disease that had been refractory to paclitaxel. Only one of the participants who responded to third-line paclitaxel had responded to second-line topotecan.

Response according to participants' sensitivity to first-line platinum therapy

Response to third-line treatment was also analysed according to participants' sensitivity to first-line platinum-based therapy. Only participants who had a treatment-free interval of >6 months (platinum-sensitive diseases) responded to third-line topotecan, but four participants who relapsed within 6 months of first-line platinum-based therapy (platinum-resistant disease) responded to paclitaxel as the third-line therapy.

Adverse events

Haematological toxicities

The toxicity profiles between the two treatment groups for participants who received third-line crossover therapy were similar to those recorded in the randomised study. The incidence of haematological toxicities was higher in the topotecan treatment group than the paclitaxel treatment arm. Grade 4 neutropenia was recorded in 81% of participants in the topotecan group compared with 23% in the paclitaxel arm. Grade 4 thrombocytopenia was also higher in the topotecan arm, 22 versus 2% in the paclitaxel group. Both grade 3 and 4 anaemia were also reported more frequently in the topotecan group relative to the paclitaxel treatment group, grade 3: 27% versus 0% and grade 4: 2% versus 0%. *Table 22* shows the percentage of haematological toxicities recorded during third-line crossover therapy for both the topotecan and paclitaxel treatment groups.

Non-haematological toxicities

Non-haematological toxicities associated with both topotecan and paclitaxel were generally mild or moderate (grade 1–2). The haematological toxicities reported for this stage of treatment are displayed in *Table 23*. The toxicities associated with topotecan were generally gastrointestinal disturbances, and were similar to those observed in the randomised phase of the study. The incidences of nausea, vomiting, abdominal pain and fatigue were greater with topotecan (59, 36, 25 and 23, respectively) than with paclitaxel (39, 27, 20 and 16%, respectively). However, the participants who received paclitaxel were premedicated with dexamethasone, which may have reduced the incidence of nausea and vomiting within this group. The incidences of arthralgia, myalgia, and paresthesia were greater with paclitaxel (37, 33, and 31%, respectively) than with topotecan (15, 18, and 8%, respectively).

Summary of effectiveness data for topotecan versus paclitaxel

One RCT was included that compared the efficacy and safety of topotecan with paclitaxel in patients with advanced epithelial ovarian cancer who had

TABLE 23 *Non-haematological toxicity to crossover (third-line) treatment for topotecan versus paclitaxel (% of participants)*

	Grade 1–2 toxicity		Grade 3–4 toxicity	
Adverse event	**Topotecan (*n* = 61)**	**Paclitaxel (*n* = 49)**	**Topotecan (*n* = 61)**	**Paclitaxel (*n* = 49)**
Nausea	59	39	13	10
Vomiting	36	27	12	8
Diarrhoea	33	35	3	2
Abdominal pain	25	20	8	8
Constipation	26	35	5	0
Fatigue	23	16	8	0
Alopecia	21	41	0	0
Myalgia	16	31	0	2
Arthralgia	13	37	2	0
Paresthesia	8	31	0	0

progressed during or after one platinum-based chemotherapy regimen.

There were no statistically significant differences between the groups on any outcome measure, apart from time to response. This favoured paclitaxel.

Overall survival

There were no significant differences between the two treatment groups in terms of overall survival. The median survival time was 63 weeks in the topotecan group compared with 53 weeks in the paclitaxel group; HR = 0.914 (95% CI: 0.681 to 1.226).

Time to progression

There were no significant differences between the two treatment arms. Median TTP was 19.8 weeks in the topotecan group versus 14.7 weeks in the paclitaxel group; HR = 0.811 (95% CI: 0.603 to 1.092).

Response rate

No significant differences were observed between the groups in terms of response rates; 20.5% of the topotecan group and 13.2% of the paclitaxel group had either a complete or partial response.

Response duration

There were no significant differences between the groups. Median duration of response was 32.1 weeks in the topotecan group compared with 19.7 weeks in the paclitaxel group.

Time to response

There was a statistically significant difference in time to response in favour of paclitaxel. The median time to response was 9.0 weeks in the topotecan group compared with 6.0 weeks in the paclitaxel group.

Quality of life

No results were reported for QoL.

Adverse events

The reported grade 3–4 haematological toxicities (leucopenia, neutropenia, thrombocytopenia and anaemia) were significantly higher in the topotecan group than the paclitaxel arm, apart from grade 3 neutropenia, which was higher in the paclitaxel treatment group.

The grade 3–4 adverse events reported more commonly in the topotecan group than the paclitaxel group were nausea, vomiting, constipation, abdominal pain, asthenia, fatigue and fever/infection. The grade 3–4 adverse events reported more commonly in the paclitaxel treatment arm relative to the topotecan treatment arm were alopecia, arthralgia, myalgia and skeletal pain.

Results reported from crossover to third-line therapy

Overall survival

There were no significant differences between the two treatment groups. Median survival time was 40 weeks in the topotecan group compared with 48 weeks in the paclitaxel arm.

Time to progression

The median time to progression was 9 weeks in both treatment arms.

Response

There were no significant differences in the response rates in the two treatment groups; 13%

TABLE 24 *Summary of overall survival data for all participants for PLDH versus paclitaxel*

Intervention	*N*	Censored (%)	Median (weeks)	Range (weeks)	*p*-Value	HR[a]	95% CI for HR
PLDH	108	7.4	46.6	2.3–263.7[b]	0.0618	0.932	0.702 to 1.234
Paclitaxel	108	6.5	56.3	1.4–211.4			

[a] An HR >1 indicates an advantage for PLDH.
[b] A censored observation.

TABLE 25 *Summary of overall survival data based on PLDH versus paclitaxel: platinum-sensitive disease subgroup*

Intervention	*N*	Censored (%)	Median (weeks)	Range (weeks)	*p*-Value	HR[a]	95% CI for HR
PLDH	44	13.6	65.4	3.9–263.7[b]	0.833	1.051	0.66 to 1.67
Paclitaxel	41	7.3	57.0	1.4–172.3			

[b] A censored observation.
[a] An HR >1 indicates an advantage for PLDH.

of the topotecan group and 10% of the paclitaxel group had a complete or partial response.

Adverse events

The toxicity profiles for the two treatment groups for participants who received third-line crossover therapy were similar to those recorded in the randomised study. The incidence of haematological toxicities was higher in the topotecan treatment group than the paclitaxel treatment arm. Non-haematological toxicities associated with both topotecan and paclitaxel were generally mild or moderate (grade 1–2). The incidences of nausea, vomiting, abdominal pain and fatigue were greater with topotecan than with paclitaxel. The incidence of arthralgia, myalgia and paresthesia were greater with paclitaxel.

Effectiveness of PLDH versus paclitaxel

The results presented in this section of the report summarise those presented in a trial report submitted by Schering-Plough as part of the industry submission.[27] However, this trial was terminated prematurely, therefore the results should be interpreted with caution.

Overall survival

The primary outcome in this trial was overall survival. The median overall survival was 46.6 weeks (range: 2.3–263.7+ weeks) in the PLDH-treated participants compared with 56.3 weeks (range: 1.4–211.4 weeks) in the paclitaxel-treated participants. The HR of 0.931 (95% CI: 0.702 to 1.234) indicated that there were no statistically significant differences between the two treatment groups in terms of overall survival. A summary of the overall survival data for all participants is displayed in *Table 24*.

A further analysis of the results for overall survival by the subgroups of patients with platinum-sensitive or platinum-resistant disease indicated that for participants with platinum-sensitive disease the median overall survival was 65.4 weeks (range: 3.9–263.7+ weeks) for PLDH-treated participants and 57.0 weeks (range: 14–172.3 weeks) for paclitaxel-treated participants. The corresponding HR of 1.051 (95% CI: 0.663 to 1.667) showed that there was no statistically significant difference between the two treatment arms in relation to overall survival in this subgroup of platinum-sensitive patients. A summary of the overall survival in the platinum-sensitive disease subgroup is displayed in *Table 25*.

The results of the analysis for the subgroup of patients with platinum-resistant disease showed that the median overall survival was 36.7 weeks (range: 2.3–241.1+ weeks) for the PLDH-treated participants and 54.3 weeks (range: 1.7–211.4+ weeks) for the paclitaxel-treated participants. There were no statistically significant differences between the two groups in terms of survival, as indicated by an HR of 0.865 (95% CI: 0.61 to 1.24). *Table 26* summarises the long-term survival data for the participants with platinum-resistant disease.

Progression-free survival

No data were reported for this outcome.

TABLE 26 *Summary of overall survival data based on PLDH versus paclitaxel: platinum-resistant disease subgroup*

Intervention	*N*	Censored (%)	Median (weeks)	Range (weeks)	*p*-Value	HR[a]	95% CI for HR
PLDH	64	3.1	36.7	2.3–242.1[b]	0.427	0.865	0.61 to 1.24
Paclitaxel	67	6.0	54.3	1.7–211.4[b]			

[a] An HR > 1 indicates an advantage for PLDH.
[b] A censored observation.

Response
The data for this outcome measure were not analysed and therefore no data are reported.

Quality of life
There were no results reported for the QoL assessment.

Adverse events
Overall in this trial, 16.7% (18/108) of the PLDH-treated participants and 6.5% (7/108) of the participants in the paclitaxel group discontinued treatment owing to adverse events.

The five most commonly reported treatment-emergent adverse events for the PLDH-treated participants were nausea (51.9%), PPE (50.9%), stomatitis (48.1%), alopecia (43.5%) and asthenia (38.9%). For the paclitaxel-treated participants, 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 reported in *Table 27*, and RRs of experiencing a grade 3 toxicity are displayed in *Figure 14*.

Grade 3 and 4 adverse events
The incidence of grade 4 adverse events was relatively low in both of the treatment arms.

Neutropenia was the only grade 4 event reported in both of the treatment groups, 0.9% in the PLDH group compared with 2.8% in the paclitaxel treatment arm. The other grade 4 toxicities reported in the PLDH group were infection (0.9%), nausea (0.9%), vomiting (1.9%), leucopenia (0.9%), dyspnoea (0.9%) and PPE (0.9%). None of these toxicities were reported at the grade 4 level of severity in the paclitaxel group. Both grade 4 asthenia (0.9%) and alopecia (0.9%) were reported in the paclitaxel arm, with there being no incidence of these within the PLDH group.

At the grade 3 level of toxicity classification, the following toxicities were reported significantly more often in the PLDH group than the paclitaxel treatment arm:

- PPE (14.8 versus 0%), RR = 0.031 (95% CI: 0.003 to 0.297)
- ascites (10.2 versus 0.9%), RR = 0.17 (95% CI: 0.027 to 1.029)
- stomatitis (10.2 versus 0.9%), RR = 0.091 (95% CI:0.02 to 0.53)
- dyspnoea (5.6 versus 0.9%), RR = 0.17 (95% CI: 0.03 to 1.03).

The only toxicity that occurred more frequently in the paclitaxel treatment group than the PLDH group was alopecia (18.5 versus 2.8%), RR = 6.67 (95% CI: 2.20 to 20.66).

Summary of effectiveness data for PLDH versus paclitaxel
One RCT was identified that evaluated the efficacy and safety of PLDH compared with paclitaxel in women with epithelial ovarian carcinoma following failure of first-line platinum-based chemotherapy. This trial had been terminated early owing to poor participant accrual.

Overall survival
There were no significant differences between the two treatment groups in terms of overall survival. The median survival time was 46.6 weeks in the PLDH group compared with 56.3 weeks in the paclitaxel group; HR = 0.0932 (95% CI: 0.702 to 1.234).

There were no further significant differences in overall survival between the two treatment arms when this was assessed in the subgroups of participants with platinum-resistant and platinum-sensitive disease.

Adverse events
The most commonly reported adverse events in the PLDH treatment group were nausea, PPE, stomatitis, alopecia and asthenia. The most frequently reported events were alopecia, nausea,

TABLE 27 *Treatment-emergent adverse events in at least 10% of participants by preferred term: all grades, grade 3 and grade 4*

	PLDH (*n* = 108)			Paclitaxel (*n* = 108)		
Body system and adverse event	**All grades *n* (%)**	**Grade 3 *n* (%)**	**Grade 4 *n* (%)**	**All grades *n* (%)**	**Grade 3 *n* (%)**	**Grade 4 *n* (%)**
Body as a whole						
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
Leucopenia	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						
Dyspnoea	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

paresthesia, constipation and asthenia in the paclitaxel-treated participants.

The incidence of grade 4 adverse events was relatively low in both of the treatment arms. At the grade 3 level of toxicity classification, PPE, stomatitis, dyspnoea and ascites occurred more frequently in the PLDH treatment arm than the paclitaxel group. Alopecia occurred more frequently in the paclitaxel group than the PLDH group.

Effectiveness of single-agent paclitaxel compared with a combination of cyclophosphamide, doxorubicin and cisplatin (CAP)

Overall survival

Overall survival was defined as the time from randomisation to death by any cause. Participants still alive at the time of analysis were censored at the time of last follow-up. At a median follow-up of 49 months (range: 40–54 months), 61 participants had died; 27 of these were in the CAP treatment

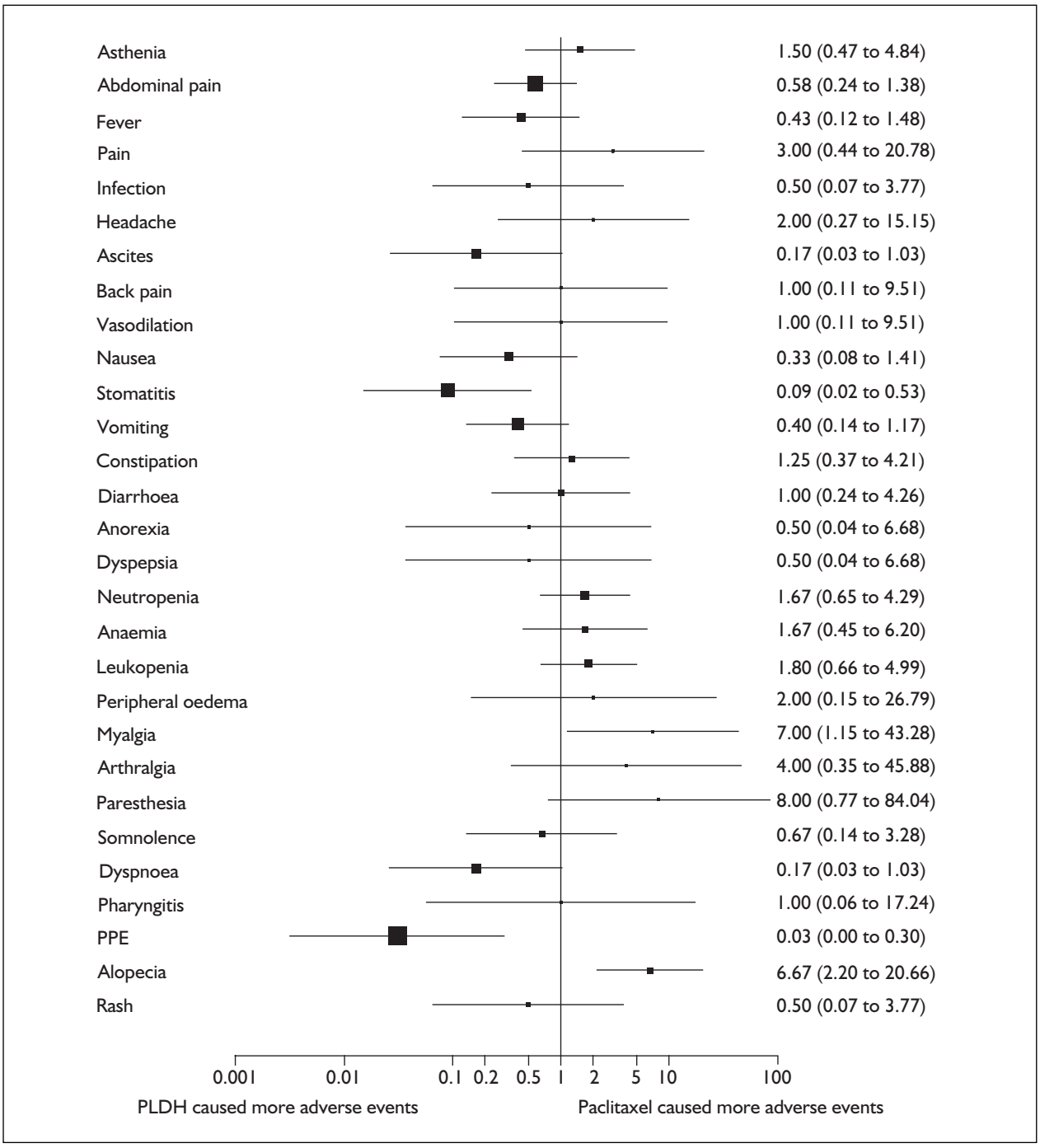

FIGURE 14 *Relative risks of grade 3 treatment-related adverse events for PLDH versus paclitaxel*

group (57% of group) and 34 in the paclitaxel treatment arm (72% of group). Median survival times were 34.7 months for the CAP treatment participants and 25.8 months for the paclitaxel treatment group.

Comparison of the Kaplan–Meier curves showed an insignificant trend in favour of CAP; HR = 0.70 (95% CI: 0.42 to 1.15); $p = 0.160$. However, after an adjustment for prognostic factors using a Cox multivariate regression analysis, with residual tumour, treatment-free interval and age adjusted for, the HR was 0.58 (95% CI: 0.34 to 0.98); $p = 0.043$ in favour of CAP. The regression analysis showed that the presence of a larger residual tumour (>2 cm) at the time of first surgery was associated with lower mortality; HR = 0.49 (95% CI: 0.28 to 0.86); $p = 0.013$.

TABLE 28 *Response to CAP compared with paclitaxel treatment*

Response	CAP (*n* = 47)		Paclitaxel (*n* = 47)		Total	
	No.	%	No.	%	No.	%
CR	14	30	8	17	22	23
PR	12	25	13	28	25	27
SD	14	30	10	21	24	26
PD	7	15	16	34	23	24
Total	47		47		94	
NE	0	0	0	0	3	3
Response after crossover						
CR	7	23	3	13	10	19
PR	7	23	2	9	9	17
SD	7	23	7	30	14	26
PD	9	30	11	48	20	38
Total	30		23		53	

Progression-free survival

A progression-free interval was defined as the time from randomisation to first appearance of progressive disease. ECOG criteria were used to assess response to chemotherapy.

Eighty-five patients had disease progression or had died (41 in the CAP arm and 44 in the paclitaxel treatment group) at a median follow-up time of 49 months (range: 40–54 months). Of these, 24 had disease progression and were still alive at the time of analysis, 54 had disease progression and died, and seven died without evidence of progression.

The median progression-free interval was 15.7 months in the CAP group compared with 9 months in the paclitaxel-treated participants. Comparison of the Kaplan–Meier curves for progression-free intervals by treatment showed an insignificant trend in favour of CAP; HR = 0.65 (95% CI: 0.41 to 1.01); $p = 0.08$.

Again, after adjustment for prognostic factors (residual tumour, treatment-free interval and age) by Cox regression analysis, the HR was 0.60 (95% CI: 0.37 to 0.97); $p = 0.038$ in favour of CAP compared with paclitaxel. There were no other significant associations between either age, residual tumour size or treatment-free interval and the risk of progression.

Response

In total, 94 participants were assessable for response. The overall response for both groups combined was 50% (22 CR and 25 PR). Twenty-four participants (26%) had stable disease and 23 participants (24%) evidenced disease progression during treatment. *Table 28* shows the responses to CAP compared with paclitaxel.

Fourteen participants in the CAP treatment group (30%) versus eight participants (17%) in the paclitaxel group had CR, RR = 0.57 (95% CI: 0.27 to 1.20). Twelve participants in the CAP arm (25%) compared with 13 participants in the paclitaxel-treated group (28%) had a PR, RR = 1.08 (95% CI: 0.56 to 2.11). In relation to stable disease, 14 participants in the CAP arm (30%) had stable disease compared with 10 participants (21%) in the paclitaxel arm, RR = 0.71 (95% CI: 0.35 to 1.42). None of these differences in response rates were significantly different between the two treatment groups. However, a significant difference was observed in relation to disease progression. Seven (15%) of the participants in the CAP treatment arm had progressive disease compared with 16 (34%) of the participants in the paclitaxel arm, RR = 2.29 (95% CI: 1.07 to 5.03).

Overall, a total of 53 patients were crossed over because of treatment failure. Twenty-three participants who did not respond to CAP were crossed over to paclitaxel treatment; three of these participants (13%) achieved a CR and a further two (9%) showed a PR. Thirty participants who initially did not respond to paclitaxel crossed over to the CAP treatment arm. In these participants, seven (23%) achieved a CR and seven (23%) achieved a PR. There were no statistically significant differences observed in the response rates between the two groups after crossover of regimen.

Figure 15 shows the RR of responding to CAP versus paclitaxel by response to initial treatment,

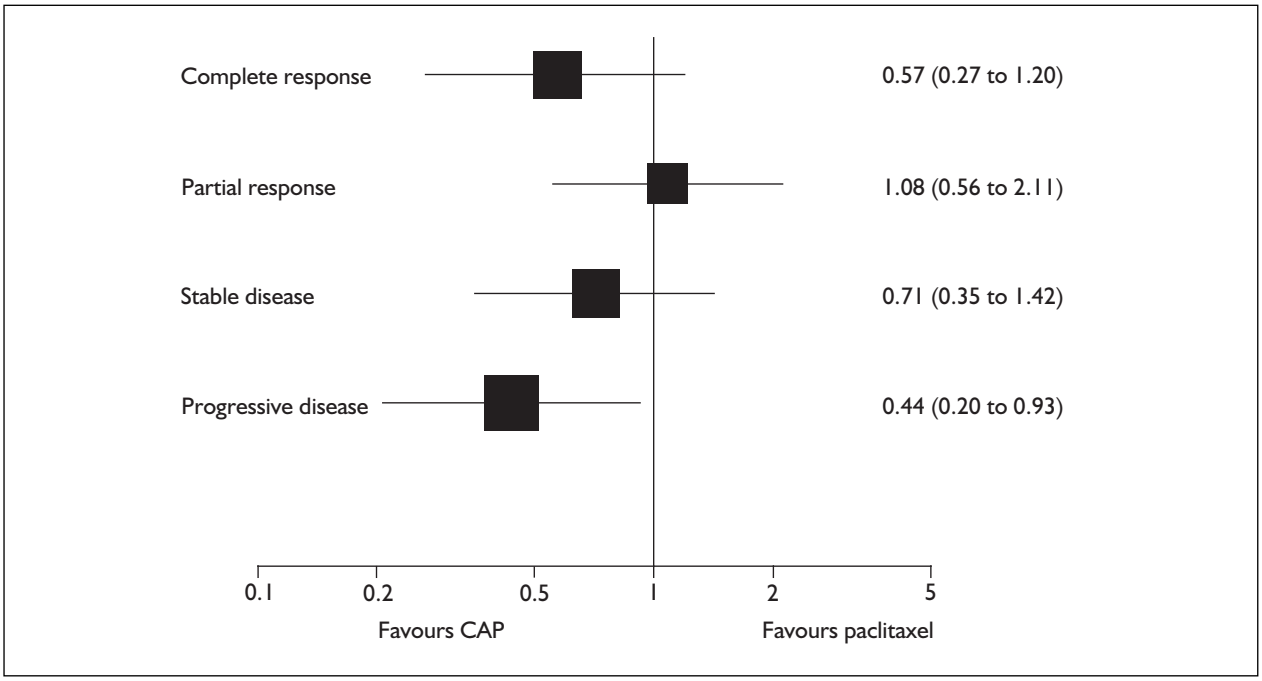

FIGURE 15 *Relative risk for response to CAP versus paclitaxel for initial treatment*

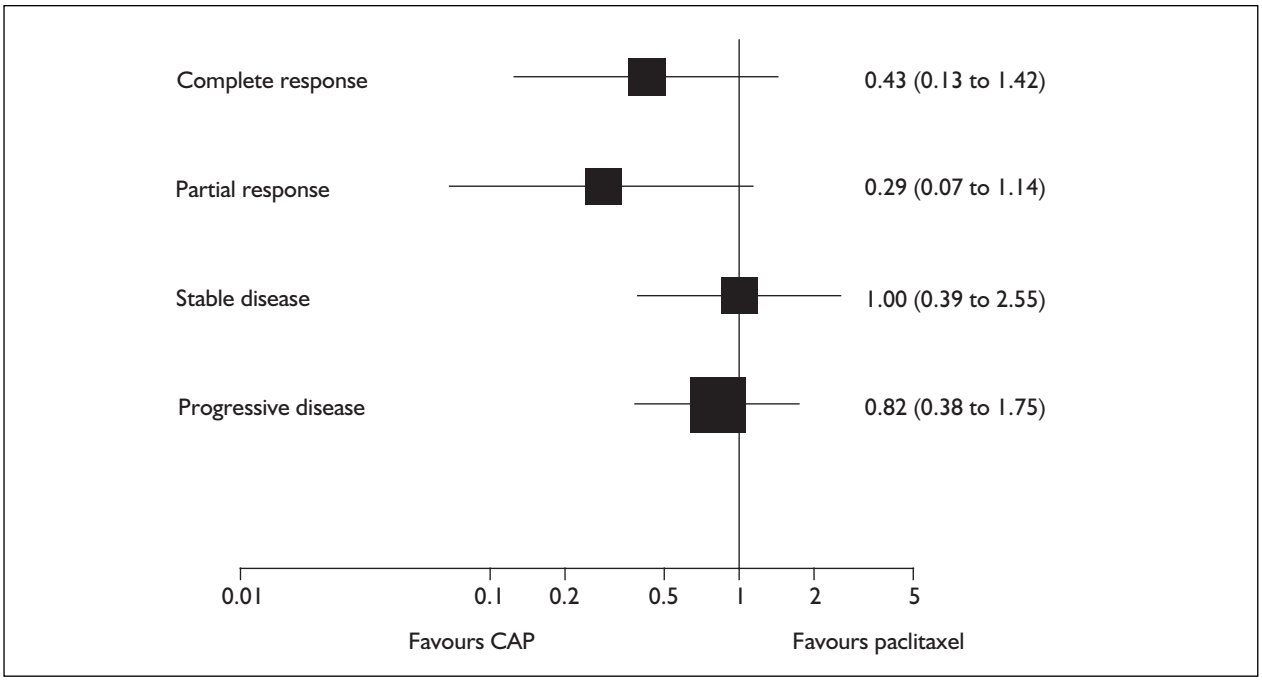

FIGURE 16 *Relative risk for response to CAP versus paclitaxel after treatment crossover*

and *Figure 16* displays the RR of responding to CAP versus paclitaxel by response after treatment crossover.

Quality of life

This outcome was not assessed in the trial, and therefore no data were reported.

Adverse events

The median number of treatment cycles administered was six in both trial arms. The major reason for stopping treatment was disease progression. *Table 29* and *Figure 17* display the maximum grade toxicities experienced during treatment.

TABLE 29 *The maximum grade toxicities during treatment with paclitaxel compared with CAP*

	CAP (n = 47)		Paclitaxel (n = 47)		
Toxicity	**No.**	**%**	**No.**	**%**	***p*-Value**
Leucopenia (grade 3–4)	16	34	2	4	0.001
Neutropenia (grade 3–4)	17	36	6	13	0.009
Thrombocytopenia (grade 3–4)	6	13	–	–	0.012
Nausea and vomiting (grade 2–3)	24	51	8	17	0.004
Alopecia	28	60	41	87	0.010
Allergic reactions	1	2	7	15	0.085
Sensory neuropathy (≥ grade 2)	3	6	5	11	0.002
Myalgia (grade 2)	2	4	9	19	0.025
Other (cardiac toxicity, renal toxicity, stomatitis)	1	2	4	8	>0.05

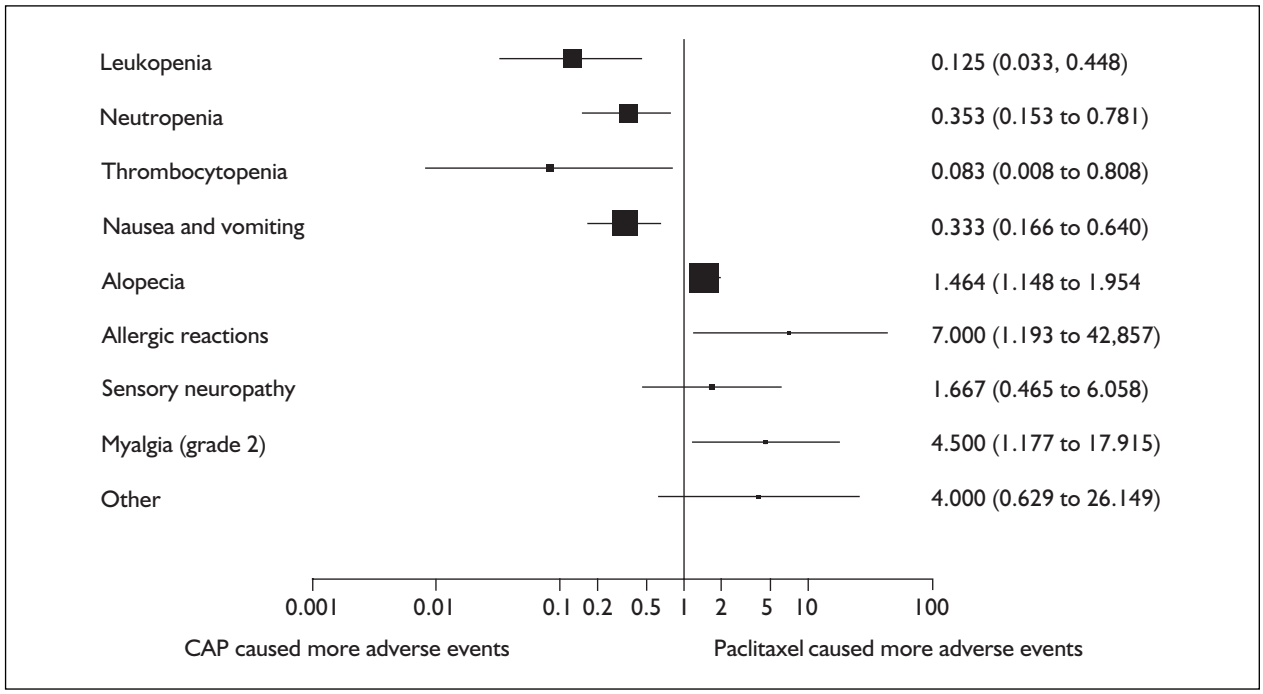

FIGURE 17 *Relative risks of treatment-related toxicities for paclitaxel compared with CAP*

As is shown in *Table 29* and *Figure 17*, the toxicity profiles were different between the paclitaxel and CAP treatment arms. CAP was associated with significantly higher rates of grade 3–4 haematological toxicity compared with paclitaxel:

- leucopenia (34 versus 4%), RR = 0.13 (95% CI: 0.033 to 0.45)
- neutropenia (36 versus 13%), RR = 0.35 (95% CI: 0.15 to 0.78)
- thrombocytopenia (13 versus 0%), RR = 0.083 (95% CI: 0.008 to 0.808).

Grade 2–3 nausea and vomiting was also significantly higher in the CAP treatment group, 51% compared with 17% in the paclitaxel-treated arm, RR = 0.33 (95%CI: 0.17 to 0.64).

The rates of alopecia were high in both groups, but significantly higher rates were associated with paclitaxel treatment (87%) compared with CAP treatment (60%), RR = 1.46 (95% CI: 1.48 to 1.95). Allergic reactions were also significantly higher in the paclitaxel group, 15% compared with 2% in the CAP treatment arm, RR = 7.00 (95% CI: 1.19 to 42.86). The incidence of sensory neuropathy, myalgia and other toxicities (cardiac, renal and stomatitis) were all higher in the paclitaxel-treated group than in the CAP arm, with rates of 11 versus 6%, 19 compared with 4%

and 8 versus 2%, respectively. All other toxicities were rare in both treatment arms.

Summary of effectiveness data for paclitaxel versus CAP

One RCT was included that compared single-agent paclitaxel and a platinum-containing regimen (CAP) in participants who had been previously treated, with recurrent ovarian cancer.

Overall survival

There was a significant difference between the two treatment groups in terms of overall survival in favour of CAP; HR = 0.58 (95% CI: 0.34 to 0.98). The median survival times were 34.7 months for the CAP treatment group compared with 25.8 months for the paclitaxel treatment group.

Progression-free survival

There was a statistically significant difference in PFS between the CAP treatment arm and the paclitaxel treatment group in favour of CAP; HR=0.60 (95% CI: 0.37 to 0.97). The median progression-free interval was 15.7 months in the CAP treatment group and 9 months in the paclitaxel treatment group.

Response

There were no significant differences between the treatment groups in response rates; 55% of participants in the CAP arm and 45% in the paclitaxel arm had a complete or partial response.

Quality of life

This outcome was not assessed, therefore no data were reported.

Adverse events

Grade 3–4 haematological toxicities were reported significantly more often in the CAP treatment arm than the paclitaxel treatment group. Grade 2–3 nausea and vomiting were also significantly higher in the CAP treatment group. The rates of alopecia were high in both groups, but significantly higher rates were associated with paclitaxel treatment. Allergic reactions were also significantly higher in the paclitaxel group. The incidence of sensory neuropathy, myalgia and other toxicities (cardiac, renal and stomatitis) were all higher in the paclitaxel treated group than in the CAP arm. All other toxicities were rare in both treatment arms.

Effectiveness of paclitaxel in combination with platinum-based chemotherapy versus platinum-based therapy alone

This section of the report summarises the trial by the ICON and AGO Collaborators.[29]

Overall survival

The primary outcome was overall survival, which was defined as the time from randomisation to death from any cause. Patients known to still be alive at the time of the analysis were censored at the time of their last follow-up. At a median follow-up time of 42 months, 530 (66%) of participants in the trial had died. *Figure 18* shows the Kaplan–Meier curves for overall survival.

The survival curves indicated an HR of 0.82 (95% CI: 0.69 to 0.97) in favour of the participants in the paclitaxel and platinum-based combination group relative to the platinum-based monotherapy group for overall survival. This translates into an absolute difference in 2-year survival of 7% in favour of the paclitaxel combination therapy compared with the conventional monotherapy treatment group [57 versus 50% (95% CI for difference: 1 to 12%)]. For median survival the HR translates into a difference of 5 months [29 versus 24 months (95% CI for difference: 1 to 9)].

Effect of paclitaxel plus platinum chemotherapy on overall survival in sub-groups

An analysis was undertaken to explore the effect of the two different treatment regimens on survival in the different subgroups defined by randomisation group, time since completion of last chemotherapy, number of previous lines of chemotherapy, previous exposure to taxanes, intended platinum agent (carboplatin or cisplatin), age and WHO performance status. This analysis indicated that there were no significant differences between the paclitaxel plus platinum chemotherapy treatment group and the conventional treatment group in any of the subgroups in relation to overall survival. However, many of the subgroups were small and therefore may have lacked the power to detect any real differences between the groups. There were, however, a number of statistically insignificant trends and interactions observed within the subgroup data. Trends were observed within the subgroups of age (<55, 55–65, >65 years) and the number of previous lines of chemotherapy (1, 2, >2). The interactions were observed within the subgroups of randomisation group (ICON4 MRC CTU, ICON4 Italy, AGO), WHO performance (WHO = 0, WHO > 0), intended platinum agent (carboplatin, cisplatin), time since completion of last chemotherapy cycle in months (≤ 12, >12) and previous exposure to taxanes (yes, no).

Progression-free survival

The secondary outcomes included PFS, which was defined as the time from randomisation to first

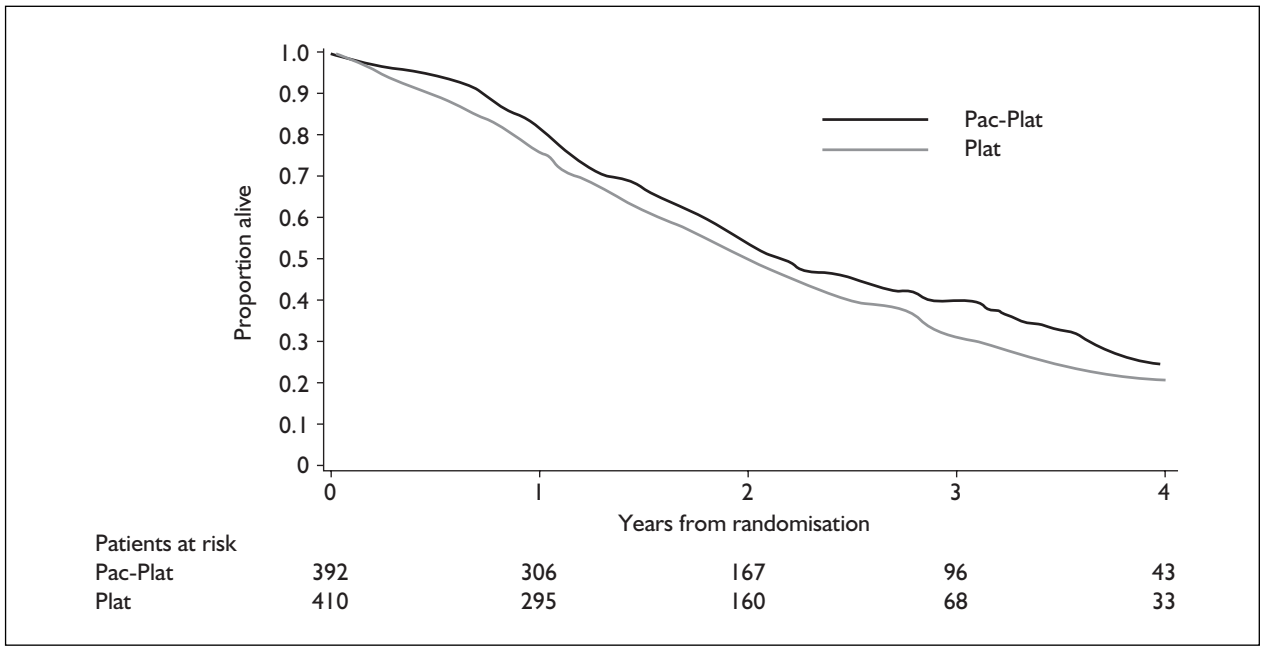

FIGURE 18 *Kaplan–Meier curves for overall survival for paclitaxel–platinum combination therapy versus platinum-based therapy alone. Reproduced with permission from PowerPoint presentation by Lederman JA on behalf of all ICON and AGO Collaborators, ASCO Gynecologic Care: Advances in management, 1 June 2003.*

appearance of progressive disease or death from any cause. Again, patients known to be alive and without progressive disease at the time of analysis were censored at their last follow-up. At a median follow-up time of 42 months 717 (89%) of patients had developed progressive disease or died. *Figure 19* shows the Kaplan-Meier curves for PFS.

The survival curves showed an HR of 0.76 (95% CI: 0.66 to 0.89) in favour of paclitaxel plus platinum chemotherapy relative to platinum-based chemotherapy alone for PFS. This translated into an estimated absolute difference in 1-year progression-free survival of 10% [40 versus 50% (95% CI for difference: 4 to 15%)]. Further analysis by the trial collaborators indicated that the results translated into an absolute difference in median PFS of 3 months in favour of the combination chemotherapy group relative to the conventional monotherapy group [9 versus 12 months (95% CI for difference: 1 to 4)].

Effect of paclitaxel plus platinum chemotherapy on progression-free survival in subgroups

An analysis was undertaken to explore the effect of the two different treatment regimens on PFS in the different subgroups. These were again defined by randomisation group (ICON4 MRC CTU, ICON4 Italy, AGO), WHO performance (WHO = 0, WHO > 0), intended platinum agent (carboplatin, cisplatin), time since completion of last chemotherapy cycle in months (≤ 12, >12) and previous exposure to taxanes (yes, no). Once again the analysis showed that there were no significant differences between the paclitaxel plus platinum chemotherapy treatment group and the conventional treatment group in terms of PFS in any of the subgroups. There were again, however, a number of statistically insignificant trends and interactions shown within the subgroup data. Trends were observed within the subgroups of age and the number of previous lines of chemotherapy regimens. The interactions were observed within the subgroups of randomisation group, WHO performance, intended platinum agent, time since completion of last chemotherapy cycle in months and previous exposure to taxanes.

Response rate

There were no statistically significant differences observed between the two treatment groups in relation to response rate, defined as a complete or partial response. However, 66% (78/119) of participants in the paclitaxel plus platinum chemotherapy group had a response to treatment compared with 54% (69/128) of participants in the conventional monotherapy group. This showed a difference of 12% (95% CI: 0.1 to 24%) in response rate in favour of the paclitaxel plus platinum group.

Quality of life

Quality of life was assessed using the EORTC QLQ-C30. In total 482 (90%) of 536 patients

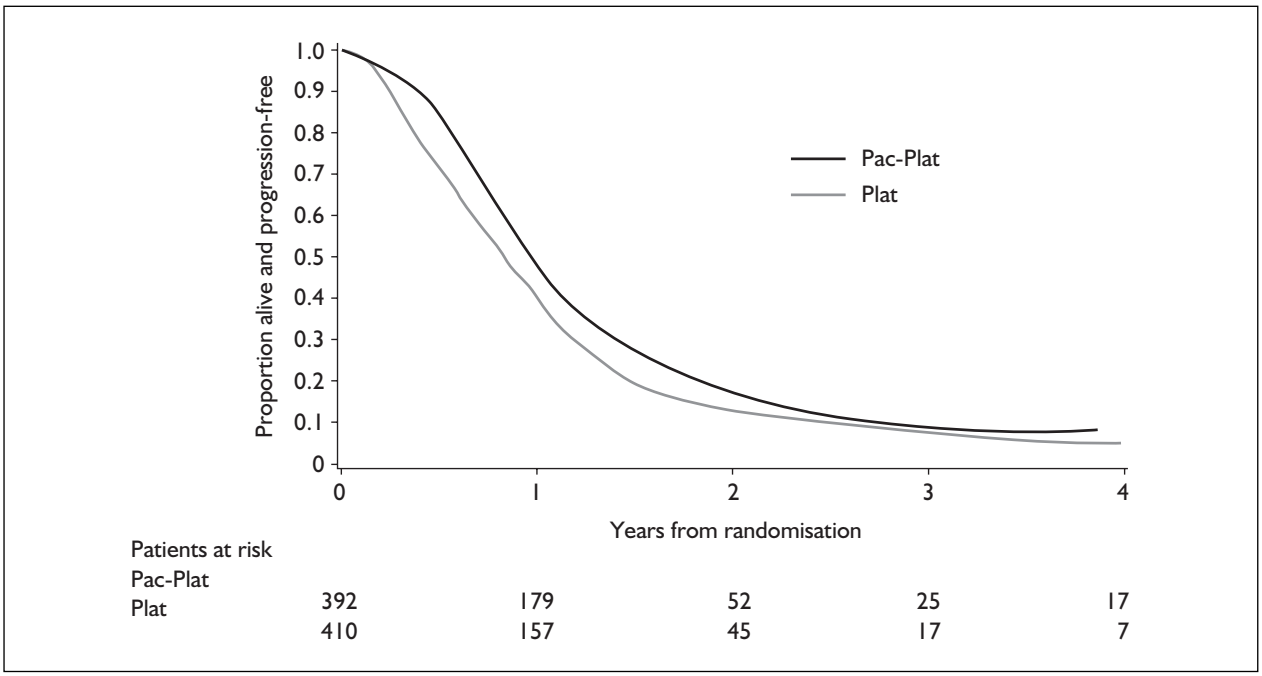

FIGURE 19 *Kaplan–Meier curves for progression-free survival for paclitaxel–platinum combination therapy versus platinum-based therapy alone. Reproduced with permission from Powerpoint presentation by Lederman JA on behalf of all ICON and AGO Collaborators; ASCO Gynecologic care: Advances in management, 1 June 2003.*

completed the questionnaire at baseline, before receiving any study drug. All the scales were balanced across the two treatment groups at this time. The majority of the participants had little or no functional difficulties and few moderate or severe symptoms at baseline.

In the first 6 months postrandomisation there were no significant differences between the treatment groups for the worst scores or AUCs for all of the five functional scales for eight out of the nine symptoms scales and for the global health status. There was a significant difference observed between the two groups on the nausea and vomiting symptom scale. This symptom was worse for the participants receiving the conventional platinum-based monotherapy ($p = 0.0014$ for worst score; $p = 0.005$ for AUC). However, this difference appeared to be transient, lasting only for the first 15 weeks of treatment.

Adverse events

Data were only reported for the moderate and severe toxic effects experienced during treatment. The incidence of grade 2–4 neurological toxicities was significantly higher in the paclitaxel plus platinum chemotherapy regimen group compared with the conventional platinum-based therapy group (20 versus 1%), RR = 19.10 (95% CI: 7.37 to 49.93). The rates of alopecia were also significantly higher in this group (86%) compared with the conventional monotherapy regimen group (25%), RR = 3.47 (95% CI: 2.92 to 4.17).

The rates of haematological toxicity were significantly higher in the conventional platinum chemotherapy group. In this group, 46% of participants experienced haematological toxicity compared with 29% in the combination therapy group, RR = 0.63 (95% CI: 0.52 to 0.75). The incidence of grades 2–4 nausea and vomiting was also higher in the conventional platinum-based therapy group, 40% compared with 35% in the combination therapy group. However, this difference in the rates was not statistically significant. The rates of other reported toxic effects (infection, mucositis and renal) were low in both treatment groups.

Table 30 shows the incidence of moderate or severe toxic effects experienced in both treatment groups, and *Figure 20* displays the relative risks of experiencing a moderate or severe toxicity during treatment.

Summary of the effectiveness of paclitaxel in combination with platinum-based chemotherapy versus platinum-based therapy alone

One RCT was included which investigated the use of paclitaxel in combination with platinum-based chemotherapy in patients with epithelial ovarian

TABLE 30 *The proportion of patients in each treatment group who experienced moderate or severe toxic effects during treatment, along with the RR and 95% CI*

Toxic effect	Conventional platinum-based chemotherapy (*n* = 410)	Paclitaxel plus platinum chemotherapy (*n* = 392)	RR	95% CI
Neurological (grade 2–4)	4 (1%)	76 (19%)	19.10	7.37 to 49.93
Not yet known	31	15		
Haematological[a]	182 (44%)	111 (28%)	0.63	0.52 to 0.75
Not yet known	16	8		
Infection[a]	53 (13%)	64 (16%)	1.24	0.89 to 1.73
Not yet known	24	15		
Renal[a]	37 (9%)	31 (8%)	0.86	0.55 to 1.35
Not yet known	16	8		
Mucositis (grade 2–3)	21 (5%)	26 (7%)	1.24	0.72 to 2.16
Not yet known	31	15		
Nausea and vomiting (grade 2–4)	153 (37%)	131 (33%)	0.87	0.72 to 1.04
Not yet known	29	15		
Alopecia (grade 2–4)	95 (23%)	322 (82%)	3.47	2.92 to 4.17
Not yet known	28	19		

[a] Toxic effect leading to treatment modification or interruption reported.

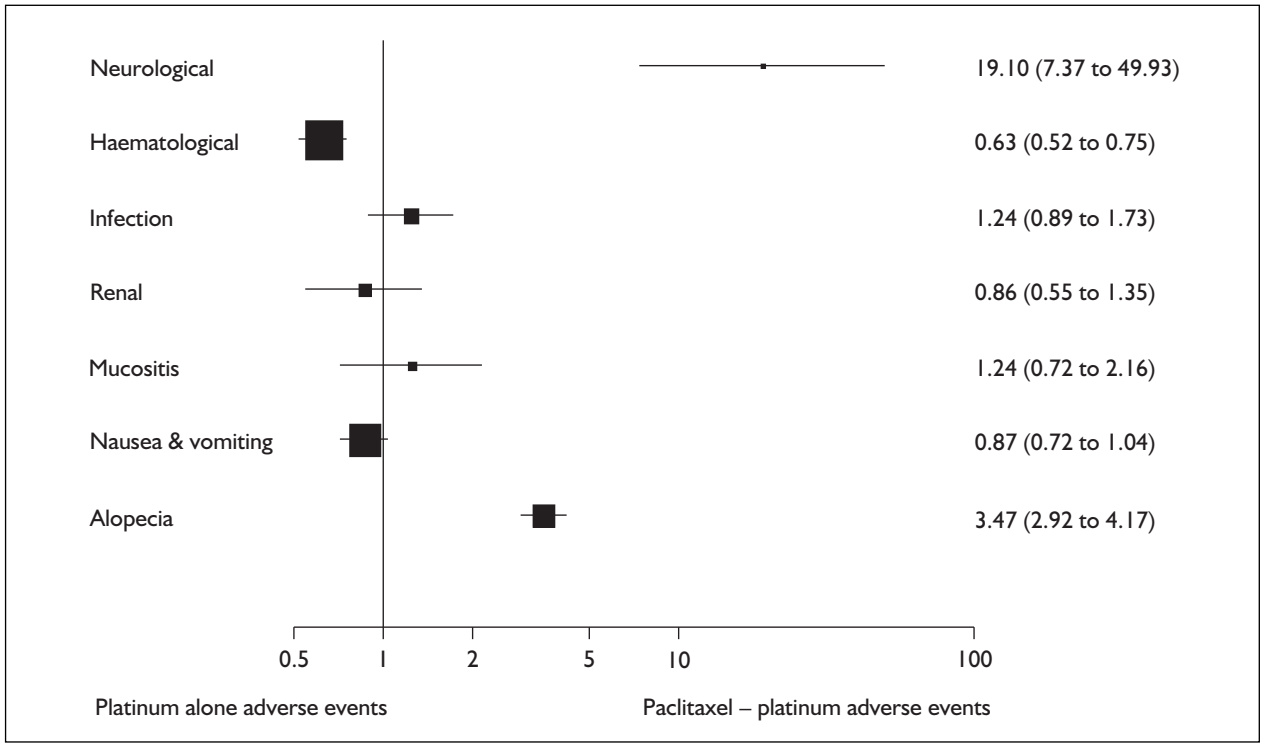

FIGURE 20 *Relative risks of moderate to severe toxicity for paclitaxel plus platinum chemotherapy compared with conventional platinum-based therapy alone*

carcinoma who had relapsed after 6 months following first-line platinum-based chemotherapy.

Overall survival

There was a significant difference in overall survival observed between the two groups in favour of the paclitaxel and platinum-based combination group, HR = 0.82 (95% CI: 0.69 to 0.97). This showed an absolute difference in the 2-year survival rates of 7% in favour of this group, 57 versus 50%. For median survival the HR translated into a difference of 5 months, 29 versus 24 months.

There were no significant differences between the two treatment regimens in any of the subgroups in relation to overall survival.

Progression-free survival

There was a significant difference in PFS rates between the two treatment regimens that favoured the paclitaxel plus platinum-based chemotherapy group relative to the platinum-based chemotherapy group; HR = 0.76 (95% CI: 0.66 to 0.89). This translated into an estimated absolute difference in 1-year PFS of 10% (40 versus 50%) and an absolute difference in median PFS of 3 months in favour of the combination therapy group (9 versus 12 months).

There were no significant differences between the two therapy regimen groups in terms of PFS in any of the subgroups.

Response rate

There were no statistically significant differences between the two treatment groups in response rates, complete or partial response; 66% of the participants in the paclitaxel plus platinum chemotherapy group had a response compared with 54% in the conventional monotherapy group. This showed an insignificant difference of 12% between the two treatment groups.

Quality of life

In the first 6 months postrandomisation, there were no significant differences between the two treatment groups for the worst scores or AUCs for the functional scales, the global health status or eight out of nine symptoms scales. There was a significant difference between the groups on the nausea/vomiting subscale which was transient, lasting for the first 15 weeks of treatment only. This symptom was worse for the participants in the conventional platinum-based monotherapy group.

Adverse events

The rates of grade 2–4 neurological toxicities and alopecia were significantly higher in the paclitaxel plus platinum chemotherapy regimen group compared with the conventional monotherapy group.

The incidence of haematological toxicity was significantly higher in the conventional platinum-based monotherapy group compared with the combination therapy group. The incidence of grades 2–4 nausea and vomiting was also higher in this group, but this was not statistically significant.

Effectiveness of single-agent paclitaxel versus oxaliplatin

This section of the report summarises the trial by Piccart and colleagues.[30]

Overall survival

At the time of cut-off, 45 participants had died out of the 86 randomised in total, 25/41 in the paclitaxel arm and 20/45 in the oxaliplatin treatment arm. The estimated median overall survival was 37 weeks in the paclitaxel treatment arm compared with 42 weeks in the oxaliplatin treatment group.

Time to progression

The median TTP in the paclitaxel-treated participants was 14 weeks compared with 12 weeks in the oxaliplatin arm. At the time of analysis 9/41 participants in the paclitaxel arm had not progressed relative to 8/45 in the oxaliplatin treatment group. In both treatment arms the median times to treatment failure were comparable, 13 weeks for the paclitaxel arm and 12 weeks for the oxaliplatin arm.

Response rate

The primary efficacy end-point in this trial was the confirmed response rate. Confirmed response, verified by two independent radiologists, was defined as PR or CR that was observed in at least two consecutive evaluations that were at least 4 weeks apart. Overall response rate was defined by the total number of participants in each treatment arm.

All participants who received at least two treatment cycles were considered by the investigators to be assessable for response. Five participants, two in the paclitaxel arm and three in the oxaliplatin arm, were not assessable. Four of these participants were ineligible to be included in the trial and one died 6 days after the first dose of oxaliplatin due to causes unrelated to treatment. *Table 31* shows the response to treatment with paclitaxel versus oxaliplatin in the total treatment population.

Overall, the results showed that there were seven PRs to treatment in each of the trial arms. The response rate in the paclitaxel arm was 17% (95% CI: 7 to 32%) compared with 16% (95% CI: 7 to 29%) in the oxaliplatin-treated group. Of the participants who were categorised as potentially platinum sensitive, two out of 10 (20%) in the paclitaxel treatment group and five out of 13 (38%) in the oxaliplatin arm had a PR. Of the participants who were categorised at baseline as

TABLE 31 *Response to treatment with paclitaxel versus oxaliplatin in the total treatment population*

	Paclitaxel (n = 41)		Oxaliplatin (n = 45)	
Response category	**No. of participants**	**%**	**No. of participants**	**%**
CR	0	0	0	0
PR	7	17	7	16
NC	18	44	20	44
PD	14	34	15	33
NE	2	5	3	7
Total	41	100	45	100

NC, no change.

being platinum resistant, five out of 31 (16%) in the paclitaxel arm compared with two out of 32 (6%) in the oxaliplatin group had a PR.

Response duration
The median duration of response was 33 weeks in the paclitaxel-treated participants compared with 31 weeks in the oxaliplatin-treated arm. At the time of cut-off, eight out of the 14 participants who had achieved a PR had progressed, 3/7 in the paclitaxel arm and 5/7 in the oxaliplatin arm.

Quality of life
Sixty-six participants completed the QoL assessment at baseline, but only 47 completed questionnaires at the end of the second treatment cycle (6 weeks) and 31 at the end of the fourth treatment cycle (12 weeks). The mean QoL score increased by more than 10 points between baseline and cycle 4 for the participants in the paclitaxel treatment group, regardless of study withdrawal. In the oxaliplatin group, the mean QoL score decreased, but by less than 10 points through cycle 2, and then returned to baseline levels thereafter for the majority of participants.

Adverse events
All of the 86 participants in the trial received at least one treatment cycle and therefore were assessable for the toxicity analysis. A summary of the haematological and non-haematological toxicities associated with treatment is given in *Table 32*.

Haematological toxicities
Severe neutropenia (grades 3 and 4) occurred in the paclitaxel treatment group in nine patients (22%), whereas grade 3 thrombocytopenia occurred only in two patients (4%) in the oxaliplatin treatment arm. Severe anaemia occurred once in each treatment group; in the paclitaxel group it was rated as being of grade 4 severity and in the oxaliplatin group of grade 3.

Gastrointestinal
All instances of nausea and vomiting were rated as being mild to moderate (grade 3). One occurrence of nausea and one of vomiting occurred in the paclitaxel treatment arm in comparison with two occurrences of nausea and three of vomiting in the oxaliplatin treatment group. Diarrhoea was only reported in the oxaliplatin treatment group, of which there were two reports.

Neurosensory
Grade 3 neurosensory toxicity was reported in three participants in the paclitaxel arm and in four participants in the oxaliplatin treatment group.

Lethargy and pain
Lethargy was reported in three participants in each of the treatment groups. Pain was reported in five participants in the paclitaxel treatment arm compared with two participants in the oxaliplatin treatment arm.

Summary of the trial comparing single-agent paclitaxel and oxaliplatin
One Phase II RCT was identified that evaluated the efficacy of oxaliplatin compared with single-agent paclitaxel in a relapsing progressive ovarian cancer patient population.

Overall survival
There were significant differences between participants treated with paclitaxel and those treated with oxaliplatin in overall survival. The estimated median overall survival was 37 weeks in the paclitaxel treatment arm compared with 42 weeks in the oxaliplatin treatment group.

TABLE 32 *Severe (grade 3 and 4) toxicity by treatment group for paclitaxel compared with oxaliplatin*

Toxicity	Paclitaxel (*n* = 41)				Oxaliplatin (*n* = 45)			
	Grade 3		Grade 4		Grade 3		Grade 4	
	No.	%	No.	%	No.	%	No.	%
Haematological								
Neutropenia	6	15	3	7	–	–	–	–
Anaemia	–	–	1	2	1	2	–	–
Thrombocytopenia	–	–	–	–	2	4	–	–
Liver function								
AST	–	–	–	–	–	–	–	–
ALT	2	5	–	–	–	–	–	–
Gastrointestinal								
Nausea	1	2	NA	NA	2	4	NA	NA
Vomiting	1	2	–	–	3	7	–	–
Diarrhoea	–	–	–	–	2	4	–	–
Neurosensory	3	7	NA	NA	4	9	NA	NA
Other								
Lethargy	3	7	NA	NA	3	7	NA	NA
Pain	5	12	–	–	2	4	–	–

ALT, alanine aminotransferase; AST, levels of aspartate aminotransferase; NA, not applicable.

Time to progression

The median TTP was 14 weeks in the paclitaxel treatment group compared with 12 weeks in the oxaliplatin arm. This difference was not statistically significant. There were also no differences between the two treatment groups in terms of time to treatment failure, which was 13 weeks in the paclitaxel arm and 12 weeks in the oxaliplatin arm.

Response rate

There were no CRs in either of the treatment groups. In the paclitaxel group 17% of participants had a PR compared with 16% in the oxaliplatin group.

Response duration

There were no significant differences between the treatment groups in response duration. The median response duration was 33 weeks in the paclitaxel arm compared with 31 weeks in the oxaliplatin arm.

Quality of life

The mean QoL score increased by more than 10 points between baseline and cycle 4 for participants in the paclitaxel treatment group. In the oxaliplatin group, the mean QoL score decreased slightly through cycle 2, and then returned to baseline levels. These data from the QoL outcome assessment should be interpreted with caution given the very small number of participants upon which they are based.

Adverse events

Severe neutropenia was more common in the paclitaxel treatment group than the oxaliplatin group (22 versus 4%). Thrombocytopenia was more common in the oxaliplatin group than the paclitaxel treatment arm (4 versus 0%). All other adverse events were similar between the two treatment arms.

Effectiveness of paclitaxel given weekly versus every 3 weeks

This section of the report summarises the results reported by Rosenberg and colleagues.[31]

Overall survival

The median survival for the weekly group was 13.6 months (95% CI: 10.5 to 18.7) compared with 14.7 months (95% CI: 12.3 to 19.1) for the every 3 weeks group. This difference in the median survival times between the two treatment regimens was not statistically significant.

Time to progression

There were no statistically significant differences between the weekly and every 3 weeks group in terms of TTP. The median time to progression was 6.1 months (95% CI: 5.0 to 8.0) in the weekly

TABLE 33 *Response rate by treatment group for weekly versus 3-weekly paclitaxel*

Response	Paclitaxel 67 mg/m^2/week (n = 105)	Paclitaxel 200 mg/m^2/3 weeks (n = 103)
CR[a]	13 (12.4%)	17 (16.5%)
PR[b]	24 (22.8%)	21 (20.4%)
Overall response rate	37 (35.2%)	38 (36.9%)
SD	43 (41.0%)	33 (32.0%)
PD	15 (14.3%)	19 (18.5%)
NE	9 (8.6%)	11 (10.7%)
Not treated	1 (0.9%)	2 (1.9%)

[a] Three participants in each group had unconfirmed CR.
[b] Seven and six participants in the weekly and every 3 weeks group, respectively, had unconfirmed PR.

group versus 8.1 months (95% CI: 6.4 to 9.7) for the every 3 weeks group.

Response

The primary outcome in the study was response rate, which was categorised according to WHO tumour response criteria.

There were no significant differences between the two groups in terms of response rate. Thirty-seven participants in the weekly group and 38 in the every 3 weeks group responded to treatment. *Table 33* displays the tumour response rate for all participants in the ITT analysis by group.

Response duration

The overall median response duration did not differ significantly between the two treatment groups. The median response duration was 9.4 months (95% CI: 6.2 to 13.9) for the weekly group compared with 12.4 months (95% CI: 9.1 to 14.3) for the every 3 weeks group (p = 0.57). The CR duration was also shorter in the weekly group at 4.5 months (95% CI: 3.6 to 10.7) compared with 7.8 months (95% CI: 4.2 to 10.2) in the every 3 weeks group. However, again this did not reach a level of statistical significance (p = 0.84).

Quality of life

This outcome was not assessed in the trial, therefore no data were reported.

Adverse events

The safety analysis was based on 205 participants who received at least one dose of paclitaxel. There were no treatment-related deaths reported in the trial. *Table 34* shows the adverse events reported in the trial.

Haematological toxicity

Significantly more participants in the paclitaxel every 3 weeks group experienced grade 3 or 4 neutropenia, 45/101 (45%) compared with 19/104 (18%) in the weekly group. Thrombocytopenia was uncommon in both of the treatment groups.

Non-haematological toxicity

Grade 1–3. Grade 1–3 non-haematological toxicity was frequently observed in both of the treatment arms. Neuropathy occurred in 84/104 (81%) of participants in the weekly treatment group and in 86/101 (85%) of the participants in the every 3 weeks group. Alopecia occurred in 85/104 (82%) and 91/101 (90%) of participants in the weekly and 3-weekly groups, respectively. Although arthralgia/myalgia occurred frequently in both groups, it occurred significantly more often in the every 3 weeks group, 85/101 (84%), compared with the weekly group, 61/104 (59%), RR = 1.30 (95% CI: 1.17 to 1.69). Problems with nail changes (discoloration and/or loosening from the nail bed) occurred significantly more often in the weekly treatment arm, 37/104 (36%), compared with the every 3 weeks treatment arm, 2/101 (2%). Participants in both treatment arms reported nausea and vomiting relatively frequently. In the weekly group 48/104 (46%) and in the every 3 weeks group 42/101 (42%) reported this as a side-effect of treatment.

Grade 3. Grade 3 neuropathy was observed significantly more frequently in the every 3 weeks treatment arm, 29/101 (29%), compared with the weekly treatment group, 11/104 (11%), RR = 2.71 (95% CI: 1.46 to 5.12). Likewise, alopecia was also observed significantly more often in this group, 80/101 (79%) compared with 48/104 (46%) in the weekly treatment arm. Problems with nail changes were observed significantly more often in the weekly treatment group, 9/104 (9%), compared with no occurrences of this problem in the 3-weekly treatment group. There were no significant

TABLE 34 *Adverse events for weekly versus 3-weekly paclitaxel*

	Paclitaxel 67 mg/m^2/week (n = 104)	Paclitaxel 200 mg/m^2/3 weeks (n = 101)	p-Value
Haematological toxicity (lowest value per patient)			
Grade 1–4			
Haemoglobin	81 (78%)	65 (64%)	0.04
WBC	74 (71%)	79 (78%)	0.27
Neutrophils	63 (61%)	80 (79%)	<0.01
Platelets	1 (1%)	5 (5%)	0.12
Grade 3–4			
Haemoglobin	4 (4%)	4 (4%)	1.0
WBC	17 (16%)	17 (17%)	1.0
Neutrophils	19 (18%)	45 (45%)	<0.001
Platelets	0	1 (1%)	0.49
Non-haematological toxicity (worst value per patient)			
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
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

WBC, white blood cell count.

differences between the two arms in relation to the number of episodes of nausea/vomiting or arthralgia/myalgia.

Hypersensitivity reactions

The number and severity of hypersensitivity reactions were assessed for the 106 participants who received the standard premedication schedule of oral steroids 12 and 6 hours prior to paclitaxel and the 99 participants who received parenteral steroids 30 minutes prior to paclitaxel administration. There were no statistically significant differences between the two groups, either overall or for grade 3–4 reactions. The paclitaxel infusion was discontinued in ~3% of participants in both arms owing to hypersensitivity reactions. *Table 35* shows the number of hypersensitivity reactions experienced in both treatment arms.

Summary of the trial of paclitaxel given weekly versus every 3 weeks

One RCT was included that evaluated the efficacy and toxicity of paclitaxel given at the same dose intensity and administered weekly or every 3 weeks in women who had received one prior platinum-containing chemotherapy regimen without a taxane.

Overall survival

There were no significant differences between the two treatment regimens in terms of overall survival. The median survival was 13.6 months in the weekly group compared with 14.7 months in the every 3 weeks group.

Time to progression

The median TTP was 6.1 months in the weekly group compared to 8.1 months in the every 3 weeks group. This difference between the two treatment groups was not statistically significant.

Response

There were no significant differences between the two treatment regimens on this outcome measure; 35% of participants in the weekly regimen group responded to treatment compared with 35% in the every 3 weeks group.

TABLE 35 *Hypersensitivity reactions for weekly versus 3-weekly paclitaxel*

	Oral steroids 12 and 6 hours prior to paclitaxel (*n* = 106)	Parenteral steroids 30 minutes prior to paclitaxel (*n* = 99)
Grade 1–4		
Skin	17 (16.0%)	18 (18.2%)
Generalised urticaria	1 (0.9%)	0
Dyspnea	4 (3.8%)	4 (4.0%)
Respiratory distress requiring treatment	1 (0.9%)	1 (1.0%)
Hypotension	1 (0.9%)	1 (1.0%)
Grade 3–4		
Skin	3 (2.8%)	4 (4.0%)
Generalised urticaria	1 (0.9%)	0
Dyspnoea	0	1 (1.0%)
Respiratory distress requiring treatment	1 (0.9%)	0

Response duration

The overall median response duration did not differ significantly between the two treatment groups. Response duration was 9.4 months in the weekly group compared with 12.4 months in the every 3 weeks group. CR duration also did not differ significantly: 4.5 months in the weekly group compared with 7.8 months in the every 3 weeks group.

Quality of life

QoL was not assessed as an outcome measure in this trial.

Adverse events

Grade 3 and 4 neutropenia and alopecia were significantly more common in the every 3 weeks group than the weekly group. Problems with nail changes were observed significantly more often in the weekly group than the every 3 weeks group.

Effectiveness of paclitaxel 175 mg/m^2 compared with 250 mg/m^2

This section of the report summarises the results of the trial by Omura and colleagues.[32]

Overall survival

Overall survival was defined as the time from randomisation until the date of death, or last contact if the date of death was unknown.

There were no statistically significant differences between the two treatment groups in terms of overall survival. The estimated median survival time for participants in the 175 mg/m^2 group was 13.1 months compared with 12.3 months for participants in the 250 mg/m^2 treatment arm. The estimated HRs, from a proportional hazards model that included covariate adjustments for initial performance status, platinum sensitivity, cooperative group and measurable disease, showed that the adjusted survival rate was 3% lower on the 250 mg/m^2 regimen; HR = 0.972 (95% CI: 0.774 to 1.22).

Progression-free survival

There were no significant differences in PFS observed between the two treatment regimens of 175 and 250 mg/m^2 paclitaxel in terms of time to progression. The median TTP was 4.8 months for participants treated with the lower dose regimen compared with 5.5 months for participants in the higher dose treatment group.

Response rate

For participants with measurable disease, 36 out of 131 (27%) (95% CI: 20 to 36%) in the 175 mg/m^2 regimen arm demonstrated an objective response (partial and complete response) compared with 49 out of 134 (36%) (95% CI: 29 to 46%) in the 250 mg/m^2 regimen treatment group. The overall odds ratio (OR) of responding to the higher dose regimen of 250 mg/m^2 was 1.89 [(95% CI: 1.07 to 3.31); p = 0.027] times greater than that of responding to the low-dose regimen, after adjusting for histological cell type (papillary serous versus clear cell or mucinous versus other cell types), cooperative group, performance status and prior platinum sensitivity. However, further analysis indicated that the OR of responding to the 250 mg/m^2 regimen was not consistent across the subgroups of participants as defined by their classification of platinum sensitivity at baseline. There was a significant treatment – subgroup interaction (p = 0.041). The adjusted relative OR of responding to the 250 mg/m^2 regimen was 2.59 (95% CI: 1.36 to 4.95) for the 213 participants who had platinum-resistant disease compared with

TABLE 36 *Response rates by sensitivity to prior platinum therapy for paclitaxel 175 versus 250 mg/m²*

	Paclitaxel dose				
	175 mg/m² (n = 131)		250 mg/m² (*n* = 134)		Total no. of patients
Response	No. of patients	%	No. of patients	%	
Platinum resistant					
CR	5	5	13	12	18
PR	18	17	27	25	45
NR	81	78	69	63	150
Subtotal	104		109		213
Platinum sensitive					
CR	4	15	4	16	8
PR	9	33	5	20	14
NR	14	52	16	64	30
Subtotal	27		25		52
Total	131		134		265

0.630 (95% CI: 0.191 to 2.07), for the 52 participants with platinum-sensitive disease. The response rates by treatment group and prior platinum sensitivity are given in *Table 36*.

Within the participants assigned to the high-dose 250 mg/m² regimen there were no significant differences between the number of participants assigned to 5 µg/kg filgrastim who responded and those assigned to the 10 µg/kg regimen. Twenty-four (35%) of 68 participants (95% CI: 24% to 48%) assigned to the 5 µg/kg filgrastim regimen responded compared with 25 (37.9%) of 66 participants (95% CI: 26% to 51%) assigned to the 10 µg/kg dose.

Quality of life

This outcome was not assessed in the trial, therefore no data were reported.

Adverse events

Adverse events were assessed in all participants who received any study treatment.

There were no significant differences in terms of the rates of neutropenic fever after the first cycle of treatment between the participants in the 175 mg/m² dose regimen group without filgrastim and the 175 mg/m² dose group with filgrastim. Some 22% of participants in the lower dose arm experienced neutropenic fever compared with 19% of participants in the 250 mg/m² dose group.

Neutropenic fever after the first course of therapy occurred in 19% (16 of 83 participants) and 18% of participants (15 of 82 participants) on the 5 and 10 µg/kg regimens, respectively. The 95% CI for the difference between the two filgrastim doses for the number of cases of neutropenia after the first course of therapy was –11 to 13%.

The incidence of other reported toxicities was relatively rare, but was always higher in the 250 mg/m² group than the 175 mg/m² arm. Grade 3 and 4 thrombocytopenia (15 versus 7%), neuropathy (16 versus 7%) and myalgia/arthralgia (10 versus 3%) were all reported significantly more often on the 250 mg/m² regimen with filgrastim relative to the lower dose treatment group. However, comparing 5 and 10 µg/kg of filgrastim, there were no significant differences in these toxicities. *Table 37* displays the incidence of grade 3 or 4 toxicities other than neutropenia.

Summary of the effectiveness of paclitaxel 175 mg/m² compared with 250 mg/m²

One RCT was included in the assessment of clinical effectiveness that assessed whether increasing the dose of paclitaxel increases the probability of response, progression-free survival or overall survival in women who have persistent or recurrent ovarian cancer, and whether doubling the dose of prophylactic filgrastim accompanying the higher paclitaxel dose decreases the frequency of neutropenic fever.

Overall survival

There were no significant differences in overall survival between the two different dose regimen groups; HR = 0.972 (95% CI: 0.774 to 1.22). The median survival time was 13.1 months in the 250 mg/m² group compared with 12.3 months in the 175 mg/m² group.

TABLE 37 *Incidence of grade 3 or 4 toxicity other than neutropenia*

Toxicity	Paclitaxel regimen		*p*-Value
	175 mg/m^2 (%)	250 mg/m^2 + G-CSF (%)	
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

[a] G-CSF, granulocyte colony-stimulating factor.

TABLE 38 *Response to oral versus intravenous topotecan*

Response	Treatment group	
	Oral topotecan (*n* = 135)	i.v. topotecan (*n* = 131)
CR	2 (1%)	4 (3%)
PR	15 (11%)	22 (17%)
Overall response	17 (13%)	26 (20%)
95% CI	7.6 to 19.1%	13% to 26.7%
SD	39 (29%)	35 (27%)
PD	65 (48%)	59 (45%)
NE	14 (10%)	11 (8%)

Progression-free survival

The median TTP was 4.8 months for the lower dose regimen group compared with 5.5 months for the higher dose treatment arm. This difference was not statistically significant.

Response rate

Some 27% of participants in the 175 mg/m^2 group demonstrated an objective response compared with 36% in the 250 mg/m^2 arm. This difference was statistically significant. The OR of responding to the higher dose regimen was 1.89 times greater than that of responding to the low-dose regimen. This was not consistent across subgroups of participant platinum sensitivity. The adjusted OR of responding to the 250 mg/m^2 regimen was 2.59 for participants with platinum-resistant disease and 0.630 for participants with platinum-sensitive disease.

Quality of life

QoL was not assessed in this trial.

Adverse events

Grade 3 and 4 thrombocytopenia, neuropathy and myalgia/arthralgia were all significantly more common in the 250 mg/m^2 treatment arm than the lower dose regimen arm. There were no significant differences between the groups at the higher dose level who received either 5 or 10 µg/kg of filgrastim in terms of these toxicities.

Effectiveness of oral versus intravenous topotecan

This section summarises the results reported by Gore and colleagues.[33]

Overall survival

There was a statistically significant benefit in favour of intravenous topotecan for overall survival compared with participants treated with oral topotecan. The median survival was 58 weeks (range: 0.3–120.0 weeks) in the intravenous topotecan arm compared with 51 weeks (range: 1.6–109.0 weeks) in the oral topotecan arm. This corresponds to a risk ratio of death (oral versus intravenous) of 1.361 (95% CI: 1.001 to 1.850) in favour of the intravenous topotecan treatment group.

Time to progression

There were no statistically significant differences observed between the two treatment groups for TTP. The median TTP was 13 weeks (range: 1.6–76.6 weeks) for the oral topotecan-treated group compared with 17 weeks (range: 0.1–91.6 weeks) for the intravenously treated group.

TABLE 39 *Response to oral and i.v. topotecan according to baseline stratifying factors*

	Treatment group			
	Oral topotecan (*n* = 135)		i.v. topotecan (*n* = 131)	
	n	Response: no (%)	n	Response: no (%)
Platinum sensitivity				
Refractory	40	3 (8%)	39	2 (5%)
Resistant	37	3 (8%)	36	4 (11%)
Sensitive	58	11 (19%)	56	20 (36%)
Tumour size				
<5 cm	66	10 (15%)	65	15 (23%)
≥ 5 cm	68	7 (10%)	61	10 (16%)
First line treatment				
Platinum/paclitaxel	53	8 (15%)	54	12 (22%)
All patients	135	17 (13%)	131	25 (19%)

Response

There were no statistically significant differences observed between the two treatment groups in terms of PR or CR. Seventeen participants (13%) (95% CI: 7.6 to 19.1%) in the oral topotecan group compared with 26 (20%) (95% CI: 13.0 to 26.7%) in the intravenous topotecan arm responded to treatment. Of these responses, two participants in the oral treatment arm compared with four participants in the intravenous arm obtained a complete response. *Table 38* shows the response to treatment with oral and intravenous formulations.

Further analysis of the response rates according to the baseline stratifying factors of platinum sensitivity, tumour size and first-line treatment was undertaken. The results indicated that there were no significant differences between the two treatment arms in the response rates for participants who were classified as platinum refractory, resistant or sensitive at baseline. Furthermore, no difference in terms of treatment activity was observed between the two groups when this was assessed according to initial tumour size (<5 versus ≥ 5 cm) or first-line therapy. The results of the response to topotecan according to the baseline stratifying factors are given in *Table 39*.

Response duration

There were no statistically significant differences between the two treatment groups observed for response duration. The median response duration was 34 weeks (range: 13.1–62.3 weeks) for participants in the oral topotecan arm compared with 26 weeks (range: 6.6–52.7 weeks) for participants in the intravenous treatment group.

Time to response

The median time to response was 12 weeks (range: 5.6–18.1 weeks) in the oral topotecan treated participants compared with 8 weeks (range: 5.1–25.4 weeks) in the intravenous treatment group. This difference was not statistically significant.

Quality of life

This outcome was not assessed in the trial, therefore no data were reported.

Adverse events

Haematological toxicity

There were seven deaths in the trial that were reported as being due to haematological toxicity. Two of these occurred in the oral treatment group and five in the intravenous treatment group.

The most common haematological toxicities that occurred in both treatment groups were neutropenia and leucopenia, although these occurred more frequently in the intravenous topotecan group compared with the oral topotecan arm. Grade 4 neutropenia occurred in 50% of the participants in the oral treatment group compared with 81% of the participants in the intravenous treatment arm, RR = 1.69 (5% CI: 1.42 to 2.06). Grade 4 leucopenia also occurred more frequently in the intravenous treatment group, although this was not statistically significant. Leucopenia was reported in 21% of the participants in the oral treatment arm compared with 31% in the intravenous treatment group, RR = 1.47 (95% CI: 0.97 to 2.24). The occurrence of grade 4 thrombocytopenia was similar in the two treatment arms. Thrombocytopenia occurred in 20% of participants in the oral treatment arm

TABLE 40 *Grade 3 and 4 haematological toxicities, per patient and per course by oral versus intravenous topotecan*

	Treatment group			
	Oral topotecan		i.v. topotecan	
	Grade 3	Grade 4	Grade 3	Grade 4
Patients	*n* = 135		*n* = 131	
Neutropenia	40 (30%)	67 (50%)	15 (11%)	110 (84%)
Leucopenia	59 (44%)	28 (21%)	78 (60%)	40 (31%)
Thrombocytopenia	30 (22%)	27 (20%)	27 (21%)	23 (18%)
Anaemia	51 (38%)	5 (4%)	43 (33%)	10 (8%)
Courses	*n* = 729		*n* = 778	
Neutropenia	190 (26%)	106 (15%)	249 (32%)	393 (51%)
Leucopenia	163 (22%)	31 (4%)	371 (48%)	68 (9%)
Thrombocytopenia	70 (10%)	42 (6%)	90 (12%)	29 (4%)
Anaemia	85 (12%)	7 (1%)	78 (10%)	10 (1%)

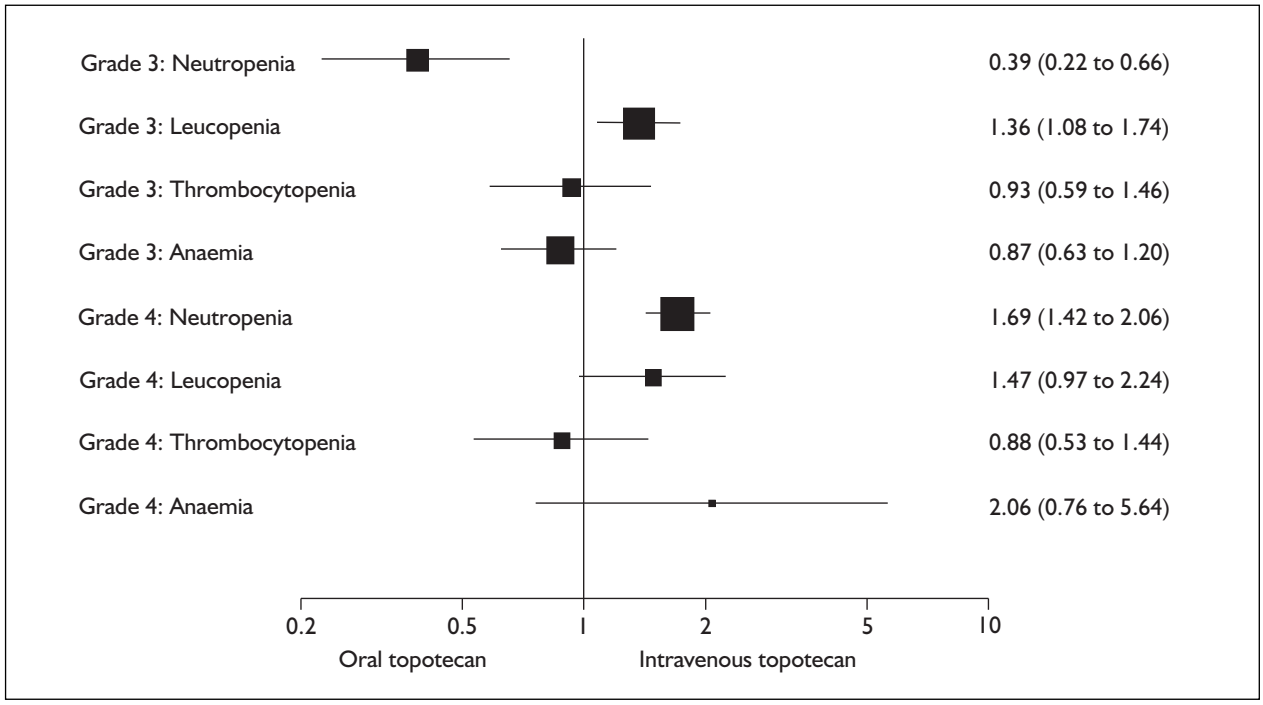

FIGURE 21 *Relative risks of grade 3 or grade 4 haematological toxicity for oral versus intravenous topotecan*

compared with 18% in the intravenous treatment group. Anaemia occurred in 4% of participants in the oral topotecan treatment group compared with 8% in the intravenous arm. *Table 40* shows the grade 3–4 haematological toxicities by treatment group and *Figure 21* displays the relative risks for these toxicities.

Non-haematological toxicities

The predominant non-haematological toxicities that occurred were gastrointestinal and fever. These were all higher in the oral topotecan group than the intravenous treatment group. The majority of these adverse events were reported as being mild to moderate in severity, with grade 3–4 toxicities occurring in ≤ 10% of participants. In the case of grade 3–4 toxicities, nausea, diarrhoea, vomiting and fever occurred more frequently in the oral topotecan group than the intravenous treatment group: nausea, 9 versus 5%, RR = 0.52 (95% CI: 0.21 to 1.28); diarrhoea, 10 versus 5%, RR = 0.48 (95% CI: 0.19 to 1.17); vomiting,

TABLE 41 *Non-haematological toxicities, all grades and worst grade per patients for oral versus intravenous topotecan*

	Treatment group			
	Oral topotecan (*n* = 135)		i.v. topotecan (*n* = 131)	
	All grades	Grades 3–4	All grades	Grades 3–4
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%0	39 (30%)	9 (7%)
Constipation	47 (35%)	4 (3%)	42 (32%)	2 (2%)
Fever	38 (28%)	14 (10%)	31 (24%)	7 (5%)

7 versus 3%, RR = 0.41 (95% CI: 0.14 to 1.21); and fever, 10 versus 5%, RR = 0.52 (95% CI: 0.22 to 1.20), respectively. *Table 41* shows the non-haematological toxicities by all grades and worst grades per patient for the two treatment arms.

Summary of the effectiveness of oral versus intravenous topotecan

One RCT was identified that compared the efficacy, safety and tolerability of oral topotecan versus standard intravenous topotecan in participants with relapsed epithelial ovarian cancer who had received one previous chemotherapy regimen that could have included a taxane.

Overall survival

There was a significant difference in overall survival in favour of the intravenous topotecan group. The median survival was 58 weeks in the intravenous topotecan group compared with 51 weeks in the oral topotecan arm. This corresponds to a risk ratio of death of 1.361 in favour of the intravenous group.

Time to progression

The median TTP was 13 weeks in the oral topotecan arm compared with 17 weeks in the intravenous treatment arm. This difference was not statistically significant.

Response rate

There were no statistically significant differences between the two treatment groups in terms of partial or complete response; 13% of participants in the oral topotecan group and 20% in the intravenous group responded to treatment.

There was also no significant difference between the two treatment groups in terms of response in the subgroups of participants who were classified as platinum sensitive, refractory or resistant at baseline.

Response duration

The median response duration was 34 weeks in the oral regimen group and 26 weeks in the intravenous regimen arm. This difference in response duration was not statistically significant.

Time to response

There was no significant difference between the two treatment groups for time to response. The median time to response was 12 weeks in the oral treatment regimen group compared with 8 weeks for the intravenous treatment group.

Quality of life

Quality of life was not assessed in this trial.

Adverse events

Two deaths occurred in the oral treatment group and five in the intravenous group due to haematological toxicity. Neutropenia and leucopenia occurred frequently in both treatment arms, although the rates were higher in the intravenous treatment group. The rates of grade 3–4 nausea, vomiting, diarrhoea and fever were all significantly higher in the oral treatment regimen compared with the intravenous treatment group.

Other related systematic reviews

Four systematic reviews were identified that had included evaluations of PLDH, topotecan and/or paclitaxel for second-line treatment of advanced ovarian cancer. The first of these reviews was a previous HTA report on the effectiveness of PLDH.[38] The report had included the trial of

PLDH versus topotecan included in the present review.[22] The previous report concluded that, overall, there were no statistically significant differences between PLDH and topotecan with regard to the main clinical outcomes. However, statistically significant differences were observed in terms of the incidence of adverse events. The second HTA review included was a previous report on the effectiveness of topotecan.[39] The report included both the trial of PLDH versus topotecan and the trial of topotecan versus paclitaxel included in this review. The report concluded that there were no significant differences between topotecan and paclitaxel and between topotecan and PLDH with regard to the main outcome measures. Statistically significant differences were observed, however, in terms of the incidence of adverse effects. A third review[41] that included both the trial of paclitaxel versus CAP[28] and the trials of PLDH versus topotecan[22] included in this review stated that one trial detected a statistically significant difference between treatments in PFS, which was longer with CAP than with paclitaxel. However, another trial did not show a difference between PLDH and topotecan overall in women with recurrent ovarian cancer, but a subgroup analysis detected a significant survival advantage for PLDH over topotecan in women with platinum-sensitive disease. The last identified related systematic review included the trial of topotecan versus paclitaxel.[24] The report describes the results of the trial and concludes that there are no statistically significant differences between the two comparators in terms of effectiveness.

Assessment of economic evaluations

Introduction

The systematic literature search detailed in the section 'Search strategy' (p. 7) identified 17 studies that were assessed for inclusion in the cost-effectiveness review. Of these, four studies met the inclusion criteria for the cost-effectiveness review. In addition, separate submissions were received from Bristol Myers Squibb, GlaxoSmithKline and Schering-Plough Ltd.

The following sections provide a detailed overview of the cost-effectiveness evidence from each of these sources and an assessment of the quality and relevance of the data from the perspective of the NHS. Full data extraction tables and a quality assessment checklist are provided in Appendix 8. An overall summary of the cost-effectiveness evidence is also provided at the end of this chapter.

Review of Smith and colleagues (2002)[50]

Overview

The analysis by Smith and colleagues[50] compared the costs of topotecan with PLDH from US and UK perspectives. A cost-minimisation analysis was undertaken, assuming equivalence in clinical outcomes based on the results of trial 30-49.[22] The costs comprised: acquisition costs of the study drugs, the costs of drug administration and the costs of managing adverse events. Resource use data obtained from the trial were supplemented with expert opinion on the management of adverse events in the separate localities. Two separate analyses were conducted, a European (UK) and a North American (US) analysis, based on expert opinion from two different sets of clinical experts. No details were provided on the composition of the expert panel or how the estimates were derived.

Summary of effectiveness data

The assumption of equivalence in clinical outcomes between topotecan and PLDH was based on the original (short-term) results of trial 30-49.[22] This study reported that there were no statistically significant differences in the main clinical outcomes between PLDH and topotecan. Based on these initial trial results, PLDH was assumed to be at least as effective as topotecan and a cost-minimisation analysis was therefore undertaken. It should be noted, however, that a subgroup analysis performed on platinum-sensitive patients in trial 30-49 showed a statistically significant increase in PFS and overall survival in the PLDH group. This issue was not addressed by using a cost-minimisation framework. In addition, the toxicity profiles of the two agents were very different, with a higher percentage of patients in the topotecan group experiencing grade 4 adverse events (see *Table 42*). Consequently, trial 30-49 does not provide a sufficient basis for assuming equivalence in overall health-related QoL. Therefore, the appropriateness of a cost-minimisation analysis could be debated [see the section 'Comments' (p. 69)].

Summary of resource utilisation and cost data

Resource utilisation and cost data were derived from a combination of patient-level data from trial 30-49 and expert opinion relating to the management of adverse events. The Smith study[50] only considered costs incurred during the treatment period and hence assumed that resource utilisation and costs beyond this period would be identical between the drugs. The acquisition costs of the drugs were based on the dosage (mean dose

TABLE 42 *Adverse event data from trial 30-49*[22]

Adverse event	No. (%) patients			
	PLDH (*n* = 239)		Topotecan (*n* = 235)	
	All severities	Grade 3–4 severity	All severities	Grade 3–4 severity
Neutropenia	84 (35%)	29 (12%)	191 (81%)	180[a] (77%)
Anaemia	86 (36%)	12 (5%)	169 (72%)	66 (28%)
Thrombocytopenia	31 (13%)	3 (1%)	152 (65%)	80 (34%)
Leucopoenia	87 (36%)	24 (10%)	149 (63%)	117 (50%)
Alopecia	45 (19%)	3 (1%)	123 (52%)	15 (6%)
PPE	121 (51%)	57 (24%)	2 (1%)	0
Stomatitis	97 (41%)	20 (8%)	35 (15%)	1 (<1%)

[a] Includes three fatal occurrences of neutropenic sepsis.

TABLE 43 *Study drugs and cycles received in trial 30-49*[22]

	Total drug used (mg)	Mean per patient (mg)	Total cycles	Mean cycles per patient	Total doses
PLDH	94,447	395.18	1164	4.87	1164
Topotecan	15,653	66.60	1349	5.74	6673

per infusion per patient, 1.50 mg/m^2 for topotecan versus 50 mg/m^2 for PLDH) and number of treatment cycles (5.75 and 4.87, respectively) obtained from clinical trial data (see *Table 43*).

Similarly, the resource use associated with drug administration was taken from the trial and included an outpatient visit for each dose and a specialist visit at the beginning of each cycle. In addition, eight adverse events associated with drug toxicity were considered: stomatitis/pharyngitis, PPE, nausea/vomiting, diarrhoea, anaemia, thrombocytopenia, neutropenia and sepsis/fever. These adverse events were chosen on the basis of patient perception, frequency and clinical importance. The adverse events occurred at four severity levels, from grade 1 (mild) to grade 4 (life-threatening). Adverse events were recorded in the trial each time they occurred, even when they were simultaneous (i.e. when more than one event occurred within a given time period). A number of assumptions were made to avoid potential double counting in the cost analysis. In those instances where a patient experienced two or more of the same event in a cycle, the most severe event was selected. When overlapping time periods were indicated for neutropenia, sepsis or fever, the most resource-consuming event was included in the cost analysis. Finally, for patients experiencing several events in a sequential unbroken period, events were discarded if they did not allow the patient to complete the maximum estimated number of visits or length of stay.

For some resource use items relating to adverse events, namely hospitalisations and some drug treatments, data were not available directly from the trial. In these instances, the resources required to manage adverse events were estimated by a panel of oncologists from the UK (for the European analysis) and the USA (for the North American analysis). To account for protocol-induced resource use, hospitalisations for adverse events were restricted to grades 3 and 4. Estimates of the resource use for the UK and the US analysis are given in *Table 44*.

For the UK analysis, it was assumed that all patients in trial 30-49 received care in the UK, and similarly in the US analysis it was assumed that all patients received care in the USA, that is, the total number of adverse events was included in the cost analysis, not just those experienced by UK patients in the UK analysis and by US patients in the US analysis. For resource use items where there were differences between resource use in the UK and the USA, extrapolation methods were used to predict the amount of resources that would have been used if patients had been treated in the relevant setting.

TABLE 44 *Quantities of resource use, per person*[50]

	Topotecan		PLDH		Difference (PLDH – topotecam)	
	USA	**UK**	**USA**	**UK**	**USA**	**UK**
Cycles of therapy	5.75	5.75	4.87	4.87	–0.88	–0.88
Units of platelets	1.10	0.30	0.05	0.02	–1.05	–0.28
Units of packed red cells	1.56	4.15	0.26	0.65	–1.30	–3.49
Units of erythropoietin	29,1091	20,786	25,670	690	–265,421	–20,096
G-CSF	3520	1494	762	31	–2758	–1463
Hospital stays	0.24	0.53	0.08	0.12	–0.17	–0.41
Office visits	12.7	4.2	4.6	3.2	–8.1	–1.0

TABLE 45 *US cost-analysis, per person in US$ (UK£*[a]*)*[50]

	Topotecan	PLDH	Difference (PLDH – topotecan)
Study drug	10,058	12,962	2,904
Administration	8,377	1,438	–6,939
Total drug + administration	**18,435**	**14,400**	**–4,035**
Stomatitis/pharyngitis	**30**	**101**	**71**
PPE	**0**	**104**	**104**
Nausea/vomiting	**83**	**49**	**–34**
Diarrhoea	**58**	**34**	**–24**
Neutropenia visits and medication	1,820	78	–1,742
G-CSF	1,936	419	–1,517
Total neutropenia	**3,756**	**497**	**–3,259**
Sepsis and fever	**111**	**56**	**–55**
Erythropoietin	3,493	308	–3,185
Transfusions	1,346	140	–1,206
Anaemia and thrombocytopenia visits and medication	342	18	–342
Total anaemia and thrombocytopenia	5,181	466	–4,715
Hospital stays	**566**	**188**	**–378**
Total cost	**28,220 (£15,735)**	**15,895 (£8,863)**	**–12,325 (–£6,872)**
95% CI	25,750 to 30, 974	14,515 to 17, 306)	–9445 to –15,415

[a] Exchange rate: 1.00 UK£ = 1.79 US$.

Costs were reported in US$ for both the UK and the US analyses. To aid comparison, we have also converted total costs to UK£. The sources of cost data for the UK analysis were the BNF for drug costs, the National Blood Authority for blood products, a national database of hospital trusts for inpatient stays, a specific UK trust for the cost of an intensive care unit and a UK cancer care centre for the cost of outpatient visits and chemotherapy administration. For the US analysis, costs of clinician visits were taken from Medicare fees, medication costs from the red book and hospital stays, laboratory tests and blood products from the hospital fee lists from an academic centre.

Summary of cost-effectiveness

The results of the cost-minimisation analysis are given in *Tables 45* and *46*.

The results of the Smith study[50] indicate that, in both the US and UK analyses, PLDH was significantly less costly than topotecan. CIs around total costs and cost differences were calculated using bootstrap methods. These showed the cost differences to be statistically significant at the 5% level. In the US analysis, the mean cost per patient was ~$12,325 (£6872) higher for topotecan compared with PLDH ($28,220 and $15,895, respectively). Although the mean costs

TABLE 46 *UK cost analysis, per person in US$ (UK£[a])*[50]

	Topotecan	PLDH	Difference (PLDH – topotecan)
Study drug	7,286	11,381	4,095
Administration	5,701	1,513	–4,187
Total drug + administration	**12,986**	**12,894**	**–92**
Stomatitis/pharyngitis	70	175	105
PPE	1	189	188
Nausea/vomiting	298	151	–147
Diarrhoea	60	36	–24
Neutropenia visits and medication	218	25	–193
Total neutropenia	**756**	**36**	**–720**
G-CSF	538	11	–526
Sepsis and fever	105	46	–59
Erythropoietin	242	8	–234
Transfusions	1,190	181	–1,009
Anaemia and thrombocytopenia visits and medication	0	0	0
Total anaemia and thrombocytopenia	**1,432**	**189**	**–1,243**
Hospital stays	1,197	280	–917
Total cost	**16,906 (£9,429)**	**13,997 (£7,805)**	**–2909 (–£1,622)**
95% CI	15,617 to 18, 847	12,863 to 15,392	–779 to –3,415

[a] Exchange rate: 1.00 UK£ = 1.79 US$.

reported in the UK analysis were also higher for topotecan, the difference in costs was lower than that reported in the US analysis [$2,909 (£1622) versus $12,325 (£6872)]. Despite higher drug acquisition costs for PLDH, the overall treatment costs incurred by patients receiving PLDH were lower in both the UK and US analyses owing to lower administration costs per treatment cycle (one outpatient visit per cycle for PLDH versus five visits per cycle for topotecan) and lower costs of managing adverse events. The differences in the costs between the UK and US analyses were due to the different assumptions made by the two expert panels for the management of side-effects and, in particular, the use of G-CSF, erythropoietin and blood transfusions.

The robustness of the base-case analysis to alternative assumptions was confirmed using sensitivity analysis. Sensitivity analysis of an extreme scenario favouring topotecan was undertaken by applying the minimum number of days for hospitalisations and the minimum number of outpatient visits estimated by the experts. In addition, the cost of hospitalisations, study drug infusion and outpatient visit associated with adverse events was also decreased. An analysis restricted to local patients (no extrapolation between settings) was also undertaken. Both of these sensitivity analyses concluded that PLDH was cost saving in the majority of bootstrap replicates (at least 83%). On the basis of these results, the authors concluded that PLDH is a dominant treatment since it is associated with lower costs and similar (or better) outcomes compared with topotecan.

Comments

There are important differences in the total costs estimated in the UK and US analyses, namely the US analysis shows a much greater cost saving associated with PLDH than the UK analysis. This is due to the increased costs of managing adverse events (which were more common in the topotecan group) in the USA and, in particular, the use of erythropoietin for the treatment of anaemia, which is not frequently used in the UK. This study helps to illustrate the importance of local practice when determining the most cost-effective treatment for a given disease.

There are, however, a number of potential limitations associated with this study, in particular, the use cost-minimisation analyses as an analytical framework. Although the initial (short-term) results of trial 30-49[22] did not show any statistically significant differences between the two drugs in terms of overall survival and progression-free survival, significant differences were found for

subgroup analyses and drug toxicity. Consequently, trial 30-49 does not provide a sufficient basis for assuming equivalence in overall health-related QoL, particularly given the differences in toxicity profiles between the two drugs. In addition, certain important cost items, such as patient costs, were excluded from the cost analysis. However, given that topotecan is administered over 5 days as opposed to 1 day for PLDH, it is likely that inclusion of such costs would have further strengthened the cost difference between the two drugs.

Second, the use of expert opinion to supplement resource use data is not ideal. As highlighted by the authors, the use of expert opinion can lead to underestimates of the variability in items. In addition, the assumption of only one severe (neutropenia, sepsis or fever) adverse event and only one event of each type per cycle, to avoid double counting, may have resulted in a rather conservative estimate of the cost of managing adverse events. The extrapolation of data from one setting to another assumes that resource use in one country can be used to predict accurately resource use in another country, which may not necessarily hold true in practice. The authors did, however, perform a sensitivity analysis using local patients for the UK and US analyses. Cost savings were still associated with PLDH in this scenario. Finally, the UK analysis actually included patients from a number of European countries, some of which may differ to the UK in terms of treatment practice. The authors did not address this issue in a sensitivity analysis.

Review of Ojeda and colleagues (2003)[51]

Overview

The analysis by Ojeda and colleagues[51] compared the costs of topotecan with PLDH using a similar approach to that reported by Smith and colleagues.[50] A cost-minimisation analysis was performed assuming equivalence in efficacy based on the initial (short-term) results of trial 30-49.[22] The costs considered in the analysis included the costs of the study drugs, the costs of drug administration and the costs of managing adverse events (medications and hospitalisations). A Spanish health service perspective was used. Expert opinion was used to supplement resource use data from trial 30-49, in particular relating to the resources required to manage adverse events that were not available from the trial.

Summary of effectiveness data

The effectiveness evidence for PLDH and topotecan was derived from trial 30-49.[22] Study characteristics and results have been described earlier (see the section 'Summary of effectiveness data' in the study by Smith and colleagues,[50] p. 66).

Summary of resource utilisation and cost data

Resource use for the two treatments was determined using data from trial 30-49 supplemented by expert opinion for the resources associated with the management of adverse events. In contrast to the study by Smith and colleagues, this analysis includes nine adverse events associated with drug toxicity: stomatitis/pharyngitis, PPE, nausea/vomiting, diarrhoea, anaemia, thrombocytopenia, neutropenia, sepsis and fever. Sepsis and fever were considered separately as opposed to combining these into a single category as in Smith and colleagues' analysis. Adverse events occurred at four severity levels, from grade 1 (mild) to grade 4 (life-threatening); however, unlike Smith and colleagues' analysis, hospitalisations associated with grades 1 and 2 adverse events are also included in the cost analysis. Likewise the assumptions used to avoid double counting of adverse events (as assumed by Smith and colleagues[50]) were not used in this analysis.

The costs associated with drugs were taken from the Spanish catalogue of medicinal products and unit costs of procedures and tests were obtained from the Spanish database of sanitary costs and published literature. The cost year was 2001.

Summary of cost-effectiveness

The results of the cost-minimisation analysis are given in *Table 47*.

The analysis showed that the total cost per patient for PLDH was €2210 (£1510) less than for topotecan (€9615 and €11,825, respectively). This was largely due to differences in the number of adverse events between the two treatments, and hence the management costs of these events. In particular, topotecan was associated with higher costs of anaemia (€1353) and neutropenia (€815). The statistical significance of the differences in total costs was not reported.

A sensitivity analysis was undertaken to assess the impact of the most significant (not defined) variables on the results of the analysis. This included increasing/reducing hospitalisations and outpatient visits associated with adverse events by 50%, assuming the same number of cycles administered for both drugs and that antiemetic drugs required during administration of topotecan have zero cost. A worst-case scenario was also

TABLE 47 *Total costs of treatment per person in € (UK£[a])*[51]

	PLDH	Topotecan	Difference (PLDH – topotecan)
Drug cost	7,785.43	4,256.66	
Administration cost	8,62.27	4,263.29	
Total drug and administration cost	**8,647.70**	**8,519.94**	**127.76**
Anaemia	334.25	1,687.19	
Thrombocytopenia	4.51	337.51	
Neutropenia	45.32	859.82	
Sepsis	48.49	209.61	
Fever	15.53	36.41	
Stomatitis/pharyngitis	163.94	23.00	
Nausea/vomiting	69.48	115.84	
Diarrhoea	210.01	35.37	
PPE	75.9	0.00	
Total cost adverse events	**967.02**	**3,304.75**	**–2,337.73**
Total cost	**9,614.71 (£6,571.05)**	**11,824.69 (£8,079.85)**	**–2,209.97 (–£1,509.9)**

[a] Exchange rate: 1.00 UK£ = 1.463193 €.

conducted assuming all of the previous sensitivity analysis in a direction that favoured topotecan and using lower doses (unlicensed) for both drugs. All sensitivity analysis showed PLDH was associated with a lower total cost than topotecan (representing savings of between €320 and 3058), although the extent of this difference varied greatly. Based on the results of this analysis, the authors conclude that PLDH dominates topotecan.

Comments

In addition to those limitations mentioned in the 'Comments' section of Smith and colleagues' review[50] (p. 69), namely the use of a cost-minimisation framework and the use of expert opinion, the study by Ojeda and colleagues[51] also has one other important limitation that is worth noting. The costing of adverse events in this study does not appear to have followed the principles of the analysis by Smith and colleagues.[50] In particular, patients can still have more than one hospitalisation and more than one of a particular event per cycle. Hence there is a potential for double counting in these cost estimates, hence the costs of adverse events may have been overestimated. This analysis also included the hospitalisation costs of grade 1 and 2 adverse events, which, as argued by Smith and colleagues, are likely to be protocol induced and may not be representative of the treatment of adverse events in practice. Despite the differences in costing methods, the cost savings associated with PLDH reported in the UK analysis by Smith and colleagues were very similar to those in the analysis by Ojeda and colleagues (€2410 and 2210, respectively). This could be due to a more conservative treatment of adverse events in Spain, which in turn could have implications concerning the generalisability of the UK estimates to all European patients in the study by Smith and colleagues.

Review of Capri and Cattaneo (2003)[52]

Overview

The analysis by Capri and Cattaneo[52] compared the costs of topotecan and PLDH. A cost-minimisation analysis was performed, assuming equivalence in efficacy as demonstrated by the short-term results of trial 30-49.[22] The costs considered in the analysis were the costs of the study drugs, costs of drug administration and the costs of managing adverse events (medications and hospitalisations). An Italian health service perspective was used. Expert opinion was used to supplement resource use data from trial 30-49 for the resources required to manage adverse events, that were not available from the trial.

Summary of effectiveness data

The effectiveness evidence for PLDH and topotecan was derived from the short-term results of trial 30-49. Study characteristics and results have been described earlier (see the section 'Summary of effectiveness data' in the study by Smith and colleagues,[50] p. 66).

Summary of resource utilisation and cost data

Resource use for the two treatments was

TABLE 48 *Base-case cost analysis in € (UK£[a])*[52]

	PLDH		Topotecan	
	Total cost	**Mean cost per patient**	**Total cost**	**Mean cost per patient**
Drug cost	1,656,419	6,931	908,077	3,864
Administration cost	164,118	687	951,011	4,047
Drug and administration costs	1,820,537	7,617	1,859,088	7,911
Nausea/vomiting	16,143	68	27,862	119
PPE	2,386	10	0	0
Stomatitis	36,428	152	4,139	18
Anaemia	187,667	785	1,009,692	4,297
Neutropenia	29,023	121	645,037	2,745
Diarrhoea	6,818	29	12,146	52
Thrombocytopenia	0	0	117,834	501
Fever	2,730	11	16,810	72
Sepsis	4,342	18	17,475	74
Total adverse events	**285,536**	**1,195**	**1,850,995**	**7,877**
Total cost	**2,106,073 (£1,438,096)**	**8,812 (£6,019)**	**3,710,083 (£2,535,109)**	**15,788 (£10,787)**

[a] Exchange rate: 1.00 UK£ = 1.463193 €.

determined using data from trial 30-49[22] supplemented by expert opinion for the resources associated with the management of adverse events. Expert opinion was provided by five Italian oncologists using the Delphi method. The analysis includes nine adverse events associated with drug toxicity: stomatitis, PPE, nausea/vomiting, diarrhoea, anaemia, thrombocytopenia, neutropenia, sepsis and fever. As in Smith and colleagues' analysis, costs of adverse events were evaluated at four severity levels, from grade 1 (mild) to grade 4 (life-threatening). In contrast to Smith and colleagues' analysis, hospitalisations associated with grade 1 and 2 adverse events are also included in the cost analysis. Also, the authors do not make any assumptions that would ensure that adverse events were not double counted (as assumed by Smith and colleagues). Costs of each adverse event are presented in Appendix 9.

Only direct medical costs were included in the analysis and were based on prices as of July 2002, reported in euros. The costs associated with drugs were taken from the Italian National Formulary. National changes were used to cost medical visits and laboratory tests and diagnostic-related group reimbursements rates were used to cost hospitalisations.

Summary of cost-effectiveness

An assumption of equivalence in efficacy between topotecan and PLDH was made (based on the initial results of trial 30-49) and a cost-minimisation analysis was performed. The results of the cost-minimisation analysis are given in *Table 48*.

Mean total costs were €6,976 (£4768) higher in the topotecan arm than the PLDH arm (€15,788 and €8812, respectively). Although PLDH was associated with higher study drug costs, this was more than offset by the higher administration costs and the costs of treating adverse events (e.g. neutropenia) in the topotecan group.

Sensitivity analysis using the minimum and maximum (as determined by the expert panel) levels of resource use for each adverse event was undertaken. For the analysis using the minimum level of resource use, total costs were reduced to €12,014 for topotecan and €8281 for PLDH. For the analysis using the maximum level of resource use, total costs for topotecan were €18,847 and €9314 for PLDH. Based on the results of the base-case and sensitivity analysis, the authors conclude that PLDH is associated with lower costs than topotecan, and therefore represents the most efficient treatment.

Comments

The study by Capri and Cattaneo[52] suffers from some of the limitations discussed in the 'Comments' section in the review of Smith and colleagues[50] (p. 69), namely the use of a cost-minimisation framework and the use of expert

TABLE 49 *Clinical outcomes of Prasad and colleagues' trial*[53]

Chemotherapy	Outcome	Value
Gemcitabine	Clinical benefit	13/56 (23.2%) (95% CI 11.9 to 34.5%)
	Median survival (months)	8.2 (range 5.9–12.1)
	Median time to progression (months)	1.8 (range 1.5–2.6)
Topotecan	Clinical benefit	28/50 (56%) (95% CI 42 to 70%)
	Median survival (months)	16.8 (range 13.9–24.9)
	Median time to progression (months)	3.6 (range 3–5.5)

opinion. In addition, the study appears to have used the same methods of costing adverse events as described in the review of the study by Ojeda and colleagues[51] (p. 70). As a result, the costing of severe adverse events (neutropenia, fever and sepsis) has not taken account of the fact that patients may already be hospitalised for another adverse event in the same period, therefore potentially overestimating the total costs of adverse events. It is understandable, however, that this type of analysis could not be undertaken by the Capri and Ojeda groups, as they did not have access to patient-level data, as in the Smith analysis. As in the Ojeda analysis, however, the authors could have considered the exclusion of hospital costs relating to grade 1 and 2 adverse events as these are not likely to receive hospital-based treatment outside a trial setting.

Review of Prasad and colleagues (2004)[53]

Overview

The analysis by Prasad and colleagues[53] aimed to compare the costs of topotecan and gemcitabine (Gemzar) in platinum- and paclitaxel-resistant patients. A cost–consequence analysis (cost and effects were not formally combined) was performed from a US perspective, using survival and resource use data collected in a non-randomised cohort study. Costs included in the cost analysis were study medications, hospitalisations and other clinical visits, laboratory tests and costs of managing adverse events. Outcomes were PFS, overall survival, response and toxicities experienced.

Summary of effectiveness data

This study was a non-randomised follow-up of 51 (46 for the cost analysis) patients receiving topotecan and 56 patients receiving gemcitabine. The non-randomised nature of this study meant that it was not included in the main review of clinical effectiveness evidence. All patients were receiving chemotherapy as part of second-line or subsequent treatment for persistent or recurrent platinum-resistant ovarian cancer. Patients were identified from retrospective hospital records and from prospective recruitment via the clinic.

Topotecan was administered over 5 days every 21 days with a median dose intensity of 1.64 mg/m^2 per week and a median number of four cycles. Gemcitabine was administered every 7 days for 21 days, followed by 7 days of no therapy. Patients received a median dose intensity of 497 mg/m^2 and a median number of five cycles.

The assessment of response was based on CT scans and/or Rustin criteria. The occurrence of either an objective response or stable disease was defined as a clinical benefit. PFS was calculated as the difference between the initiation of therapy and documented disease progression. Likewise, overall survival was calculated as the difference between initiation of therapy and death/last follow-up. Kaplan–Meier methods were used to estimate PFS and overall survival. Potential predictors of PFS and overall survival were investigated using the Cox proportional hazards model. Multivariate logistic regression was used to analyse the covariates associated with clinical benefit.

The outcomes of the study can be seen in *Table 49*. Response and survival times (TTP and overall survival) were greater in the topotecan group than the gemcitabine group; for example, median time to progression was 1.8 months in the gemcitabine group compared with 3.6 months in the topotecan group.

A number of variables were thought to be associated with the clinical outcomes, namely age, prior salvage therapy, time from last treatment and duration of first clinical remission. Regression analysis showed no significant association between any of these variables and clinical benefit, overall survival and disease progression. However, for the gemcitabine group, there was some positive association reported between increased time from

last treatment and increased TTP and longer overall survival.

With regard to toxicities, topotecan and gemcitabine patients were reported to be equally likely to experience events, with ~50% of patients in both treatment arms experiencing grade 3 or 4 toxicities. The data presented on toxicities was limited and data were reported only in those instances where there were differences between the two groups.

Summary of resource utilisation and cost data

Charge data on study medications, hospitalisations, clinical visits, laboratory tests; radiotherapy, administration, blood products and adverse events were collected directly from hospital database records for patients in the study. Charges were then converted to costs using appropriate ratios of charges to costs. The cost year was not stated and costs were in US$. Data on resource use items were not presented.

Summary of cost-effectiveness

Although both total costs and clinical outcomes were recorded in the study, these were not combined to provide an estimate of cost-effectiveness; instead, the focus of the study was on the differences in costs between the two groups.

The mean costs per cycle per patient were significantly higher for topotecan than gemcitabine ($7832 compared with $2732). This was largely due to the higher study drug acquisition and administration costs for topotecan. Individual cost items, however, were not presented, so it is not possible to verify this. Mean costs per course delivered were $13,937 (range $1824–82,340) for gemcitabine and $28,098 (range $5384–157,170) for topotecan. The cost of individual items, such as management of adverse events, was not reported. Instead, the authors only reported the total costs for both groups. The total cost of drugs in the topotecan arm was $14,161 (£7897) higher than the gemcitabine arm ($28,098 and $13,937, respectively). Sensitivity analysis was not undertaken.

Survival in the topotecan group was greater than that in the gemcitabine group (median survival 16.8 months in the topotecan group compared with 8.2 months in the gemcitabine group). It is not clear if this difference was statistically significant. No attempt was made to combine the cost and outcome data in the form of a cost-effectiveness ratio. Given the results derived from this study, the authors conclude that although patients receiving topotecan had a greater clinical benefit, the costs of treatment were considerably higher.

Comments

The economic evaluation by Prasad and colleagues[53] used different methods to assess the cost-effectiveness of second-line ovarian cancer treatments from those used in the studies by the Smith,[50] Ojeda[51] and Capri[52] groups. In particular, estimates of resource use were obtained directly from patients in the study, and hence expert opinion was not required. Although this is preferable to the methods used by the Smith, Ojeda and Capri groups, the non-randomised nature of the study does not make it a reliable source of data for clinical and resource outcomes. That is, it is likely that there was a degree of patient selection for topotecan and gemcitabine. Indeed, the authors note that this is likely to be the reason for the large cost differences between the drugs.

The authors did not undertake any type of sensitivity analysis. Given the large ranges that are reported for total costs, it is likely that individual cost items are associated with some uncertainty. The use of probabilistic analysis, explicitly accounting for this uncertainty, would have produced results that were more useful for decision-makers, that is, an estimate of the degree of uncertainty associated with a treatment being the most cost-effective (or cost-saving in this instance) option.

Following on from this, it is apparent from the outcome data reported that there were some important differences between the treatments. The authors, however, do not make any attempt to combine the estimates of survival (progression free and overall) with the cost differences observed. It is therefore not possible to ascertain if topotecan is cost-effective.

Finally, the reporting of important data in this study is particularly poor. No data on resource use or individual cost items were reported. It is therefore difficult to interpret the sources of the cost differences and hence the validity of the total costs estimated.

Review of the GlaxoSmithKline (GSK) submission

Overview

The GSK submission compared the cost-effectiveness of topotecan and PLDH, using new evidence made available since the previous NICE guidance was issued.[17] The previous submission

compared topotecan and PLDH based on the short-term results of trial 30-49.[22] Assuming equivalence in efficacy between topotecan and PLDH, a cost-minimisation analysis was performed.[50] This analysis showed that PLDH was significantly less costly than topotecan because of lower administration costs and lower costs associated with the management of adverse events.

Recently, an audit of current practice for relapsed ovarian cancer in UK has been undertaken by GSK.[54] The purpose of the audit was to provide an overview of the current management of ovarian cancer and to investigate the outcomes associated with second-line or subsequent chemotherapy. In this new submission, a cost-minimisation analysis was conducted based on the clinical results of the previous pivotal trial but using data for some resource use items (e.g. mean dosage with associated administration costs or strategies to manage adverse events) obtained from the audit. In addition, the potential savings to the NHS via home administration of topotecan were estimated and the results of a survey that assessed the patient convenience with topotecan home delivery were presented.

Summary of effectiveness data

The effectiveness evidence for PLDH and topotecan was derived from trial 30-49. Study characteristics and results have been described earlier (see 'Summary of effectiveness data' in the review of the study by Smith and colleagues,[50] (p. 66).

Summary of resource utilisation and costs data

Data for resource utilisation from trial 30-49 were combined with the audit of current practice for relapsed ovarian cancer in the UK. The submission justified this approach on the basis that the audit was considered more representative of UK management of patients with epithelial ovarian cancer than a clinical trial.

Audit data were obtained from nine UK centres. Each centre completed a centre registration form agreeing to participate in the data collection exercise. Patients were included in the audit if they were 18 years of age or older, had a diagnosis of ovarian cancer and required treatment with second-line or subsequent chemotherapy. The number of patients available for the analysis was 198. More than 75% of patients had received surgery as initial treatment and the most frequently prescribed drugs for first-line chemotherapy were carboplatin or carboplatin with paclitaxel (about 80% of patients). All patients entering the study were prospectively followed up every 6 months and their status at each follow-up was documented. The results of the audit were used to estimate the number of treatment cycles with topotecan and PLDH, the associated administration costs and the resource use and costs relating to the management of adverse events.

The results of the audit showed that the mean dosage and the number of cycles for topotecan and PLDH were lower than that reported in the trial (see *Table 43*). The mean dose per cycle of topotecan was 1.49 mg/m^2 with a mean of 3.88 cycles, whereas the mean dose per cycle of PLDH was 49.07 mg/m^2 with a mean of 3.54 cycles (more details are presented in Appendix 9). A lower mean number of cycles together with a lower mean dose is likely to have implications for both drug and administration costs and the risk of adverse events. Therefore, new estimates of costs were made using data for drug dosage and treatment cycles obtained from the audit.

In costing the adverse events, particular attention was given to the incidence of neutropenia and the associated use of G-CSF and hospitalisations. Neutropenia was the most common adverse event (see *Table 42*) for topotecan patients in trial 30-49 with an incidence of 77% (for grades 3–4). Some 29.1% of patients in trial 30-49 received G-CSF with a mean dosage of 1494 μg. In the UK audit, only 17.39% of patients suffered from neutropenia and only 4.35% of patients received G-CSF. The mean units of G-CSF used in the trial (1494 μg) were thus multiplied by the factor 0.149 (4.35/29.1), giving 223 μg mean units of G-CSF. The same process was applied for office visits and other medications for treating neutropenia, in order to reflect that only 4.35% of patients received some treatment (rather than 29.1% reported in trial 30-49).

In addition, the audit findings showed that the majority of inpatient stays were due to neutropenia. The rate of hospitalisations not related to neutropenia was taken from trial 30-49 (39%); however, the rate of hospitalisation for neutropenia obtained from trial 30-49 was substituted by the rate found in the audit. The mean number of inpatient hospitalisations in the trial was 0.53 days, and 61% of hospitalisations were due to neutropenia. Inpatient hospitalisations (per patient) due to neutropenia, as recorded in the trial, were therefore 0.323 days (0.53×0.61). In the audit, however, inpatient hospitalisation stay (per patient) due to neutropenia was 0.163 days. The total mean inpatient hospitalisation stay used in this

TABLE 50 *Quantities of resources used included in the GSK submission (only those different from trial 30-49)*

	Topotecan	PLDH
Mean dose per infusion/patient (mg/m^2)	1.49	49.07
Cycles of therapy	3.88	3.54
G-CSF (μg)	223	N/A
Hospital stay (days)	0.37	N/A

reanalysis was therefore estimated as 0.37 days (0.53 – 0.323 + 0.163), that is, inpatient stay in the trial minus inpatient stay due to neutropenia in the trial plus inpatient stay due to neutropenia in the audit. *Table 50* presents the alternative resource use estimates used in the GSK submission, compared with the original analysis of trial 30-49 reported in Smith and colleagues' study.[50]

For adverse events other than neutropenia, given the lack of data from the audit, it was considered appropriate to adjust the costs associated with adverse events for each treatment used in Smith and colleagues' study[50] to reflect the lower cycle lengths (3.88 versus 5.75 for topotecan; 3.54 versus 4.87 for PLDH). Therefore, for topotecan patients, costs for all adverse events were multiplied by a rate of 0.675 (3.88/5.75); and for PLDH patients all adverse event costs were multiplied by 0.727 (3.54/4.87). The rationale for this adjustment is that fewer cycles may reduce the incidence of adverse events associated with both therapies.

The resources required to administer topotecan in hospital were obtained directly from trial 30-49. This was multiplied by the cost per cycle estimated by Smith and colleagues. However, since fewer cycles were reported in the audit (3.88 instead of 5.75 cycles), the total costs of administration were reduced. The same approach was applied for PLDH (3.54 instead of 4.87 cycles). In Smith and colleagues' study, the administration costs for PLDH did not appear to include cardiac monitoring. Therefore, it was assumed that patients receiving PLDH would need to receive one ECG and one echocardiogram or multigated angiography per cycle (assumed at a rate 2:1) and these costs were added to the administration costs.

Unit costs were obtained from the NHS Reference Costs (2003), the National Tariffs (2004) and Smith and colleagues' study. A unique price year was not reported. Unit costs and their sources were presented transparently and in detail in the submission.

Summary of cost-effectiveness

An assumption of equivalence in efficacy between topotecan and PLDH was made based on the results of trial 30-49,[22] so a cost-minimisation analysis was performed. This analysis was based on Smith and colleagues' study[50] but updated to reflect the results of the UK audit. As described previously, drug costs, administration costs, costs of neutropenia management and related hospitalisations were directly calculated using resource use data found in the audit, applying UK unit costs. The costs associated with adverse events were calculated by multiplying the number of events reported in Smith and colleagues' study by 0.675 (i.e. 3.88/5.75) for topotecan and by 0.727 (i.e. 3.54/4.87) for PLDH. The results of the cost-minimisation analysis by GSK are given in *Table 51*.

The use of the audit reduced the total cost of topotecan and PLDH compared with Smith and colleagues' study (see *Tables 45* and *46*). The reduction in treatment cycles from 5.75 to 3.88 for topotecan and from 4.87 to 3.54 for PLDH led to a reduction in the study drug costs from £5204 to £3738 for topotecan and from £8129 to £5799 for PLDH. Similarly, the administration costs for topotecan decreased from £4072 to £2681. The administration costs of PLDH, however, rose from £1081 to £1702 owing to the inclusion of cardiac monitoring costs.

With regard to adverse events, there was an important reduction in costs associated with neutropenia for topotecan owing to the lower percentage of patients receiving G-CSF in the audit compared with trial 30-49 and the lower rate of hospitalisations and office visits. Costs associated with other adverse events were lower owing to the assumption that fewer cycles may reduce the incidence of adverse events associated with both therapies. The total cost per patient receiving topotecan was slightly lower than the cost per patient of treatment with PLDH (£7773 versus £8080). This is contrary to the results of Smith and colleagues' study, where topotecan was associated with higher treatment costs (£12,076 versus £9997).

TABLE 51 *Results of the GSK cost-minimisation reanalysis*

	Topotecan (£)	PLDH (£)
Study drug costs	3737.52	5799.26
Administration costs	2680.50	1701.89
Total drug administration cost (per patient)	**6418.02**	**7501.15**
G-CSF	57.40	5.79
Neutropenia, office visits and other medications	23.27	12.98
Total neutropenia	**80.66**	**18.77**
Erythropoietin	116.22	4.15
Transfusions	304.28	93.98
Total anaemia and thrombocytopenia	**420.49**	**98.13**
PPE	0.48	98.13
Stomatitis	33.74	90.86
Diarrhoea	28.92	25.71
Sepsis and fever	50.61	23.88
Nausea and vomiting	143.63	78.40
Total other adverse event management costs	**257.38**	**316.99**
Adverse event costs	758.54	433.90
Hospital stays	596.47	145.38
Total adverse event cost (per patient)	**1,355.01**	**579.28**
Total treatment cost (per patient)	**7,773.03**	**8,080.43**

An additional scenario was presented to estimate whether there were potential savings to the NHS in administering topotecan via home delivery. Home delivery was assumed to save costs associated with outpatient appointments (or ward attendance) to receive infusion and nurse consultations. Given a frequency of five infusions and five nurse consultations per cycle, it was estimated that home delivery of topotecan would save the NHS £575 per cycle (per patient) and £2300 over four cycles. However, the cost of a nurse consultation does not appear to have been added in the calculations presented.

Comments

The use of an audit was justified by the need to obtain results that were more representative of UK management of patients with epithelial ovarian cancer than those available in a clinical trial setting. However, the analysis undertaken in the submission presents some important limitations. First, although the audit may be more representative of UK current practice, it does not guarantee the same internal validity of a clinical trial. Second, many assumptions were made owing to the lack of data from the audit associated with some important items. For example, it was assumed that the reduction in adverse events (except neutropenia) would occur at the same rate of the reduction in the cycle treatments for topotecan and PLDH. The rationale for this assumption is clear, although the appropriateness of applying exactly the same rate is not fully justified in this reanalysis. Also, the most important adverse event for topotecan was neutropenia with high associated costs of management. The results of the audit showed that a lower percentage of patients experienced neutropenia compared with trial patients and it was assumed that the associated use of G-CSF, hospitalisations and office visits was reduced at the same rate. However, there was no information on G-CSF dose and visits due to neutropenia for patients included in the audit. Given the importance of the costs associated with neutropenia for topotecan, more information regarding the treatment of this particular adverse event for patients included in the audit would have been useful.

In addition, the audit results were only used for resource use and costs estimates and not for effectiveness evidence. The authors partly justified this approach, mentioning that the efficacy of topotecan with reduced dosage had been shown in a recent study by Rodriguez and Rose.[55] However, it is not clear why effectiveness data for topotecan and PLDH from the audit were not used in this analysis. The assumption that reduced dosage in UK clinical practice would alter only the costs results without any impact on the effectiveness needs further investigation.

The analysis assuming the home delivery of topotecan appears to suggest that patients visit a specialist at the beginning of each 5-day cycle, but then have no further contact with the medical profession for the remaining 4 days of therapy. The costs of community nurse visits should therefore be added to the cost of topotecan at home, calculated in the GSK submission (estimated in our own analysis to require five 1-hour visits at £56/hour = £280). It is also worth noting that the estimates of efficacy (in this case assumption of equivalence between topotecan and PLDH) were based on administration of topotecan on an outpatient basis, and one should therefore be cautious when extrapolating the efficacy estimates for topotecan to administration in an alternative setting.

As discussed in the review of Smith and colleagues,[50] the use of a cost-minimisation framework is not ideal. Although significant differences between PLDH and topotecan were not apparent in the main analysis, differences were reported for platinum-sensitive patients and drug toxicity. The submission highlighted the impact that different adverse events could have on patients on QoL. By using a cost-minimisation framework, the impact on QoL has not been considered. Furthermore, in a 3-year follow-up of patients included in trial 30-49, it was reported that survival was higher for PLDH than topotecan (HR=1.216; 95% CI: 1.000 to 1.478; $p = 0.05$) and significantly prolonged in platinum-sensitive patients (HR=1.432; 95% CI: 1.066 to 1.923; $p = 0.0017$).

In addition, an assessment of uncertainty was not undertaken. Mean values were reported for each cost category and the issue of the variability around these values was not addressed. No statistical analyses were performed in order to determine the significance of the cost differences and CIs were not presented. Given that the reduction in number of cycles for topotecan and PLDH found in the audit was the key factor in driving the cost estimates (including drug, administration and and adverse event costs), a sensitivity analysis on this parameter appears necessary and relevant. In the submission the number of treatment cycles for topotecan and PLDH was based on a weighted average of the number of cycles over all lines of chemotherapy (3.88 and 3.54). We performed a one-way sensitivity analysis just using the number of cycles for topotecan and PLDH as second-line treatment (4.19 and 3, respectively; see Appendix 9). In this sensitivity analysis, drug costs, administration costs and costs associated with adverse events (except neutropenia) were recalculated applying the same methodological approach used in the submission, but assuming 4.19 treatment cycles for topotecan and three treatment cycles for PLDH. The methods to estimate costs associated with neutropenia applied in this submission were used in this sensitivity analysis. The results of this sensitivity analysis show that the total cost per patient for topotecan increases to £8328 whereas the total cost per patient for PLDH decreases to £6845. This demonstrates the high variability around the mean values used in the analysis and raises some doubts as to the validity of the final results.

Finally, subgroup analyses in trial 30-49[22] indicated PLDH as the preferred option for platinum-sensitive patients. This issue was not addressed or acknowledged in this submission and subgroup analyses were not undertaken.

Review of Schering-Plough Ltd submission

Overview

In the Schering-Plough submission, an economic evaluation was performed to assess the cost-effectiveness of PLDH compared with topotecan. Effectiveness evidence was taken from the short-term results of trial 30-49[22] that showed equivalence in outcomes between the two drugs. In addition, results of long-term survival analysis were presented showing a trend favouring PLDH both in terms of overall survival and for a subgroup of platinum-sensitive patients. On the basis of these results, it was assumed that PLDH was at least as effective as topotecan and a cost-minimisation analysis was performed. The rationale for this analysis was that if PLDH was less costly than topotecan then it should be considered the preferred option. The cost-minimisation analysis presented in this submission was based on the results of a previously published study by Smith and colleagues.[50]

Summary of effectiveness data

The effectiveness evidence for PLDH and topotecan was derived from trial 30-49. Study characteristics and results have been described earlier (see 'Summary of effectiveness data' in the study by Smith and colleagues,[50] p. 66).

This submission also included long-term survival data for PLDH and topotecan, not available at the time of the previous manufacturer's submission; this new evidence was presented and discussed. In particular, overall survival results for PLDH and topotecan were reported based on a 3-year follow-

TABLE 52 *Results from the long-term follow-up of patients in study 30-49 (with 95% CI in parentheses)*

	All patients		Platinum-sensitive patients only		Platinum-refractory patients only	
	PLDH	**Topotecan**	**PLDH**	**Topotecan**	**PLDH**	**Topotecan**
Median survival (weeks)	62.7	59.7	107.9	70.1	38.3	42.1
HR (median)	1.216 (1.000 to 1.478)		1.432 (1.066 to 1.923)		1.069 (0.823 to 1.387)	
Survival rate (1 year) (%)	56.3 (50.0 to 62.6)	54.0 (47.6 to 60.3)	74.1 (65.8 to 82.4)	66.2 (57.4 to 75.1)	41.5 (32.8 to 50.1)	43.2 (34.5 to 51.9)
Survival rate (2 years) (%)	34.7 (28.6 to 40.8)	23.6 (18.1 to 29.1)	51.2 (41.6 to 60.7)	31.0 (22.2 to 39.7)	21.1 (14.1 to 28.2)	17.2 (10.5 to 23.8)
Survival rate (3 years) (%)	20.2 (14.9 to 25.5)	13.2 (8.8 to 17.1)	28.4 (19.6 to 37.1)	17.5 (10.2 to 24.7)	13.8 (7.6 to 20.0)	9.5 (4.2 to 14.7)

up of an ITT population from trial 30-49. Survival rates and median survival (weeks) were reported. Overall survival was estimated using the Kaplan–Meier method and HRs were presented. Subgroup analyses for platinum-sensitive patients and platinum-refractory patients were also performed and discussed. The main results of this analysis are presented in *Table 52* (HR > 1.0 favours PLDH).

The long-term analysis shows that PLDH is associated with a survival benefit over topotecan. The median survival in a 3-year follow-up was 62.7 weeks for PLDH versus 59.7 weeks for topotecan ($p = 0.05$). The trend in favour of PLDH was more evident when platinum-sensitive patients were considered. A statistically significant difference in median survival was found and a higher percentage of patients were alive at 2- and 3-year follow-ups. These differences were less relevant in the platinum-refractory group.

Adverse events associated with PLDH and topotecan were taken directly from trial 30-49. More patients in the topotecan group suffered from grade 3 and 4 adverse events, particularly in the case of neutropenia. A higher proportion of patients in the PLDH group suffered from PPE and stomatitis, although these were reported to be managed successfully with dose modifications.

Finally, the impact of the two therapies on the patients' health-related QoL was discussed. Results from trial 30-49 (where presented) assessed QoL using the self-administered QLQ-30. Overall, the impact of PLDH and topotecan on patients' QoL was similar, although some differences were found for single items. In particular, the percentage of patients with reduced pain was higher in the topotecan group than in the PLDH group. This difference was possibly due to the higher number of patients experiencing PPE in the PLDH group (see Appendix 9).

It was concluded that PLDH was associated with survival benefit in the long term, similar QoL and lower severe adverse events compared with topotecan. Hence PLDH should be considered dominant, if less costly than topotecan.

In addition, comparative data on PLDH versus paclitaxel were presented based on trial 30–57. This was a Phase III study initially enrolling 460 patients with relapsed ovarian cancer who did not respond to a first-line platinum-based chemotherapy. Paclitaxel and PLDH were comparable in terms of overall survival (56.1 versus 45.7 weeks, $p = 0.44$), overall progression-free survival (22.4 versus 21.7 weeks, $p = 0.15$), response rate (22.4 versus 17.8%, $p = 0.34$) and drug toxicity. However, it was noted that the trial 30–57 results should be interpreted with caution. The trial was terminated prematurely because paclitaxel became part of standard first-line therapy. Hence in the submission an economic analysis comparing PLDH and paclitaxel was not conducted.

Summary of resource utilisation and costs data

Resource use data were taken mainly from trial 30-49 (see Smith and colleagues[50] for details). In addition, nine adverse events associated with drug toxicity were considered: stomatitis/pharyngitis, PPE, nausea/vomiting, diarrhoea, anaemia, thrombocytopenia, neutropenia, sepsis and fever. These adverse events occurred at four severity levels, from grade 1 (mild) to grade 4 (life-threatening). Adverse events were recorded in the trial each time they occurred, even when they were coincident. For those occasions on which two or

TABLE 53 *Results of the Schering-Plough cost-minimisation analyses*

	Base case (£)		Analysis of extremes (£)	
	PLDH	**Topotecan**	**PLDH**	**Topotecan**
Drug cost	8,129	5,204	8,129	5,204
Administration	1,058	4,043	1,058	4,043
Subtotal	**9,187**	**9,247**	**9,187**	**9,247**
Stomatitis/pharyngitis	93	26	161	50
PPE	99	0	172	1
Nausea/vomiting	222	355	222	355
Diarrhoea	34	56	34	56
Anaemia	250	1,361	250	1,361
Thrombocytopenia	0	272	0	272
Neutropenia	35	892	21	637
Sepsis	22	213	17	159
Fever	15	186	14	149
Subtotal	**770**	**3,362**	**892**	**3,038**
Total	**£9,957**	**£12,610**	**£10,078**	**£12.286**
95% CI	9,067 to 10,847	11,512 to 13,708	9,176 to 10,980	11,216 to 13,356

more events occurred at the same time, the most resource-consuming event was selected and only one adverse event per patient at each cycle was included.

Only limited data were available from the trial for some resource items associated with adverse events (e.g. G-CSF dosage, transfusions, clinical visits, hospitalisations). It was also felt that the management of adverse events may vary between countries and locations. Expert opinion was therefore used to estimate resource utilisation related to the management of adverse events for topotecan and PLDH. No data on resource consumption for the long-term follow-up were presented. Findings for some of the resources used from trial 30-49 have been shown in *Table 45* (Smith and colleagues' analysis[50]).

Unit costs were taken from the BNF (for drugs; year 2000), from the CIPFA database (inpatient stays; year 1999), from tariffs at a UK cancer centre (administration costs) and from the literature (ICU visits). A unique price year was not reported.

Summary of cost-effectiveness

A cost-minimisation analysis was conducted based on the assumption that PLDH was at least as effective as topotecan. Mean per patient drug costs were higher for PLDH than topotecan (£8129 versus £5204). However, this was compensated for by lower administration costs for PLDH (£1058 versus £4043) due to higher dosing frequency and number of treatment cycles for topotecan. The total drug costs were therefore similar between the two therapies (£9187 for PLDH versus £9247 for topotecan). In addition, topotecan was associated with more severe and resource-consuming adverse events (see *Table 45*[50]). In particular, important differences were found for the costs of managing anaemia and neutropenia. Therefore, the mean total cost per patient was lower for PLDH than for topotecan (£9957 versus £12,610). CIs (95%) were calculated based on a normal distribution assumption and checked with the bootstrap method. In the base-case analysis, PLDH was significantly less costly than topotecan.

This submission reports on a sensitivity analysis previously described by Smith and colleagues,[50] where an analysis of extremes favouring topotecan was performed. Even in this best-case scenario for topotecan, PLDH was significantly less costly, with a total per patient cost of £10,078 versus £12,286. The results of these analyses (base-case and analysis of extremes) are presented in *Table 53*.

The Schering-Plough submission concluded, "even if the clinical results of PLDH were equal to those of topotecan, PLDH would be a preferred therapy as its overall cost is lower". Given that long-term follow-up findings showed survival advantages over topotecan, PLDH was considered as the dominant option.

Comments

The economic analysis conducted in the Schering-Plough submission was based on resource use data

from a clinical trial. The patient population appears representative of individuals with relapsed ovarian cancer, given that ~60% of patients had received a taxane as first-line therapy. Also, the study design ensures high internal validity. In addition, details on resource use and unit costs were presented transparently and the replication of the study appears feasible. However, some limitations and issues should be highlighted.

In the clinical trial, complete economic data were not collected for management of adverse events, hospitalisations and outpatient visits. Expert opinion was therefore used when limited trial data were available. It is likely that the variability in patient-level data was minimised using this approach. This issue was partly addressed by conducting an extreme analysis that favoured topotecan but, given that the costs associated with adverse events are the main driver for differences in costs between the two drugs, it seems important to highlight this issue. Also, it is not clear whether the administration costs for PLDH included cardiac monitoring. The inclusion of these costs would increase the total costs per patient in the PLDH group.

The general limitations of cost-minimisation analyses and the usefulness of more recent and advanced techniques have already been underlined (see the section 'Comments' in the review of the GSK submission, p. 77]. In this submission, the use of bootstrap methods has been mentioned but little information was given. For example, in the Smith and colleagues' analysis,[50] a curve representing the cumulative probability distribution of the cost difference between the two drugs (obtained by performing 1000 bootstrap replicates) was presented and the probability of PLDH being cost saving was estimated. The use of this or similar methods in the submission would have given more information to decision-makers for the cost comparison between PLDH and topotecan.

Review of Bristol-Myers Squibb Ltd (BMS) submission

Overview

In this submission, four alternative second-line chemotherapies for patients with advanced ovarian cancer were compared: paclitaxel monotherapy, topotecan, PLDH and paclitaxel in combination with a platinum agent. The rationale for this analysis was that whereas paclitaxel as monotherapy has shown similar results in terms of response rate, progression-free survival and overall survival, compared with topotecan and PLDH, paclitaxel in combination with platinum has demonstrated survival benefits over platinum monotherapy. Given the lack of head-to-head comparisons for the four therapies under study, a model was constructed to estimate costs and effects associated with these alternatives. Life-years gained (LYGs) over 3 years were calculated for each of the chemotherapies based on clinical trial survival curves obtained from the literature. An incremental cost-effectiveness analysis was performed, including drug costs and administration costs. One-way sensitivity analyses on key parameters were conducted in order to assess the robustness of base-case findings.

Summary of effectiveness data

Effectiveness evidence for the comparison between PLDH and paclitaxel as monotherapy were taken from trial 30-49 and data for the comparison between paclitaxel monotherapy and topotecan were obtained from trial 039.[22] In addition, efficacy and tolerability of paclitaxel in combination with platinum have been recently shown in two parallel international trials (ICON4).[29] In these trials, 802 platinum-sensitive ovarian cancer patients were randomised to receive paclitaxel (175 mg/m^2, as a 3-hour infusion every 3 weeks) in combination with a platinum agent (carboplatin or cisplatin) or conventional platinum therapy (carboplatin or cisplatin). Kaplan–Meier curves were used to estimate progression-free survival and overall survival and HRs were presented. With a median follow-up of 42 months, significant differences in favour of the combination therapy were reported for both progression-free survival (HR = 0.76, 95% CI: 0.66 to 0.99; $p = 0.0004$) and overall survival (HR = 0.82, 95% CI: 0.69 to 0.97; $p = 0.02$). Subgroup analyses confirmed a trend favouring paclitaxel plus platinum. Similar results were found for patients' QoL and drug toxicity. It was concluded that a paclitaxel–platinum therapy is likely to improve survival and PFS in relapsed platinum-sensitive ovarian cancer patients compared with conventional platinum therapy. Full details of this trial are available in the section 'Assessment of clinical effectiveness' (p. 22).

No direct comparisons of paclitaxel monotherapy, paclitaxel in combination with platinum therapy, topotecan and PLDH are available from the trial data. In order to compare effectiveness evidence from the three trials (30-49, 039 and ICON4), a model was developed. LYGs associated with each of the chemotherapeutic agents were estimated on the basis of the survival curves found in the trials. The ICON4 trial was used to provide survival data for paclitaxel combination, trial 039 was used for

TABLE 54 *Results of LYG estimations for paclitaxel–platinum, paclitaxel monotherapy, topotecan and PLDH*

Years	Paclitaxel–platinum		Paclitaxel		Topotecan		PLDH	
	Proportion alive (%)	LYG	Proportion alive (%)	LYG	Proportion alive (%)	LYG	Proportion alive (%)	LYG
0	100		100		100		100	
1	78	0.89	50	0.75	56	0.78	56	0.78
2	43	0.60	22	0.36	22	0.39	30	0.43
3	24	0.33	15	0.18	18	0.20	18	0.24
Total		1.83		1.29		1.37		1.40

topotecan and paclitaxel monotherapy and trial 30-49 was used for PLDH. Survival curves were available from the ICON 4 and 039 trial reports. For PLDH, survival curves observed in trial 30-49 were obtained from a previous Schering-Plough submission to NICE.[38] Life-years gained were calculated as follows:

$$(\text{proportion of patients alive year}_n + \text{proportion of patients alive year}_{n+1})/(2 \times 100)$$

That is, the proportion alive between two periods was averaged and than divided by 100 to obtain per patient values.

Given the different follow-up periods for the various trials used (4.5 years for paclitaxel/platinum and for topotecan, 4 years for paclitaxel monotherapy and 3 years for PLDH), survival curves were truncated at 3 years to allow direct comparability. This analysis showed that paclitaxel–platinum was associated with the highest number of LYGs (1.83) followed by PLDH (1.45), topotecan (1.37) and paclitaxel monotherapy (1.295) over a 3-year time-horizon. Results of LYG estimations and proportion of patients alive for each year are presented in *Table 54*.

Summary of resource utilisation and costs data

Only drug costs were considered in the analysis, including premedication costs, study drug costs and administration costs. Data on resource use for drug dosage were taken from the trial data. For topotecan a mean dose of 1.5 mg/m^2 per cycle (for five consecutive days) was assumed, whereas for paclitaxel monotherapy a mean dose per cycle of 175 mg/m^2 was used. Both dosages were based on trial 039. The mean doses for PLDH were taken from trial 30-49, where patients received 50 mg/m^2 per cycle. Finally, for the combination therapy, carboplatin was assumed as the platinum agent of choice, given that 71% of women in the ICON4 study had received this drug. In addition, for patients receiving paclitaxel (as monotherapy or in combination with carboplatin), premedication is required. Premedication drugs included cimetidine (300-mg injection), dexamethasone (2 × 20-mg tablets) and chlorpheniramine (10-mg injection). Six treatment cycles for each chemotherapeutic agent were considered. The rationale for the choice of this number of cycles was not given.

Administration costs were included assuming delivery on an outpatient basis. PLDH, paclitaxel monotherapy and paclitaxel–platinum each required one outpatient administration per cycle; for topotecan, however, five outpatient visits were necessary every cycle given the different administration process.

Unit costs for the study drugs (including premedications) were obtained from the BNF[56] and the cheapest available formulation was used. Costs per outpatient visit (£68.00) were taken from the PSSRU.[57] A unique price year was not given.

From the total per patient costs (per year) that were calculated, paclitaxel monotherapy was the least expensive therapy (£7158) followed by paclitaxel plus carboplatin (£9528) and PLDH (£10,170). Topotecan was the most expensive drug (£11,475), mainly owing to higher administration costs. Details on single cost items and methods of calculations are given in Appendix 9.

Summary of cost-effectiveness

An incremental analysis was performed to compare the alternative chemotherapeutic agents in terms of costs and effectiveness. Total costs for the different drugs over 3 years were calculated by tripling the annual costs associated with each agent on the assumption of six treatment cycles per year. LYGs estimated from the survival curves

TABLE 55 *Results of cost-effectiveness analysis for the four chemotherapeutic agents under study*

Treatment	Total costs (3 years) (£)	LYG	Average cost per LYG (£)	Incremental cost per LYG (£)
Paclitaxel–platinum	25,287.79	1.784	14,176.47	×
Liposomal doxorubicin	26,992.73	1.415	19,078.05	Dominated
Topotecan	30,297.51	1.338	22,646.89	Dominated
Paclitaxel	18,998.01	1.265	15,020.21	£12,120.07

were used as the benefit measure (see *Table 54*). A 6% discount rate was applied for costs and 1.5% for outcomes. The perspective of the analysis was that of the NHS.

Table 55 shows the results of the cost-effectiveness analysis. In the base-case analysis paclitaxel in combination with platinum was dominant compared with topotecan and PLDH (i.e. paclitaxel was less costly and associated with a higher number of LYGs). The options under consideration in the base-case analysis of the incremental cost-effectiveness ratios (ICERs) were therefore paclitaxel in combination with platinum and paclitaxel monotherapy. The incremental cost per LYG of paclitaxel–platinum compared with paclitaxel monotherapy was £12,120.

One-way sensitivity analyses were conducted on the discount rate used for benefits, varying from 0 to 6%. The results of the base-case analysis did not vary substantially. Also, uncertainty in the benefit measure was considered varying the LYG values by 15%. However, the impact of this variation was assessed only on average cost-effectiveness ratios and not in the incremental ratios, thus providing little additional information.

Based on these results, it was recommended that paclitaxel in combination with a platinum agent should be used as second-line treatment for platinum-sensitive relapsed ovarian cancer patients. This option was considered dominant compared with PLDH and topotecan and cost-effective compared with paclitaxel alone.

Comments

The main objective of this submission was to assess the cost-effectiveness of paclitaxel in combination with a platinum agent compared with other licensed therapies (PLDH, topotecan and paclitaxel monotherapy). Effectiveness data for paclitaxel–carboplatin were obtained from a randomised clinical trial (ICON4). A model was constructed to compare survival estimates from the three trials (039, 30-49 and ICON4). The use of a model was necessary owing to the lack of data for direct comparisons among the four therapies. However, the economic evaluation conducted presents some problems and limitations.

The main limitation of the study appears to be associated with the different characteristics of the patient population in the trials considered for the effectiveness analysis. For example, the ICON4 study only included platinum-sensitive patients who relapsed >6 months after the completion of a previous platinum chemotherapy. In contrast, the patient population of the clinical trials from which survival rates were obtained for topotecan (trial 039), paclitaxel monotherapy (trial 039) and PLDH (mainly from trial 30-49) included both platinum-sensitive and platinum-refractory patients. This introduces a potential source of bias since the survival rates associated with platinum-sensitive patients are (on average) much higher than those for platinum-resistant and platinum-refractory patients (as illustrated, for example, in *Table 54*). It therefore seems inappropriate to compare the survival rates found in the ICON4 study with those of the two other clinical trials. It would have been more appropriate to compare ICON4 with the subgroup of platinum-sensitive patients in trials 30-49 and 039. Using the survival rates for PLDH found in trial 30-49 (*Table 54*) for platinum-sensitive patients only, we estimated a total of 1.89 LYGs over 3 years for PLDH. This value is higher than that found for paclitaxel–platinum in this submission (1.83). Also, considering only platinum-sensitive patients in trial 039, the LYGs associated with paclitaxel alone would rise to 1.74 and to 1.56 for topotecan.

It should also be noted that, whereas in trial 30-49 censored patients were excluded from the analysis and survival rates were calculated considering only patients alive or dead for every year, survival rates used in this submission for paclitaxel–platinum were obtained considering all patients at risk for each year (thus including censored patients). This approach tends to underestimate the actual survival rate for paclitaxel–platinum because

censored patients are treated as dead. In addition, LYGs were calculated by taking the average number of patients alive between two periods (and then divided by 100 to obtain per patient values). This approach assumes that all deaths occurred exactly at the middle of the two periods considered (at month 6 of each year). Consequently, the results should be considered as an approximation of the real per patient LYGs. It is not clear whether the approach used in this submission was due to lack of patient-level data or was a methodological choice.

With regard to the cost analysis undertaken, only resource use associated with study drugs and their administration was considered. No justification was given for the exclusion of adverse event costs. Given the relevance of this category of costs (for example, adverse event costs were the main reason for cost differences between topotecan and PLDH reported in Smith and colleagues analysis[50]), their exclusion raises an issue as to the completeness of the economic analysis. In addition, the assumption that all patients receiving paclitaxel combination received carboplatin as their platinum agent may underestimate the total costs of administration, since a proportion of patients in ICON4 received cisplatin, which is administered on an inpatient basis, as opposed to carboplatin.

No justification was given for the number of treatment cycles included in the analysis (six). This was higher than the number of treatment cycles reported, for example, in trial 30-49 for both topotecan (5.75) and PLDH (4.87). This seems particularly relevant for topotecan, which is associated with administration costs five times higher than its alternatives. It would also have been appropriate to adjust costs occurred in subsequent years by patient mortality. This adjustment does not appear to have been conducted in the submission. Moreover, total per patient costs over 3 years were calculated assuming six treatment cycles per year for each agent. Given the low response rate and the high discontinuation rate found in the clinical trial, this assumption does not seem plausible.

Finally, the issue of the uncertainty around the model parameters was only partly addressed. Only mean values for total costs and LYGs were given. No statistical analyses were performed and CIs were not presented. Sensitivity analyses for incremental ratios were performed by varying the discount rate for health benefits. LYGs were varied by 15%, although the impact was assessed only for average cost-effectiveness ratios. No sensitivity analyses were conducted on other important items such as drug dosage and number of treatment cycles. Consequently, there are some legitimate concerns regarding the validity of the base-case results.

In summary, the dominance of paclitaxel in combination with platinum over topotecan and PLDH appears questionable and some potential confounding factors have been found. Further analyses with head-to-head effectiveness data for the alternative therapies under study (when available), or at least a reanalysis based on comparable patient populations, would appear necessary to corroborate the results of this submission.

Summary of findings from the cost-effectiveness review

The review of economic evidence from the literature and industry submissions has highlighted a number of significant limitations. Of the published cost-effectiveness evidence reviewed, only the study by Smith and colleagues[50] was assessed from the perspective of the NHS. This study demonstrated significant cost savings with the use of PLDH compared with topotecan. Similar findings were reported by Ojeda and colleagues[51] and Capri and Cattaneo[52] from the perspective of non-UK health providers. The study by Smith and colleagues was also used as the basis for the submissions by GSK and Schering-Plough Ltd. Both of these submissions were based on cost-minimisation analysis but used alternative assumptions related to the management of adverse events and the drug administration costs associated with topotecan. However, none of these studies directly compared the full range of possible strategies that are relevant to the NHS (paclitaxel, PLDH, topotecan). Consequently, it is not possible to make any direct comparison of the relative cost-effectiveness of these alternative treatments from this evidence.

The submission by BMS was the only study to attempt to make a direct comparison of the cost-effectiveness of the main licensed treatments in the NHS. However, as outlined earlier, the proposed approach is subject to a number of important limitations and no adjustments were made for the different characteristics of the patient population in the trials. Consequently, the dominance of paclitaxel in combination with platinum over topotecan and PLDH appears questionable.

In addition, the QoL associated with disease states (progression-free or progressive) and toxicities was not incorporated into any of the analyses undertaken previously. Ideally, a generic measure of health outcomes (e.g. QALYs) should be used to enable the cost-effectiveness results to be compared with other interventions in different disease areas.

Finally, the handling of uncertainty in all of the studies did not include a simultaneous assessment of all the uncertainty in variables included, that is, a probabilistic sensitivity analysis. In those studies that did undertaken sensitivity analysis, this was restricted to the use of one-way analyses using minimum and maximum values restricted by the information provided by the expert panels.

In summary, the existing evidence relating to the cost-effectiveness of paclitaxel, topotecan and PLDH for the second-line treatment of advanced ovarian cancer has a number of limitations which make it insufficient to inform decision-making regarding the most appropriate treatment for women treated in England and Wales. The following chapter therefore presents a new decision analytic model that has been developed to address this issue more formally.

Chapter 5
Economic model

Introduction

The review of cost-effectiveness studies in Chapter 4 identified a number of important limitations in the existing studies for assessing the cost-effectiveness of PLDH, topotecan and paclitaxel in second-line advanced ovarian cancer. These limitations meant that it was not possible to make a reliable comparison of the relative cost-effectiveness of the alternative treatments on the basis of existing evaluations. To address these limitations and to facilitate a direct comparison of the relative cost-effectiveness of all relevant comparators, a new decision analytic model was developed. The new model provides a framework for the synthesis of data from the clinical effectiveness review and the industry submissions to identify the optimal treatment for advanced second-line ovarian cancer. The following sections outline the structure of the model in detail and provide an overview of the key assumptions and data sources used to populate the model.

Methods

Overview

The model has been developed to estimate costs from the perspective of the NHS and health outcomes in terms of LYGs and QALYs for the full range of relevant treatment strategies. An overview of the basic structure of the model is provided in *Figure 22*.

The model evaluates overall survival in relation to two distinct periods: the progression-free period, and the time from progression to death (calculated as the difference between overall survival and PFS). The estimates of LYGs are calculated using the following equation:

$$LYG = mean\_ttp + (mean\_surv - mean\_ttp)$$

where mean_ttp = mean time to progression (in years) and mean_surv = mean (overall) survival time (in years). Overall survival is then quality adjusted using separate utility weights for the two periods during which the average patient is stable (i.e. progression-free) or in progression. The estimates of QALYs are calculated as follows:

$$QALYs = mean\_ttp \times utility\_sd + [(mean\_surv - mean\_ttp) \times utility\ pd]$$

where utility_sd = utility weight for stable disease and utility_pd = utility weight for progressive disease.

Although the structure of the model is relatively simple, the lack of direct data on the comparative survival for each of the relevant treatments under consideration presents a significant analytical challenge. In these situations, it is important that the approach used to synthesise the available data is based on explicit and defensible methods which can be used to combine data from all relevant sources. Owing to the relative complexity of these

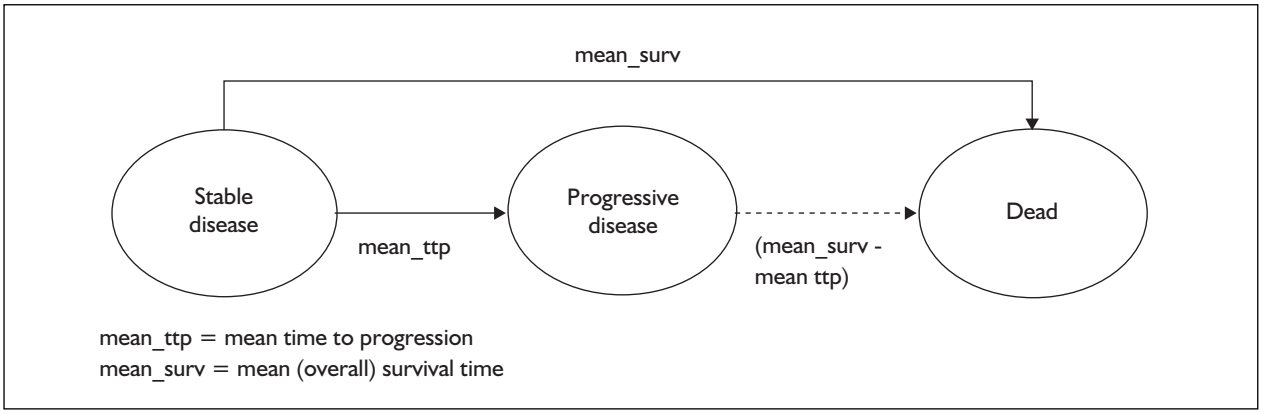

FIGURE 22 *Structure of the economic model*

approaches, the methods are described in detail in the following sections.

The costs included in the analysis comprised the costs of study drugs, premedication, monitoring, drug administration and managing adverse events. Owing to the lack of data reported on the differential impact of the alternative treatments on the long-term management of patients (including subsequent lines of chemotherapy), the analysis of costs is confined to the initial treatment period only and hence discounting is not applied to these costs.

The model is probabilistic and hence relevant input parameters are entered as probability distributions to reflect their imprecision and Monte Carlo simulation is used to reflect this uncertainty in the model's results.[58] The impact of patient heterogeneity (e.g. platinum-sensitive and platinum-insensitive/refractory patients) on the adoption decision is explored in a series of separate analyses. This approach ensures that uncertainty in the decision due to the imprecision in parameter inputs can be separated from the uncertainty of whether an intervention is cost-effective for particular subgroups of patients. In addition, sensitivity analysis was undertaken to determine the robustness of the results to alternative assumptions applied in the main analysis. A 2003–4 price base is used and annual discount rates of 1.5% for health outcomes are applied.[59]

Choice of outcome measures for the model

The model builds on the trial-based evidence summarised in the accompanying systematic review of the effectiveness data [see the section 'Assessment of clinical effectiveness' (p. 22)]. The primary health outcomes reported in the clinical trials included response rate (complete or partial), duration of response, toxicity events, PFS and overall survival. Survival data were typically presented as median number of weeks (PFS and overall survival), Kaplan–Meier survival curves and HRs between treatments. Only limited evidence was found linking response to survival data, and survival data were not presented separately in the trials for responders and non-responders. Consequently, in the absence of comparative survival data reported by response, the primary outcomes assessed in the model were PFS and overall survival reported for all patients. The use of survival data reported for all patients in the model enables a more comprehensive range of comparisons to be made and ensures a more systematic approach to study inclusion. The model evaluates overall survival in relation to two distinct periods: the progression-free period, and the time from progression to death (calculated as the difference between overall survival and PFS).

As noted previously, PFS and overall survival were reported in several ways, including median number of weeks, Kaplan–Meier survival curves and HRs. For the purposes of the model, it was necessary to identify the most appropriate summary measure that would enable comparisons to be made between the alternative treatments. The HR represents the most accurate of these measures for comparing survival between treatments, as it is specifically designed to allow for censoring and time to an event. Furthermore, the use of the (log) HR and its variance allows studies to be pooled using conventional meta-analytic approaches. However, since some of the studies did not report the HR, alternative methods were explored which would allow the ratio (and variance) to be estimated from other data reported in these studies. For those studies that did not report the HR it is possible to estimate the statistic from either the median number of weeks (progression-free and overall survival) or the published Kaplan–Meier curves; however, both methods are subject to limitations. In order to estimate the HR from the median number of weeks' survival, it is necessary to make an assumption about the distribution of survival times, for example, that they follow an exponential distribution with a constant hazard. If the actual survival curves do not follow an exponential distribution, then it is possible that the use of the approach will not reflect the actual survival difference between treatments.

In order to estimate the HR from survival curves, it is necessary to estimate the area under the survival curves. In addition, the survival curves must be extrapolated beyond the published curves to eliminate right-censoring. This method depends on the quality of the published curves, i.e. the accuracy with which they can be measured, and the validity of the assumed distribution used to extrapolate those curves. Owing to the limitations of these approaches and potential bias that the use of alternative approaches might introduce in estimating the relative treatment effects, the base-case model (Analysis 1) only included those studies which reported HRs for survival data.

Trial data utilised and treatment strategies compared

The clinical effectiveness review in the section 'Assessment of clinical effectiveness' (p. 22)

TABLE 56 *Direct comparisons of relevant treatment comparators according to the included patient population*

Trial	Treatments compared					
	Paclitaxel	Topotecan	PLDH	Paclitaxel combination	Platinum	CAP
Overall patient population						
039	✓	✓				
30-49		✓	✓			
30–57	✓		✓			
Platinum-sensitive patients						
ICON4				✓	✓	
Cantu, 2002[28]	✓					✓

identified eight published RCTs and obtained the trial report of one further RCT (30-57) in which paclitaxel, topotecan or PLDH were evaluated as second-line treatment for advanced ovarian cancer. Among these nine studies, treatment effects were available in the form of HRs from seven;[22,24,27–29,32,33] this includes the hazards relating to the longer follow-up of trial 039, provided by GSK via personal communication (see Appendix 6 for details).

Four studies[30–33] were excluded from the model because the comparator groups (all unlicensed treatments) provided no evidence on the relationship between the three main treatments under consideration. The excluded studies included the two trials that did not report HRs.[30,31] In each of these four trials, each unlicensed comparator was uniquely represented, which means that the separate pair-wise comparisons cannot be linked to provide indirect evidence about the relative treatment effects of licensed comparators (see *Table 56*). Consequently, only five of the nine studies identified in the clinical review were eligible for inclusion in the model.

Table 56 presents the direct comparisons between relevant comparators for the five studies included. Of these studies, three reported results for the overall patient population (including platinum-sensitive, -resistant and -refractory patients)[22,24,27] and two reported results for platinum-sensitive patients only.[28,29] In the two studies on platinum-sensitive patients, platinum and CAP were identified as relevant comparators (licensed for this indication) in this patient population and were therefore included in the economic model.

Table 56 shows that in the overall patient population there are three different pair-wise comparisons of three treatments of interest (i.e. paclitaxel versus topotecan, PLDH versus topotecan and paclitaxel versus PLDH), but no single trial that compares all treatments simultaneously. In the effectiveness review, no attempt was made formally to synthesise the results for each drug across the trials, owing to between-study heterogeneity. Although this is a legitimate approach for the effectiveness review, there are potentially significant limitations from a decision-making perspective, particularly if the individual pair-wise comparisons give conflicting results. Furthermore, the existing evidence does not provide direct trial data on all the possible comparisons between the relevant comparators under consideration. Consequently, is it not possible to base a single, coherent, comparative cost-effectiveness assessment of all treatments on the basis of the separate pair-wise comparisons reported in the literature.

It is possible to incorporate all this evidence simultaneously in the form of a mixed treatment comparison (MTC) model.[60,61] Such a model provides an explicit analytical framework to identify the most cost-effective treatment strategy given the combined weight of evidence from all the relevant clinical trials. There are several examples in the literature of statistical models for combining mixed comparison evidence to provide a consistent set of treatment effect estimates, relative to a common baseline, and this approach has been used in previous assessment models.[62] Using a similar approach, a model was developed to estimate a set of HRs relative to a common baseline, using the Bayesian inference software program WinBUGS [see the section 'Mixed treatment comparison for the inclusion of trial 30-57' (p. 91) for further details of this analysis].[63]

The following sections summarise the approach used to derive a common baseline and describe in

detail the MTC models developed to assess the relative effectiveness of the relevant treatment alternatives in each of the patient groups. The approaches used to address the heterogeneity in patient populations reported in the trials are also outlined.

Patient subgroups

A patient's likelihood of responding to second-line therapy and hence their survival prospects are largely governed by their sensitivity or resistance to platinum-based therapies.[64] This source of heterogeneity makes a direct comparison between the results from the various trials problematic. Whereas the patient population of the clinical trials (039, 30-49 and 30-57) included both platinum-sensitive and platinum-refractory patients, the Cantu[28] and ICON 4[29] studies included only platinum-sensitive patients who relapsed more than 6 months after the completion of a previous platinum chemotherapy. Failure to reflect this heterogeneity adequately in the model could introduce potential bias in the results due to the confounding effect of the different populations. Furthermore, the data for platinum and paclitaxel combination therapies, as assessed in ICON4, cannot be directly or indirectly linked to the data for paclitaxel, topotecan or PLDH. Since paclitaxel combination therapy and platinum therapy were not compared with any of the other comparators included in the economic model, there is no way to link their relative effectiveness to topotecan, paclitaxel or PLDH using only direct HRs.

To address this issue, two separate analyses were undertaken (Analysis 1 and Analysis 2). Analysis 1 is restricted to a comparison of the three trials (039, 0-49 and 30-57) that included both platinum-sensitive and -resistant/refractory patients. This analysis provides a comparison of the cost-effectiveness of paclitaxel monotherapy, PLDH and topotecan in the overall population. As discussed in the effectiveness review section, owing to the early termination of trial 30-57, the results of this trial are likely to be preliminary and, as such, the longer term implications of any differences observed in the treatment effect at the point are unclear. Owing to these limitations, the results of trial 30-57 are excluded from the base-case analysis. Sensitivity analysis is used to explore the impact of including the results of trial 30-57. A series of subgroup analyses are also undertaken to explore the cost-effectiveness of these interventions in the different patient populations.

Although this approach does not allow a comparison of the full range of relevant comparators for platinum-sensitive patients (paclitaxel and platinum combination, platinum monotherapy and CAP are excluded), it ensures that the potential confounding caused by differences between the inclusion criteria of the populations of the trials are minimised.

Analysis 2 then broadens the model to include the full range of relevant comparators by relaxing the requirement for direct HRs and by incorporating those licensed comparators that were not formally included in the systematic review (CAP and platinum). This approach enables data from ICON4 to be incorporated into the analysis at the expense of a less robust estimate of treatment effect. Analysis 2 focuses on data specific to platinum-sensitive patients and uses subgroup-specific data from trials 039 and 30-49.

Analysis 1: base-case model

The base-case model estimates the costs and quality-adjusted survival in an overall patient population, including platinum-sensitive, -resistant and -refractory patients. Although the evidence shows that baseline survival differs between these three groups, with platinum-sensitive patients having the most favourable prognosis, there is less evidence to support a difference in relative treatment effect among these subgroups as the clinical trials have failed to demonstrate a statistically significant difference in HRs between these groups. Hence in the subgroup analysis we also apply the overall treatment effect to subgroup-specific baseline data to estimate the cost-effectiveness in particular patient groups. The use of subgroup-specific treatment effects is explored in a sensitivity analysis to determine whether this changes the results of the model.

It is important to note that trials 30-49 and 30-57 did not report outcomes separately for platinum-resistant and -refractory patients, and instead treated these as one group. Consequently, the subgroup analysis is restricted to consideration of only two groups, platinum-sensitive patients and the combined group of platinum-resistant and -refractory patients.

Calculating baseline survival for Analysis 1

In order to build the model, it was necessary to select one of the three treatments to provide a baseline PFS and overall survival against which the HRs of the other two treatments could be compared. Trial 30-57 was ruled out as a provider of baseline information as it was terminated early and the length of follow-up was not available and was likely to have been ≤1 year. The data

concerning median weeks' survival from trial 039 were available for a longer period of follow-up of around 4 years. However, it was also limited since the data reported would not allow specification of subgroup-specific baselines. Trial 30-49 provided 4 years of follow-up, by which time 87% of patients had died, and allowed specification of subgroup-specific baselines and baselines stratified by other covariates. Consequently, trial 30-49 was chosen as the source of baseline data and hence topotecan acted as the common comparator between the two completed trials (30-49 and 039).

Since none of the trials provided estimates of the absolute hazard of progression or death, it was necessary to estimate the baseline hazard using median weeks and an exponential approximation. This approach has been used in a previous HTA report looking at treatment for advanced breast cancer.[65] The baseline hazard (λ) and its variance are calculated according to the following equations:

$$\lambda = -\ln(0.5)/t$$
$$\text{var}(\lambda) = \lambda^2/r$$

where t = median weeks survival and r = number of events.

Using this approach, the baseline hazard (λ) can then be converted into a mean survival time, for both progression-free survival and overall survival, by simply taking the inverse of the hazard ($1/\lambda$). This represents the mean survival times for topotecan. The mean PFS and overall survival for the two treatment comparators are then estimated by applying the HR (relative to topotecan) to the baseline hazard, in order to estimate the absolute hazard for each of the comparators. Mean survival times for the comparators are then estimated using a similar approach to that described for topotecan (i.e. by taking the inverse of the absolute hazards for each of the comparators). The following sections describe in detail the approach used to synthesise the effectiveness data to obtain pooled estimates for the HR for PLDH and paclitaxel relative to topotecan.

Mixed treatment comparison for the inclusion of trial 30-57 in Analysis 1

For the base-case model topotecan acts as a common comparator in both trials (039 and 30-49), and therefore the hazard ratio for PLDH and paclitaxel (relative to topotecan) can be obtained directly from the reported trial data. Hence, although there is no direct comparison between PLDH and paclitaxel in trials 039 and 30-49, an indirect comparison can be made between PLDH and paclitaxel in the economic model by applying the HRs associated with each intervention relative to this common baseline. However, the analysis is more complex when incorporating evidence from trial 30-57 as part of the sensitivity analysis.

Ideally, statistical inference concerning a comparison of three treatments, say A, B and C, would ideally be based on a direct 'head-to-head' RCT. However, in practice it is rare to find an RCT that directly compares all the relevant comparators. More often, one finds a mixture of comparisons looking at different subsets of the full set of relevant comparators. In the case of three pair-wise comparisons, AB, AC and BC, a traditional and simplistic method might be to compare direct treatment effects against a common baseline, say A, and as a consequence discard the information provided by the BC comparison. Indirect comparisons of A and C based, for example, on comparisons of AB and BC, are said to represent a lower level of evidence. However, it is evident that, based on the principle of transitivity, if the true differences between AB, AC, and BC are θ_{AB}, θ_{AC} and θ_{BC}, then we expect

$$\theta_{AC} = \theta_{AB} + \theta_{BC}$$

Hence reasonable inferences can be made about the AC comparison with few additional assumptions over those which are routinely made in simple meta-analyses. These assumptions are, first, the simple transitivity assumption outlined above, and second, that the differences are taken on an appropriate scale, for example, the log-odds scale. Hence the information provided by the BC comparison need not be discarded and can be used to update the direct comparisons of AB and AC. Higgins and Whitehead[61] have shown how the use of 'external' AB and BC evidence can substantially reduce uncertainty about an AC comparison of primary interest.

Based on these general principles, a Bayesian meta-analysis of (log) HRs assuming fixed treatment effects was conducted using Markov Chain Monte Carlo implemented in WinBUGS. The analysis assumes that the (log) HRs, observed in the clinical trials, are normally distributed about a true underlying effect size, θ, according to the precision (= 1/variance), τ^2, also observed in the trials. The underlying treatment effects are given independent vague priors, $N(0, 0.001)$. The term 'vague' is used to denote that prior information in the form of expert opinion or prior data is not included in the analysis and hence these

parameters are assigned very diffuse distributions. The main assumption of the analysis is that had paclitaxel been included as a comparator in trial 30-49, or PLDH included as a comparator in trial 039, the observed relative treatment effect of paclitaxel compared with PLDH would have been the same as that observed in trial 30-57.

$$\log(HR_{top\_pac}) \sim N(\theta_{top\_pac}, \tau^2_{top\_pac});$$
$$\theta_{top\_pac} \sim N(0, 0.001)$$
$$\log(HR_{top\_PLDH}) \sim N(\theta_{top\_PLDH}, \tau^2_{top\_PLDH});$$
$$\theta_{top\_PLDH} \sim N(0, 0.001)$$
$$\log(HR_{pac\_PLDH}) \sim N(\theta_{pac\_PLDH}, \tau^2_{pac\_PLDH});$$
$$\theta_{pac\_PLDH} = \theta_{top\_PLDH} - \theta_{top\_pac}$$

where top_pac = topotecan versus paclitaxel, top_PLDH = topotecan versus PLDH and pac_PLDH = paclitaxel versus PLDH.

Using this analysis, the model updates the HRs of topotecan versus paclitaxel and PLDH from trials 039 and 30-49 with the information on the comparison of paclitaxel and PLDH observed in trial 30-57. The WinBUGS code for the model is provided in Appendix 11. This model was used to estimate overall survival for patients receiving topotecan, paclitaxel and PLDH as second-line treatment for ovarian cancer. An important assumption of the model is that trial 30-57 is given the same weight as the two completed RCTs. Trials 039 and 30-49 provide HRs estimated after ~4 years' follow-up. The HRs from trial 30-57 were estimated after a much shorter period of follow-up, of ~1 year, although the precise length is unknown. The HRs from trial 30-57 therefore incorporate a higher degree of censored data. Another key assumption of the model is that the HR is independent of the period of follow-up, hence the difference observed after 1 year of follow-up is assumed to be equal to that which would be observed at 4 years. Finally, we note that trial 30-57 was underpowered owing to stopping recruitment early. This will be incorporated in the model in the form of higher variance around the treatment effect.

Trial 30-57 only provided HRs for overall survival, and so only trials 039 and 30-49 were used to estimate PFS in both the base-case and sensitivity analysis for Analysis 1.

$$\log(HR_{top\_pac}) \sim N(\theta_{top\_pac}, \tau^2_{top\_pac});$$
$$\theta_{top\_pac} \sim N(0, 0.001)$$
$$\log(HR_{top\_PLDH}) \sim N(\theta_{top\_PLDH}, \tau^2_{top\_PLDH});$$
$$\theta_{top\_PLDH} \sim N(0, 0.001)$$

where top_pac = topotecan versus paclitaxel and top_PLDH = topotecan versus PLDH.

The HRs for PFS and overall survival of paclitaxel and PLDH compared with topotecan are then multiplied by the respective absolute hazard for the baseline (topetecan) to calculate the absolute hazard of PFS and overall survival for paclitaxel and PLDH. The absolute hazards (λ) for each treatment are then converted into mean PFS and overall survival by taking the inverse of the hazard ($1/\lambda$).

In addition to the inclusion of trial 30-57, a further sensitivity analysis of the baseline model was conducted. This sensitivity analysis explored the cost-effectiveness for particular subgroups (platinum-sensitive -resistant/refractory) using the treatment effects reported for all patients and also the subgroup-specific treatment effects. Sensitivity analysis around particular cost assumptions, namely the inclusion of additional ECG cardiac monitoring costs for PLDH and home administration of topotecan, were also conducted.

Analysis 2: platinum-sensitive model

Calculating baseline survival for Analysis 2

Since prognosis is better in platinum-sensitive patients, it would not be appropriate to compare the absolute hazard associated with platinum combination therapy in ICON4 with the absolute hazard of topotecan estimated from a population including platinum-resistant and -refractory patients. Consequently, we used the subgroup-specific survival data reported for topotecan in trial 30-49 for platinum-sensitive patients.

Treatment strategies compared

Analysis 1, the base-case model, focused on paclitaxel, topotecan and PLDH from trials 039 and 30-49. As shown in *Table 56*, there are two further trials providing three more relevant comparators. Both of these trials (Cantu and ICON4)[28,29] looked specifically at one of the patient subgroups and recruited only platinum-sensitive patients. In the trial comparing paclitaxel and CAP (Cantu), the patient population was restricted to those patients who had relapsed >12 months after completion of therapy, rather than 6 months. The more common 6-month cut-off was used to define the platinum-sensitive population in the trials recruiting an overall patient population,[22,24] and ICON4 also included patients relapsing between 6 and 12 months after completion of therapy. Of the three additional comparators, paclitaxel combination therapy was the only one formally included in the systematic review and hence it can be compared on an equal basis with paclitaxel alone, topotecan and PLDH. However, as can be seen from *Table 56*, there is no

common comparator between ICON4 and any other trial, and consequently it was not possible to include it in an MTC as described in Analysis 1. In order to estimate a treatment effect of platinum combination therapy compared with topotecan, it was necessary to break randomisation. Specifically, it was necessary to use data reported on the median weeks' survival and 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. As a result, the estimated treatment effect of paclitaxel combination compared with topotecan in Analysis 2 is not as robust as the treatment effects estimated in Analysis 1.

Indirect estimate of treatment effect

In the same way in which the baseline is estimated in Analysis 1, the absolute hazards, λ, are calculated using median weeks' survival and an exponential approximation. The log absolute hazard is assumed to be normally distributed around a true underlying absolute effect, θ, which is given a vague prior, $N(0, 0.001)$. Relative treatment effects for paclitaxel combination compared with topotecan can then be estimated as the difference between the respective log absolute hazards:

$$\ln(\lambda_{pacpt}) = \ln[-\ln(0.5)/t_{pacpt}] \sim N(\theta_{pacpt}, \tau^2_{pacpt});$$
$$\theta_{pacpt} \sim N(0, 0.001)$$
$$\ln(\lambda_{top}) = \ln[-\ln(0.5)/t_{top}] \sim N(\theta_{top}, \tau^2_{top});$$
$$\theta_{top} \sim N(0, 0.001)$$
$$\theta_{top\_pacpt} = \theta_{top} - \theta_{pacpt}$$

where pacpt = platinum combination, top = topotecan, top_pacpt = topotecan versus paclitaxel combination and t = median weeks survival.

Using this method, one can also obtain a relative treatment effect for platinum compared with topotecan. With respect to CAP, the Cantu trial[28] provides us with an HR of CAP compared with paclitaxel, which can be used directly in the MTC to maintain randomisation and the use of the most reliable estimate of treatment effect, the HR. The WinBUGS code for Analysis 2 is provided in Appendix 11. To maintain correlation between the posterior survival estimates, the simulated outputs were exported directly into Excel.

Model inputs

Data used to populate the two analyses came from a variety of sources; these are listed in detail below.

Survival

Five of the nine trials identified in the clinical review were used to inform the survival estimates used in the models.[22,24,27–29] The data available from the trials were utilised differently for the two main analyses (detailed above) and the various sensitivity analyses. The (log) hazards for PFS and overall survival used in the two main analyses are presented in *Table 57*. The estimates used for the various sensitivity analyses are shown in Appendix 12.

As detailed above, survival data were utilised in the following ways: Analysis 1 used overall survival and PFS HRs generated from trials 039 and 30-49 to compare topotecan, paclitaxel and PLDH for the overall trial population, platinum-sensitive patients and platinum-resistant/refractory patients (assuming a common treatment effect across subgroups). Sensitivity analyses were undertaken to incorporate evidence from trial 30-57 and to explore the impact of using subgroup-specific treatment effects. Analysis 2 incorporates additional evidence available from the ICON4 and Cantu trials to explore the impact of extending the cost-effectiveness analysis to include the full range of treatment comparators that are relevant in the platinum sensitive group (topotecan, paclitaxel monotherapy, PLDH, paclitaxel + platinum and CAP).

Quality of life

The survival analysis described in previous sections details the approaches and inputs used to generate mean estimates for the survival times (overall survival and PFS) associated with each intervention. For the purposes of estimating QALYs, it was necessary to quality-adjust these survival times using an appropriate utility or preference score.[66]

In addition to the differences in relative survival estimated for each treatment, the different toxicity profiles and impact on progression of the alternative chemotherapy drugs may have important implications for the QoL of patients. As previously reported in the effectiveness review, QoL data were reported in both the ICON4 and 30-49 trials, using the EORTC QLQ-C 30.[67] This questionnaire encompasses six domain and eight symptom scales and is designed to assess the impact of cancer treatments on patients' QoL. For the purposes of the economic model these data present a number of potential limitations. First, the reported data only provide a profile of a person's QoL and are therefore unsuitable for inclusion in an economic evaluation, where a

TABLE 57 *Survival data used in Analyses 1 and 2 (95% CI in parentheses)*

		Name	Overall trial population	Platinum-sensitive patients	Platinum-resistant/ refractory patients	Source
Analysis 1	Overall survival hazards	Topotecan vs paclitaxel	0.914 (0.681 to 1.226)	1.01 (0.663 to 1.541)	0.738 (0.498 to 1.093)	039
		Topotecan vs PLDH	1.216 (1 to 1.478)	1.432 (1.066 to 1.923)	1.069 (0.823 to 1.387)	30-49
	PFS hazards	Topotecan vs paclitaxel	0.811 (0.603 to 1.092)	0.823 (0.538 to 1.261)	0.749 (0.501 to 1.121)	039
		Topotecan vs PLDH	1.118 (0.928 to 1.347)	1.287 (0.977 to 1.694)	0.992 (0.77 to 1.279)	30-49
Analysis 2	Overall survival hazards	Topotecan vs paclitaxel	–	1.01 (0.663 to 1.541)	–	039
		Topotecan vs PLDH	–	1.432 (1.066 to 1.923)	–	30-49
		Paxlitaxel combination vs platinum[a]	–	Paxlitaxel + Pt = 0.005 (0.004 to 0.006) Pt = 0.006 (0.005 to 0.007)	–	ICON4
		Paclitaxel vs CAP	–	1.724 (1.02 to 2.94)	–	Cantu
	PFS hazards	Topotecan vs paclitaxel	–	0.823 (0.538 to 1.261)	–	039
		Topotecan vs PLDH	–	1.287 (0.977 to 1.694)	–	30-49
		Paxlitaxel combination vs platinum	–	Paxlitaxel + Pt = 0.012 (0.01 to 0.013) Pt = 0.015 (0.013 to 0.017)	–	ICON4
		Paclitaxel vs CAP	–	1.66 (1.03 to 2.70)	–	Cantu

[a] Median survival was used to calculate absolute hazards for two treatments. HRs compared with topotecan baseline were then calculated. Absolute hazards derived from trial data are reported in Appendix 6.

single index preference weighted score is required. Second, QoL estimates using the reported EORTC data were not available for all treatments considered.

Owing to the limitations of QoL data reported in the main trials, a separate systematic search was undertaken to identify potential sources of utility data in ovarian cancer. Full details of the search strategy are reported in Appendix 10. Five studies were identified that reported utility estimates for advanced ovarian cancer, by Tengs and Wallace,[68] Ortega and colleagues,[69] Bennett and colleagues,[70] Grann and colleagues[71] and Calhoun and colleagues.[72] Four of these studies provided utility estimates relating to specific toxicity events experienced as a result of chemotherapy.[69–72] However, these events were not consistent with the toxicity events reported in the trials and could not be linked to the trial data identified in the clinical review. Since it was not possible to reflect accurately the difference in toxicity events between the treatments using a utility adjustment, an overall utility weight was applied to the survival estimates to reflect the different lengths of time spent on the progression-free and progressive states differed between drugs.

Although an overall estimate for stable disease (0.63) in advanced ovarian cancer was reported by Tengs and Wallace,[68] no separate utility estimates were identified as part of the systematic search for the utility associated with progressive disease. In the absence of direct estimates, alternative estimates from other related areas were identified in order to provide a proxy measurement. Teng and Wallace's study provided a comprehensive list of utility values in a range of other female cancers that provided estimates of the utility decrement between stable and progressive disease. Although these utilities were not in ovarian cancer patients, it was possible to calculate the utility decrement between the progression-free and progressive states and apply this decrement as a proxy estimate of progression-free QoL for ovarian cancer patients (0.63) obtained from the literature.[68] We selected a single study in breast cancer as the best proxy measure, since the estimate of stable disease was identical with that reported for ovarian cancer patients. In addition, the study by Brown and Hutton[73] provided estimates utilities using the time trade-off technique,[74] a method with strong theoretical foundations that has been well validated for estimating utilities for health states in cancer. The utility for the progressive period was then calculated by applying the utility decrement of 0.29, estimated as the difference between the utility of stable and progressive disease, to the overall estimate of 0.63 for stable disease.

Cost analysis

The costs included in the model are those considered to be the key components of treatment costs associated with advanced ovarian cancer and which are likely to differ between the various treatments considered. These include the acquisition costs of the drug, the costs of monitoring and administration and the costs of managing the adverse events. For the analysis of adverse events it was necessary to synthesise the data from the various trials. The approach is described in detail in this section.

Adverse events

All patients, in all trials, experienced some form of adverse event, but the grade and type of adverse event are often related to the regime received. Topotecan in particular is associated with the occurrence of neutropenia and PLDH with PPE. Each of the adverse events has different resource use implications. In addition, the resource use associated with adverse events increases dramatically for high-grade (3 and 4) events. It was therefore necessary to cost the different types and grades of adverse events observed in the trials for each of the treatment comparators.

The proportions of patients experiencing the adverse events neutropenia, thrombocytopenia, PPE, diarrhoea, nausea/vomiting, stomatitis/pharyngitis, anaemia, sepsis and fever, during treatment, were available from the 30-49, 039, 30-57, ICON4 and Cantu trials, although some of the data were missing for the Cantu and ICON4 trials. Data for the platinum therapies CAP (from Cantu) and carboplatin/cisplatin (from ICON4) were not reported for some events, and therefore an additional trial by Bolis and colleagues[75] reporting on adverse events for platinum therapy was used to supplement these. As reported by Smith and colleagues,[50] the use of the proportions of adverse events is likely to involve double counting for certain resource use items such as hospitalisations and assumes that each patient only sustained one of each type of adverse event. However, without access to patient-level data it was not possible to account for simultaneous adverse events and multiple events for all comparators. Although a detailed patient-level analysis was conducted by Smith and colleagues,[50] this analysis was also only relevant for the comparison between topotecan and PLDH. In order to apply a consistent method, which

would enable the full range of comparators to be assessed, it was necessary to use data on adverse events that were reported using a common format.

Data on grade 1 and 2 adverse events were particularly poor. This is probably because the trials concentrated on reporting adverse events that would require a change in therapy or discontinuation. Owing to the paucity of data reported for grade 1 and 2 adverse events, these events were not included in the cost analysis. However, these are likely to incur little or no cost as the majority of hospitalisations for grade 1 and 2 adverse events will only occur as part of trial protocol,[50] hence the remaining cost of adverse events 1 and 2 is likely to be negligible (zero in many cases).

Given that this analysis only includes grade 3 and 4 adverse events, the possibility of multiple events and more than one adverse event (requiring hospitalisation) in the same period is likely to be less than if we were to include all adverse events (grades 1–4). The proportion of grade 3 and 4 adverse events reported in each of the trials was therefore used to calculate the total cost of adverse events for each of the treatments by applying resource use data reported in the Schering-Plough Ltd submission. As with the survival data, a mixed comparisons model was used to estimate the probabilities of adverse events using data from the trials included in the analysis. For Analysis 1, adverse event data from the 30-49, 039 and 30-57 trials were used, and for Analysis 2, adverse event data from the 30-49, 039, 30-57, Cantu, ICON 4 and Bolis trials were used.

Using a similar approach to that undertaken for the meta-analysis of survival data, the analysis of adverse events was undertaken using a Bayesian meta-analysis to account for the mixed and indirect comparisons for the various treatments reported in the different trials. The WinBUGS model used to estimate probabilities of adverse events assumes a regression-like structure, with the logit of the probability of an adverse event for any treatment k, depending on a 'baseline' term (for topotecan) μ_i in trial i, $i = 1, 2, \ldots, 5$, and a fixed treatment effect d^k. The trial-specific baselines are drawn from a common random normal distribution, whose parameters must be estimated from the data, given vague priors. Formally, this can be expressed as

$$\text{logit}(p_i^k) = \mu_i + d^k$$
$$\mu_i \sim N(\mu b, tb); \qquad \mu b \sim N(0,0.0001), \quad tb \sim \text{gamma}(0.01,0.01)$$

The treatment effects d^k are also given independent vague priors, $N(0,0.0001)$. A binomial likelihood is assumed from the available data points:

$$r_i^k \sim \text{Bin}(p_i^k, n_i^k)$$

where k denotes all treatment indices in study i.

The WinBUGS codes for Analysis 1 (topotecan, paclitaxel and PLDH) and Analysis 2 (topotecan, PLDH, paclitaxel montherapy, paclitaxel combined with platinum, platinum and CAP) are reported in Appendix 11. Unlike the survival data, adverse event data from trial 30-57 were used for the base-case model, since adverse events were observed only during the treatment period. The problem of short follow-up, as observed with the trial 30-57 survival data, should not apply to the adverse event data. The mean probabilities of adverse events estimated using the mixed comparisons model are reported in *Table 58*.

Unit costs and resource use

The cost inputs used in the model are listed in *Table 59*. Drug costs were taken from the BNF.[56] Other sources included industry submission data, earlier published estimates in the area and national unit cost databases. Resource use associated with adverse events was taken from information supplied as part of the Schering-Plough submission.[23]

Drug costs were calculated according to the dosages reported in the trials; this was also the licensed dose. Dosages for paclitaxel, topotecan, PLDH and CAP were multiplied by a body surface area of 1.7 m^2. Dosage for carboplatin was determined using the Cockcroft formula [AUC(6) × glomerular filtration rate (GFR) + 25 ml, where GFR = 85 ml/min]. Premedication as reported in the trials was also included. This consisted of the intravenous administration of metoclopramide, chlorpheniramine and cimetidine, for relevant drugs, prior to administration of the study drug. Saline was used to administer the intervenous concentrate; this was costed according to millilitres as specified by our clinical advisor (50–500 ml at £0.06/ml). In the base-case analysis we assumed that unfinished vials could be reused in further treatments. We explored the robustness of the model results to this assumption in the sensitivity analysis. The total cost of drugs was calculated by multiplying the cost per cycle by the average number of cycles received, reported in *Table 58*.

Chemotherapy was assumed to be administered on an outpatient basis for all regimes not containing

cisplatin, that is, topotecan, PLDH and paclitaxel. A single visit was required for each cycle, apart from for topotecan, which was administered over 5 days, thus requiring five separate outpatient visits per cycle. For CAP, the 11% of patients in ICON4 receiving cisplatin platinum therapy and the 10% of patients in ICON4 receiving cisplatin plus paclitaxel chemotherapy were assumed to be treated on an inpatient basis. This is because cisplatin is potentially severely nephrotoxic and therefore to administer it safely it is necessary to create a sodium chloride diuresis. This is most often achieved by intravenous infusion of saline solution (usually 0.9%) and a diuretic (most commonly mannitol). This diuresis is maintained during the cisplatin infusion and for several hours afterwards. This whole process may take between 7 and 12 hours for moderate and high doses of cisplatin, and therefore is likely to require an overnight admission to hospital.

The home administration of topotecan was only included as a sensitivity analysis, as it is not common practice in the UK and does not represent the method of administration used in the trials. Home administration of topotecan requires a daily visit by a district nurse and a consultation with a specialist physician each cycle. The total cost of administration was calculated by multiplying the cost per cycle by the average number of cycles received, reported in *Table 58*.

The cost of monitoring patients for toxicity events, in terms of chemical pathology monitoring, haematological toxicity monitoring and biochemical monitoring, was added to all comparators in the model. The total cost of monitoring was calculated by multiplying the cost per cycle by the average number of cycles received reported in *Table 58*. The potential elevated risk of cardiac toxicity in the PLDH strategy was highlighted in the industry submissions.[76,77] The Summary of Product Characteristics for PLDH recommends that all patients should routinely undergo frequent ECG monitoring. However, after clinical consultation it was concluded that tests for cardiac function (e.g. ECG, echocardiogram and MCUG) would not be routinely used in practice for these patient groups for PLDH. This is due to the lower cardiac toxicity observed with PLDH compared with doxorubicin and its use in the palliative setting, when life expectancy is short and patients and clinicians are often prepared to give concerns about late toxicity less weight than in the curative setting. Hence in the base-case analysis no additional costs are assigned to PLDH for cardiac monitoring. The robustness of this assumption is explored in a sensitivity analysis that included the cost of an ECG for each cycle of PLDH. The use of echocardiography and multigated angiography were not included since the use of these more costly and invasive tests (mainly used for the evaluation of left ventricular function) is only considered mandatory before each additional administration that exceeds a lifetime dose of PLDH of 450 mg/m^2, which exceeds the lifetime dose considered in this model.

Grade 3 and 4 adverse events were costed using resource use data reported in the Schering-Plough submission.[23] In this submission, resource use associated with various adverse events by level of severity were estimated by a group of clinical experts. The adverse events that incurred a cost were consistent with the adverse events reported by trials, namely neutropenia, thrombocytopenia, anaemia, stomatitis/pharyngitis, PPE, nausea/vomiting, diarrhoea, sepsis and fever. Some of these resource use items are associated with uncertainty, and the distributions used to reflect this uncertainty are shown in Appendix 12. These were again taken from data reported in the Schering-Plough submission.[23]

Analytical methods

The output from the meta-analyses undertaken in WinBUGS were imported directly into Microsoft Excel 2000. These were then combined with data on resource use and cost in order to obtain the mean estimates for the outcomes of interest and their associated uncertainty. The results are presented in two ways. First, mean costs and QALYs for the various comparators are presented and their cost-effectiveness compared using standard decision rules and estimating ICERs as appropriate. The ICER examines the additional costs that one strategy incurs over another and compares this with the additional benefits. When more than two interventions are being compared, the ICERs are calculated using the following process:

1. The strategies are ranked in terms of cost (from the least to the most expensive).
2. If a strategy is more expensive and less effective than the previous strategy, then this strategy is said to be dominated and is excluded from the calculation of the ICERs.
3. The ICERs are calculated for each successive alternative, from the least to the most expensive. If the ICER for a given strategy is higher than that of the next more effective

TABLE 58 *Other trial data*

	Name	Value	Distribution	Source
Average no. of cycles	Topotecan	5.72	Fixed	Mean of 039 and 30-49
	Paclitaxel	4.82	Fixed	039
	PLDH	4.87	Fixed	30-49
	Paclitaxel + platinum	5.56	Fixed	ICON4
	Platinum	5.26	Fixed	ICON4
	CAP	6	Fixed	Cantu

		Topotecan	Paclitaxel	PLDH	Paclitaxel + platinum	Platinum	CAP	Sources (s)
Probability of experiencing adverse events (Analysis 1)	Stomatitis/pharyngitis grade 3	0.01	0.01	0.09	–	–	–	039, 30-49, 30-57
	Stomatitis/pharyngitis grade 4	0.01	0.00	0.01	–	–	–	
	PPE grade 3	0.00	0.01	0.20	–	–	–	
	PPE grade 4	0.00	0.01	0.01	–	–	–	
	Neutropenia grade 3	0.13	0.21	0.09	–	–	–	
	Neutropenia grade 4	0.58	0.13	0.06	–	–	–	
	Thrombocytopenia grade 3	0.19	0.01	0.01	–	–	–	
	Thrombocytopenia grade 4	0.21	0.01	0.00	–	–	–	
	Anaemia grade 3	0.29	0.04	0.05	–	–	–	
	Anaemia grade 4	0.04	0.02	0.051	–	–	–	
	Diarrhoea grade 3	0.01	0.02	0.02	–	–	–	
	Diarrhoea grade 4	0.01	0.01	0.01	–	–	–	
	Nausea/vomiting grade 3	0.16	0.04	0.13	–	–	–	
	Nausea/vomiting grade 4	0.04	0.01	0.02	–	–	–	
	Sepsis grade 3	0.01	0.01	0.00	–	–	–	
	Sepsis grade 4	0.00	0.00	0.00	–	–	–	
	Fever grade 3	0.06	0.02	0.04	–	–	–	
	Fever grade 4	0.02	0.01	0.00	–	–	–	
Probability of experiencing adverse events (Analysis 2)	Stomatitis/pharyngitis grade 3	0.01	0.01	0.01	0.01	0.01	0.01	039, 30-49, 30-57, Cantu, ICON4, Bolis
	Stomatitis/pharyngitis grade 4	0.00	0.01	0.01	0.01	0.01	0.00	
	PPE grade 3	0.00	0.01	0.20	0.01	0.01	0.20	
	PPE grade 4	0.00	0.01	0.01	0.01	0.01	0.01	
	Neutropenia grade 3	0.11	0.18	0.07	0.18	0.16	0.23	
	Neutropenia grade 4	0.52	0.09	0.04	0.09	0.17	0.38	
	Thrombocytopenia grade 3	0.18	0.01	0.01	0.01	0.13	0.12	
	Thrombocytopenia grade 4	0.20	0.01	0.00	0.01	0.01	0.02	
	Anaemia grade 3	0.3	0.04	0.05	0.04	0.05	0.07	

continued

TABLE 58 *Other trial data (cont'd)*

	Topotecan	Paclitaxel	PLDH	Paclitaxel + platinum	Platinum	CAP	Sources (s)
Anaemia grade 4	0.04	0.02	0.00	0.02	0.05	005	
Diarrhoea grade 3	0.05	0.02	0.03	0.02	0.03	0.03	
Diarrhoea grade 4	0.01	0.01	0.01	0.01	0.01	0.01	
Nausea/vomiting grade 3	0.15	0.37	0.13	0.08	0.09	0.06	
Nausea/vomiting grade 4	0.04	0.01	0.02	0.01	0.02	0.03	
Sepsis grade 3	0.01	0.01	0.01	0.01	0.01	0.01	
Sepsis grade 4	0.01	0.01	0.01	0.01	0.01	0.01	
Fever grade 3	0.07	0.03	0.04	0.03	0.02	0.04	
Fever grade 4	0.02	0.01	0.01	0.01	0.02	0.00	

TABLE 59 *Details of cost data*

	Name	Value (£)	Distribution	Source
Drug costs (including premedication)	Topotecan, per cycle	1341	Fixed	BNF
	Paclitaxel, per cycle	1117	Fixed	30-49, 039,
	PLDH per cycle	1385	Fixed	ICON4 and
	Paclitaxel + platinum	1391	Fixed	Cantu trials for
	Platinum	279	Fixed	dosages
	CAP	194	Fixed	
Drug administration	Topotecan, per cycle	450	Fixed	Schering-Plough
	Paclitaxel, per cycle	90	Fixed	submission
	PLDH, per cycle	90	Fixed	and clinical
	Paclitaxel + platinum	113	Fixed	advice
	Platinum	111	Fixed	
	CAP	293	Fixed	
Home administration of topotecan	Per cycle	387	Fixed	GSK submission, PSSRU and clinical advice
Monitoring	Topotecan, per cycle	8.85	Fixed	BNF
	Paclitaxel, per cycle	8.85	Fixed	
	PLDH, per cycle	8.85	Fixed	
	Paclitaxel + platinum	8.85	Fixed	
	Platinum	8.85	Fixed	
	CAP	8.85	Fixed	
	ECG (PLDH sensitivity analysis)	65.24	Fixed	GSK submission
Adverse events	Stomatitis/pharyngitis grade 3	143.81	See resource	Schering-
	Stomatitis/pharyngitis grade 4	2013.77	use table,	Plough submission
	PPE grade 3	93.38	Appendix 12	
	PPE grade 4	2153.50		
	Neutropenia grade 3	54		
	Neutropenia grade 4	1419.65		
	Thrombocytopenia grade 3	0		
	Thrombocytopenia grade 4	1016		

TABLE 60 *Cost results (£) broken down by category*

	Topotecan	Paclitaxel	PLDH
Cost of drug	7,169	5,388	6,748
Cost of administration	2,405	434	438
Cost of monitoring	47	43	43
Cost of adverse events	1,773	490	484
Total cost	11,394	6,354	7,714

strategy, then this strategy is ruled out on the basis of extended dominance.

Finally, the ICERs are recalculated excluding any strategies that are ruled out by principles of dominance or extended dominance.

Given that mean costs and QALYs gained are estimated with uncertainty, the output from the simulations were then used to generate cost-effectiveness acceptability curves (CEACs) for the alternative analyses. These curves detail the probability that each intervention is cost-effective over a range of potential maximum values that the health service is prepared to pay for an additional QALY.[78]

Results

Costs

Table 60 presents the results of the analysis of total costs broken down by the cost of the study drug, the cost of administration, the cost of monitoring

TABLE 61 *Cost-effectiveness results from Analysis 1: base-case model*

Treatment	PFS (weeks)	OS (weeks)	Quality-adjusted survival (weeks)	Cost (£)	ICER[a] (£)	Probability cost-effective for a maximum WTPG		
						£10,000	£30,000	£50,000
Analysis 1 – overall patient population								
Topotecan	24.5	86.0	34.2	11,394	D	0.00	0.00	0.00
Paclitaxel	20.1	79.7	30.9	6,354	–	0.31	0.10	0.08
PLDH	27.5	104.8	40.9	7,714	7,033	0.69	0.90	0.92
Analysis 1 – treatment effects applied to platinum-sensitive baseline								
Topotecan	33.2	101.6	41.8	11,394	D	0.00	0.00	0.00
Paclitaxel	27.2	94.1	37.6	6,354	–	0.24	0.09	0.07
PLDH	37.2	123.6	49.8	7,714	5,777	0.76	0.91	0.93
Analysis 1 – treatment effects applied to platinum-resistant/refractory baseline								
Topotecan	19.8	61.2	25.1	11,394	D	0.00	0.00	0.00
Paclitaxel	16.3	56.7	22.6	6,354	–	0.47	0.13	0.09
PLDH	22.2	74.6	30.0	7,714	9,555	0.53	0.87	0.91

D, dominated – higher costs and lower QALYs than another comparator; OS, overall survival; WTP, willingness to pay per QALY.
[a] Cost per QALY.

for adverse events and the total cost of managing any adverse events. As noted earlier, the total cost does not vary between subgroups, as cost parameters were not available by specific subgroups and they apply only to the active treatment phase during which all patients are assumed to be alive in the model.

Paclitaxel emerges as the cheapest treatment strategy in nearly every category and overall. PLDH is the next cheapest option owing to the higher drug acquisition costs compared with paclitaxel. Topotecan is the most expensive treatment strategy; this is due almost entirely to the higher costs of administration (as each cycle is given over 5 days, instead of 1 day as is the case with paclitaxel and PLDH) and higher costs of adverse events associated with a higher incidence of neutropenia. In terms of the cost of managing adverse events, PLDH is associated with the lowest cost of managing adverse events (approximately £1289 less than topotecan and £4 less than paclitaxel).

In the submission by GSK, the monitoring cost for PLDH included a cardiac monitoring component not attributed to the other drugs (ECG followed by either echocardiogram or MCUG). As discussed earlier, after consultation with our clinical advisor, we assumed that additional cardiac monitoring for PLDH was unlikely to occur in practice. As a sensitivity analysis, the results of the model were re-estimated, including the cost of an ECG before every cycle of PLDH. In this scenario, the total cost of PLDH increased from £7714 to £8031.

The submission by GSK also described a novel method of home administration of topotecan. In the GSK submission the costs of community nurse visits were not considered in their costings. In this sensitivity analysis, we assumed that provision of topotecan at home would require five 1-hour visits (at £56 per hour), plus the costs of a consultation with a consultant at every cycle. The total cost associated with topotecan administered at home was estimated to be £11,058, representing a saving of £336 compared with the estimates for topotecan applied in the base-case analysis.

Analysis 1 – base case

Table 61 presents the analysis of the ICER in the overall patient population and also where those same treatment effects are applied to a platinum-sensitive or -resistant/refractory baseline. In Analysis 1 the treatments compared are topotecan, paclitaxel and PLDH.

Using the decision rules for calculating the ICERs described earlier, topotecan is dominated by PLDH. The options under consideration in the base-case analysis of the ICER are therefore PLDH and paclitaxel. The ICER for PLDH compared with paclitaxel is £7033 per QALY in the overall patient population. Topotecan continues to be dominated in the subgroup analyses undertaken

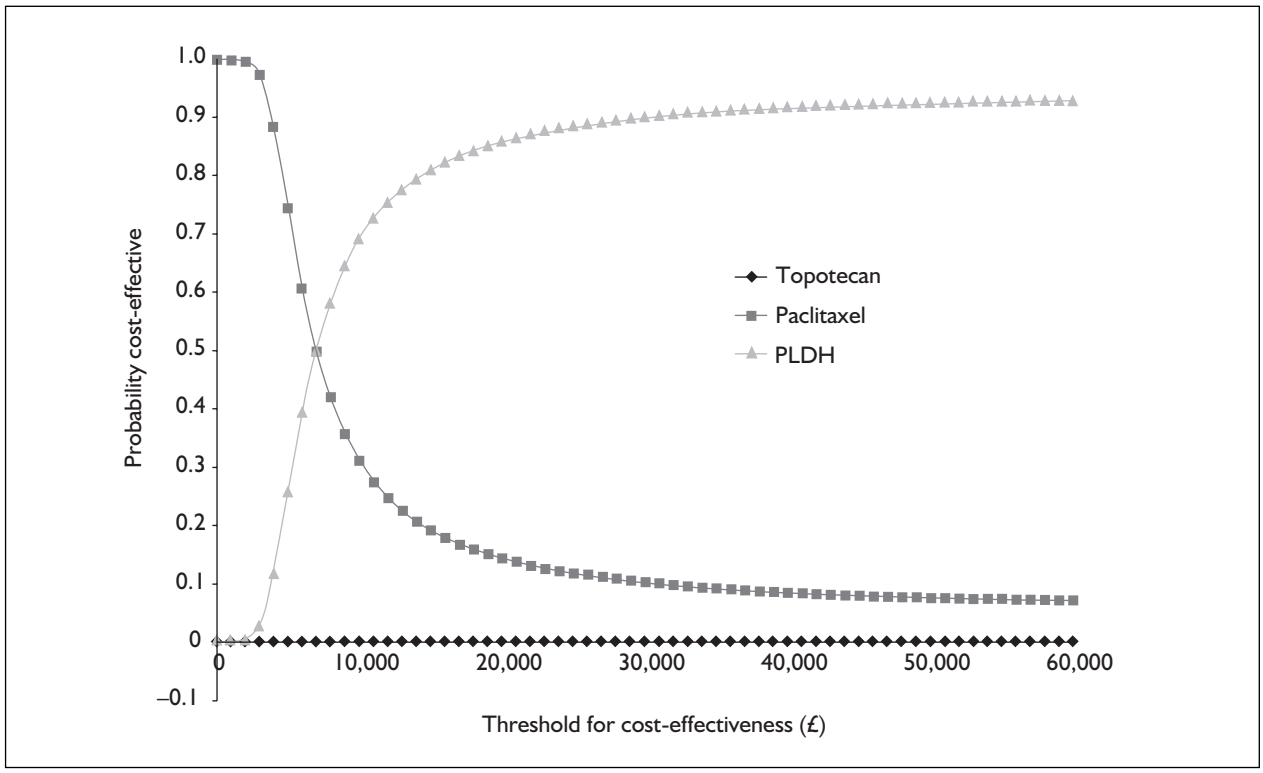

FIGURE 23 *Analysis 1, overall population*

for platinum-sensitive and -resistant/refractory patients. The ICER for PLDH compared with paclitaxel is £5777 per additional QALY in the platinum-sensitive population and £9555 per additional QALY in the platinum-resistant and -refractory population.

In the overall population and in each of the subgroups, as the willingness to pay (WTP) per QALY increases, so does the likelihood that PLDH is the most cost-effective treatment strategy. In the overall patient population, at a WTP of £10,000 per QALY, PLDH has a 69% probability of being the most cost-effective treatment strategy, rising to 90% at a WTP of £30,000 per QALY and 92% at a WTP of £50,000 per QALY. The CEACs for the overall population, demonstrating the probability that each comparator is cost-effective over a range of threshold values, are provided in *Figure 23*.

The pattern observed for the overall population is similar in the platinum-sensitive and platinum-resistant/refractory populations, although the estimate of the ICER varies slightly. PLDH appears more favourable in a platinum-sensitive population because the relative treatment effects estimated for PLDH are applied to a higher baseline survival (and a lower baseline survival for resistant refractory patients; hence the less favourable ICER in this subgroup). The decision uncertainty, in the form of a CEAC, for platinum-sensitive patients and refractory patients, can be seen in *Figures 24* and *25*, respectively.

Patients in the platinum-resistant and -refractory subgroup may not be eligible to receive paclitaxel as second-line therapy if they received it as part of their first-line treatment. Consequently, in platinum-resistant and -refractory patients who received paclitaxel as first-line therapy, the relevant comparators may be limited to topotecan and PLDH. In this scenario PLDH appears to be the most cost-effective treatment strategy, as it dominates topotecan (higher QALYs and lower costs).

Sensitivity analysis – subgroup-specific treatment effects

In the base-case analysis we applied the treatment effects estimated from the full trial populations, including a mixture of platinum-sensitive, -resistant and -refractory patients, to subgroup-specific baseline data. In a sensitivity analysis we applied subgroup-specific treatment estimates taken from the trials and applied those to subgroup-specific baseline survival. *Table 62* presents the analysis of the ICER in the platinum-

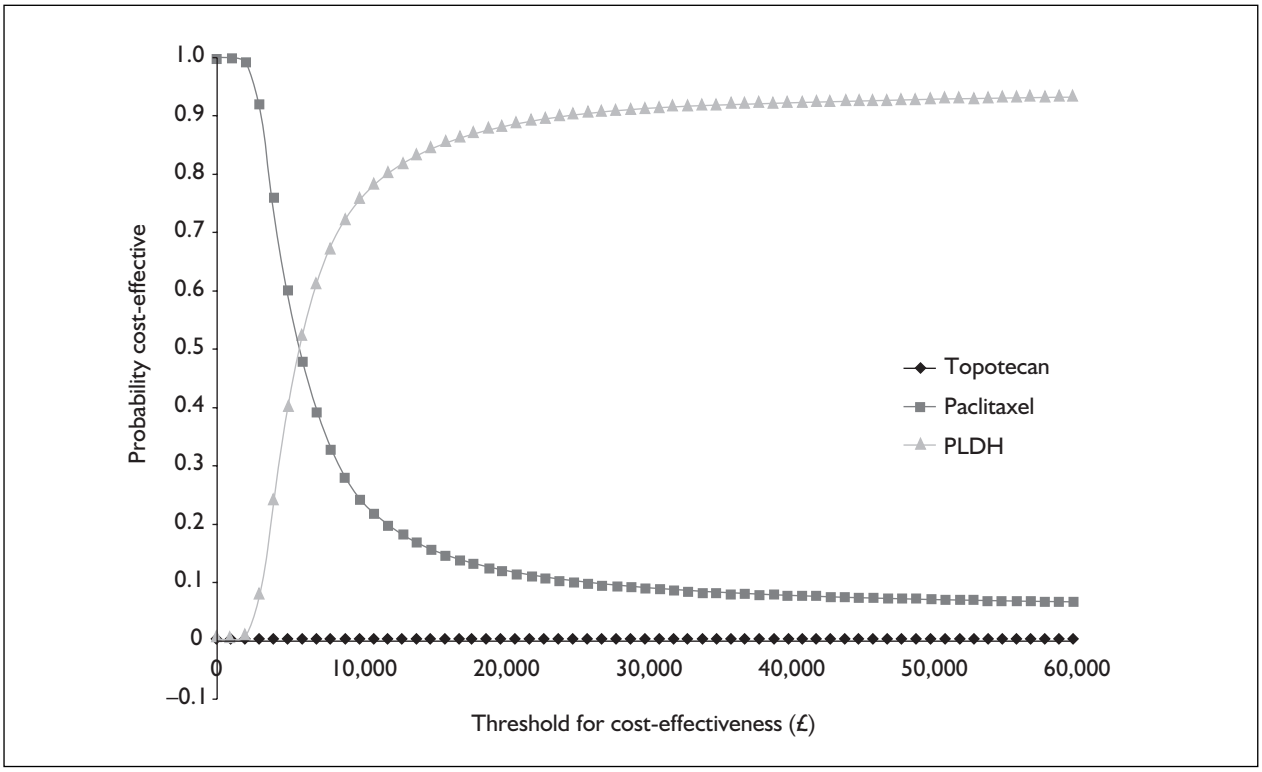

FIGURE 24 *Analysis 1, platinum-sensitive patients*

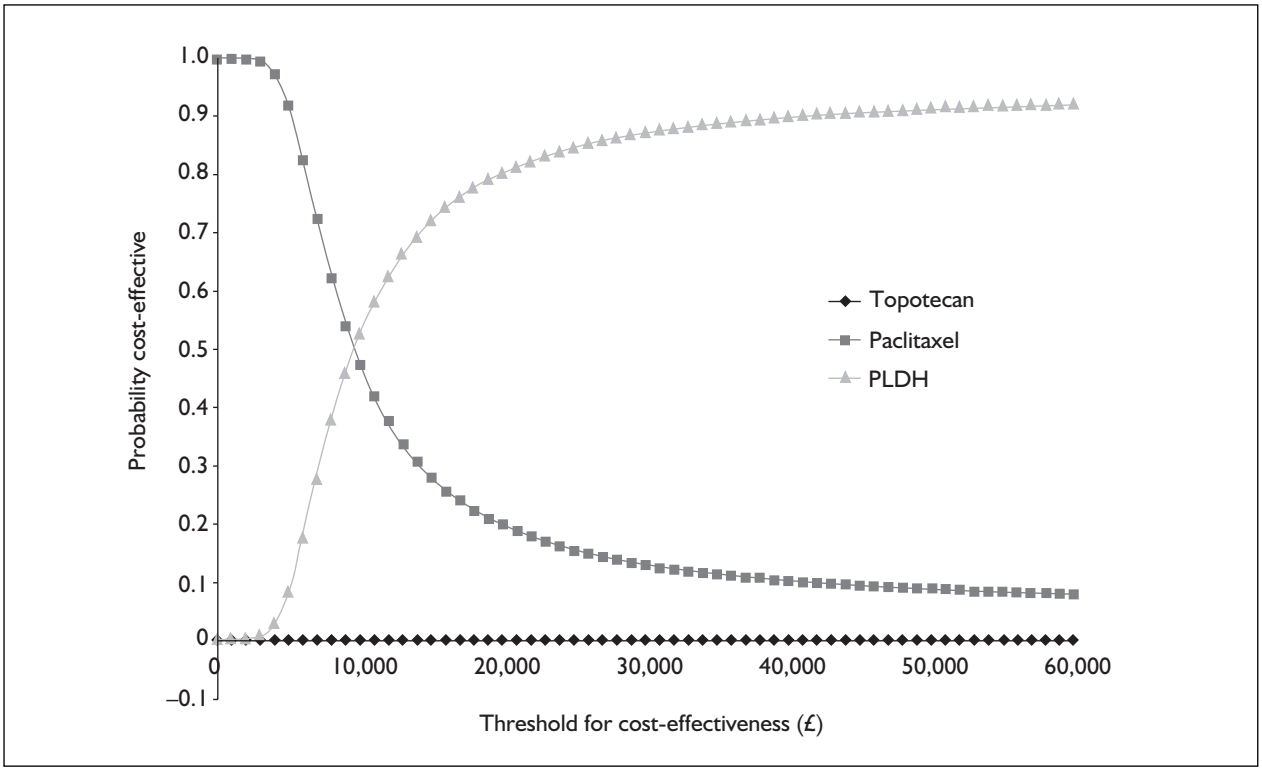

FIGURE 25 *Analysis 1, platinum-resistant/refractory patients*

TABLE 62 *Cost-effectiveness results applying subgroup-specific treatment effects*

Treatment	PFS (weeks)	OS (weeks)	Quality-adjusted survival (weeks)	Cost (£)	ICER[a] (£)	Probability cost-effective for a maximum WTPG		
						£10,000	£30,000	£50,000
Sensitivity analysis – platinum-sensitive patients								
Topotecan	33.1	101.3	41.7	11,394	D	0.00	0.00	0.00
Paclitaxel	27.8	104.3	40.9	6,354	–	0.19	0.10	0.09
PLDH	43.0	145.7	58.4	7,714	4,024	0.81	0.90	0.91
Sensitivity analysis – platinum-resistant/refractory patients								
Topotecan	19.8	61.2	25.1	11,394	D	0.00	0.00	0.03
Paclitaxel	15.2	46.3	19.1	6,354	–	0.47	0.16	0.12
PLDH	19.8	65.9	26.6	7,714	9,465	0.53	0.84	0.85

[a] Cost per QALY.

TABLE 63 *Cost-effectiveness results applying alternative costs assumptions*

Treatment	PFS (weeks)	OS (weeks)	Quality-adjusted survival (weeks)	Cost (£)	ICER[a] (£)	Probability cost-effective for a maximum WTPG		
						£10,000	£30,000	£50,000
Analysis 1 – overall patient population – cost of ECG added to each cycle of PLDH								
Topotecan	24.5	86.0	34.2	11,394	D	0.00	0.00	0.00
Paclitaxel	20.1	79.7	30.9	6,354	–	0.41	0.12	0.08
PLDH	27.5	104.8	40.9	8,031	8,677	0.59	0.88	0.92
Analysis 1 – overall patient population – home administration of topotecan								
Topotecan	24.5	86.0	34.2	11,058	D	0.00	0.00	0.00
Paclitaxel	20.1	79.7	30.9	6,354	–	0.31	0.10	0.08
PLDH	27.5	104.8	40.9	7,714	7,033	0.69	0.90	0.92
Analysis 1 – overall population – disposal of unused powder for reconstitution								
Topotecan	24.5	86.0	34.2	12,657	D	0.00	0.00	0.00
Paclitaxel	20.1	79.7	30.9	6,399	–	0.68	0.18	0.11
PLDH	27.5	104.8	40.9	8,902	12,948	0.32	0.82	0.89

[a] Cost per QALY.

sensitive and platinum-resistant/refractory subgroups.

The results are similar to those observed in Analysis 1, with topotecan ruled out by extended dominance by PLDH. The ICER for PLDH compared with paclitaxel is reduced to £4024 per QALY in the platinum-sensitive population (compared with £5777 per QALY in the base-case analysis), and £9465 per QALY in the platinum-resistant and -refractory population (compared with £9555 in the base-case analysis).

For patients who have received paclitaxel as part of their first-line treatment, PLDH is again the most cost-effective treatment as it dominates topotecan.

Sensitivity analysis – changing cost assumptions for PLDH and topotecan

In the base-case analysis, patients receiving PLDH were assumed to receive no additional tests to monitor cardiac function. In a sensitivity analysis, we added the cost of an ECG test to each cycle of PLDH received. We also undertook sensitivity analyses to look at the home administration of topotecan via a community nurse and disposal of unused powder for reconstitution. The ICERs for these sensitivity analyses regarding cost assumptions (described above) are presented in *Table 63*.

For all sensitivity analyses, the results are similar to those observed in the overall population of Analysis 1. Topotecan is still ruled out on the

TABLE 64 *Cost-effectiveness results incorporating the results of trial 30-57 via an MTC*

Treatment	PFS (weeks)	OS (weeks)	Quality-adjusted survival (weeks)	Cost (£)	ICER[a] (£)	Probability cost-effective for a maximum WTPG		
						£10,000	£30,000	£50,000
Sensitivity analysis – overall patient population								
Topotecan	24.5	86.0	34.2	11,394	D	0.00	0.00	0.00
Paclitaxel	20.1	92.1	34.6	6,354	–	0.84	0.37	0.28
PLDH	27.5	98.1	38.9	7,714	16,714	0.16	0.63	0.72
Sensitivity analysis – treatment effects applied to platinum-sensitive baseline								
Topotecan	33.1	101.6	41.8	11,394	D	0.00	0.00	0.00
Paclitaxel	27.2	108.6	42.0	6,354	–	0.73	0.32	0.25
PLDH	37.2	115.7	47.4	7,714	13,118	0.27	0.68	0.75
Sensitivity – treatment effects applied to platinum-resistant/refractory baseline								
Topotecan	19.8	61.2	25.1	11,394	D	0.00	0.00	0.00
Paclitaxel	16.2	65.5	25.3	6,354	–	0.95	0.46	0.32
PLDH	22.2	79.8	28.5	7,714	21,778	0.05	0.54	0.68

[a] Cost per QALY.

grounds of dominance by PLDH. Consequently, the ICER for paclitaxel/PLDH in sensitivity analysis of home administration of topotecan remains unchanged. Adding in additional cardiac monitoring costs for PLDH increased the ICER compared with paclitaxel to £8677 per QALY. Assuming disposal of unused powder for reconstitution increased the ICER for PLDH compared with paclitaxel to £12,948 per QALY (compared with £7033 per QALY in the base-case analysis). The results of the model would therefore appear to be robust to these changes in costs assumptions.

Sensitivity analysis – incorporation of trial 30-57

Included in the cost-effectiveness review in the section 'Assessment of clinical effectiveness (p. 22)' alongside the eight published trials was a trial report for an aborted study comparing paclitaxel with PLDH, namely trial 30-57. The evidence from this study appeared to contradict the inferences one could draw from trials 039 and 30-49, by showing that paclitaxel may be superior to PLDH in terms of overall survival (although not statistically significant). Looking only at trials 039 and 30-49, the conclusion may have been that as topotecan and paclitaxel are shown to be of similar effectiveness in trial 039, and as PLDH is shown to be superior to topotecan in trial 30-49, PLDH would be superior to paclitaxel in a direct comparison. In a sensitivity analysis we incorporated the HR for overall survival from trial 30-57 via an MTC in order to assess the implications of including this new evidence. As mentioned earlier, the MTC gives trial 30-57 equal weight to the two completed RCTs and assumes that the HR observed at about 1 year is equal to that observed after a longer period of follow-up. *Table 64* presents the analysis of the ICER in the overall patient population, and also where those same treatment effects are applied to a platinum-sensitive or platinum-resistant and -refractory baseline.

As expected, the inclusion of trial 30-57 alters the results of the model by making paclitaxel look more effective than topotecan in terms of overall survival and by reducing the effectiveness of PLDH. Topotecan is now dominated by both paclitaxel and PLDH. Paclitaxel is now associated with marginally higher quality-adjusted survival. Owing to the improved effectiveness of paclitaxel and the less favourable estimate for PLDH, the ICER for PLDH compared with paclitaxel is higher than in Analysis 1 at £16,714 per QALY in the overall patient population, £13,118 per QALY in the platinum-sensitive population and £21,778 per QALY in the platinum-resistant and -refractory population.

For paclitaxel-experienced platinum-resistant and -refractory patients, PLDH dominates topotecan and hence is the most cost-effective strategy.

Analysis 2

Analysis 2 relaxed the need to use reported HRs and also introduced comparators not formally included in the systematic review. Analysis 2 also considered only a platinum-sensitive population as the additional comparators were only assessed in

TABLE 65 *Cost results (£) broken down by category*

	Topotecan	Paclitaxel	PLDH	Paclitaxel + platinum	Platinum	CAP
Cost of drug	7,169	5,388	6,748	7,737	1,472	1,184
Cost of administration	2,405	434	438	626	587	1,758
Cost of monitoring	47	43	43	49	47	53
Cost of adverse events	1,654	403	433	429	770	992
Total cost	£11,276	£6,274	£7,662	£8,841	£2,876	£3,988

TABLE 66 *Cost-effectiveness results from Analysis 2*

Treatment	PFS (weeks)	OS (weeks)	Quality-adjusted survival (weeks)	Cost (£)	ICER[a] (£)	Probability cost-effective for a maximum WTPG		
						£10,000	£30,000	£50,000
Analysis 2 – platinum-sensitive patient population								
Topotecan	33.1	101.4	41.7	11,276	D	0.00	0.00	0.00
Paclitaxel	28.0	105.1	41.2	6,274	D	0.00	0.00	0.00
PLDH	43.0	145.8	58.5	7,662	D	0.00	0.03	0.03
Paclitaxel + platinum	82.0	178.8	81.2	8,841	20,950	0.00	0.49	0.60
Platinum	63.5	149.7	66.3	2,876	–	0.56	0.08	0.01
CAP	47.9	176.7	69.5	3,988	16,421	0.44	0.41	0.37

[a] Cost per QALY.

this subgroup. The relevant treatment strategies in Analysis 2 are topotecan, paclitaxel, PLDH, paclitaxel combined with platinum, platinum monotherapy and CAP. The costs for the six comparators are presented, broken down by category, in *Table 65*. The cost for the three comparators included in Analysis 1 are slightly different, owing to the different data used to estimate adverse events (described above).

In Analysis 2, platinum monotherapy is associated with the lowest overall costs. Paclitaxel and platinum combination is more expensive than paclitaxel alone; this is due almost entirely to the higher cost of the drug itself. Topotecan appears to be the most expensive treatment.

The inclusion of the Cantu and ICON4 trials relates specifically to the platinum-sensitive population, in which these trials were conducted. Data from these trials are therefore added to the platinum-sensitive data from trials 039 and 30-49, reported in Analysis 1. *Table 66* presents the analysis of the ICERs in the platinum-sensitive patient population.

Topotecan, paclitaxel monotherapy and PLDH are all dominated by platinum monotherapy, that is, they have higher costs and lower QALYs. After excluding dominated alternatives, the treatments under consideration are platinum monotherapy, CAP and paclitaxel/platinum combination therapy. Platinum monotherapy was the least costly and least effective of these non-dominated treatments. The ICER for CAP compared with platinum monotherapy is £16,421 per QALY. The ICER for paclitaxel/platinum combination therapy compared with CAP is £20,950.

The CEACs for Analysis 2, showing the probability that each comparator is cost-effective over a range of threshold values, are provided in *Figure 26*. At a maximum WTP of £30,000 per QALY, the probability that the combination of paclitaxel and platinum is cost-effective is 0.49.

Budget impact analysis

In order to estimate the budget impact of the economic model recommendations, we must consider the number of people who will receive second-line therapy for advanced ovarian cancer and the cost of switching from therapies they would have received to the therapy determined optimum by Analysis 1 of the economic model. Analysis 1 concluded that PLDH was the most cost-effective therapy for an overall population,

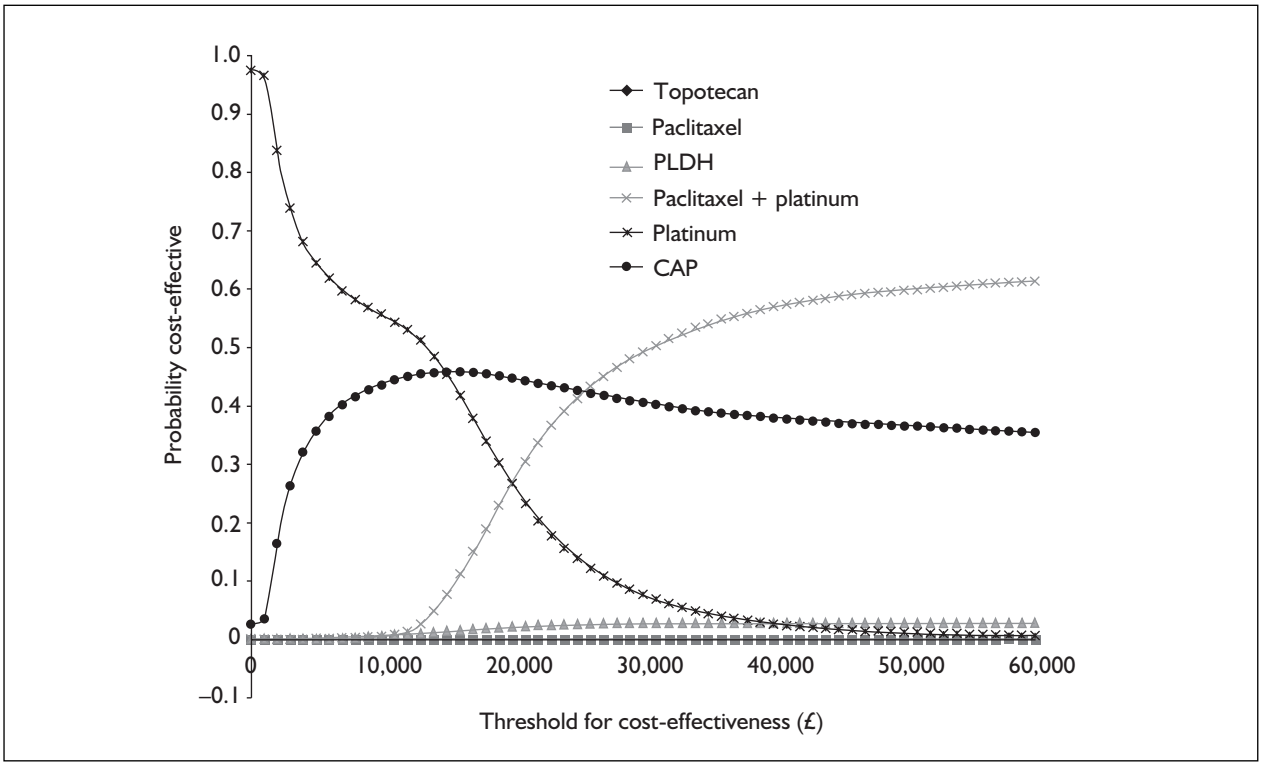

FIGURE 26 *Analysis 2, platinum-sensitive patients*

platinum-sensitive and platinum-resistant/refractory patients. Given the limitations of Analysis 2, we have not calculated the budget impact for platinum-sensitive patients based on the conclusions of this model.

Population receiving second-line therapy

Assuming an annual incidence of 6000 (NICE guidance on PLDH) and that the percentage who receive first-line chemotherapy is 75% (NICE guidance on PLDH), there are 4500 women per year who will potentially go on to second-line therapy. The percentage who actually relapse from first-line therapy is estimated at 65% (mean of 55–75% stated in NICE guidance). The population that will be affected by a change in second-line therapy is

No. of women requiring second-line therapy = $(6000 \times 0.75) \times 0.65 = 2925$

Costs of switching

The GSK audit shows that patients are receiving 23 different treatments as second-line therapy. For many of the treatments, the dosage, number of cycles received and toxicity events are not stated, and it is therefore not possible to cost second-line therapy comprehensively using all the data reported by GSK. We therefore assume that patients can only receive the three drugs considered in this appraisal (as in Analysis 1 of the economic model) by pro-rating up the percentages reported for PLDH, paclitaxel and topotecan. For our budget-impact analysis, second-line therapy currently consists of 10.53% receiving PLDH, 73.68% receiving topotecan and 15.79% receiving paclitaxel.

Given that PLDH is the most cost-effective drug in Analysis 1, all patients receiving paclitaxel and topotecan should instead receive PLDH. The cost of second-line therapy for the three drugs is £7714 for PLDH, £6354 for paclitaxel and £11,394 for topotecan. Switching to PLDH will therefore cost £3680 less for those patients who would have received topotecan and an additional £1360 for those patients who would have received paclitaxel as second-line therapy.

Total budget impact

Table 67 shows the current cost of chemotherapy for second-line advanced ovarian cancer in England and Wales.

Given a yearly incidence and using the percentages receiving PLDH, paclitaxel and topotecan as second-line therapy reported in *Table 67*, the current yearly total cost of second-line ovarian cancer in England and Wales is

TABLE 67 *Current cost of chemotherapy*

	Percentage receiving therapy	No. on therapy	Cost of 2nd-line treatment (£)	Total cost (£)
PLDH	10.53	308	7,714	2,375,912
Paclitaxel	15.79	462	6,354	2,935,548
Topotecan	73.68	2,155	11,394	24,554,070
Total		2,925		29,865,530

£29,865,530. If all patients were to receive PLDH, that is the percentage receiving PLDH therapy was 100%, the yearly cost of second-line ovarian cancer chemotherapy treatment would be £22,563,450. The budget impact of changing to PLDH as second-line therapy is therefore a reduction of £7,302,080 per year.

This analysis does not consider a patient's eligibility to receive PLDH as second-line therapy. Given that PLDH is not licensed for first-line therapy in ovarian cancer, it is assumed that no patients will be ineligible to receive PLDH second-line therapy based on their first-line treatment. There may, however, be other factors that determine which second-line treatment is offered and it is therefore possible that not all of the 2925 women that have recurrent disease each year will actually receive PLDH, even if it is the most cost-effective treatment option.

Economic model conclusions

The purpose of the economic model was to explore a range of uncertainties and sources of variability that were not fully assessed in either the published literature or the industry submissions. Two main analyses were undertaken to explore the cost-effectiveness of PLDH, topotecan and paclitaxel in advanced ovarian cancer. Two separate analyses (Analyses 1 and 2) were required in order to reflect the heterogeneity identified in the different trials and the difficulties encountered in obtaining robust estimates using a consistent approach in the methods of evidence synthesis of the relative treatment effects associated with particular treatments.

Analysis 1 assessed the cost-effectiveness of PLDH, topotecan and paclitaxel administered as a monotherapy. Sensitivity analysis was undertaken to explore the impact of patient heterogeneity (e.g. platinum-sensitive and platinum-insensitive/refractory patients), the inclusion of additional trial data (trial 30-57) and alternative assumptions regarding treatment and monitoring costs. Analysis 2 broadened the evaluation to include the full range of treatment comparators for platinum-sensitive patients (including paclitaxel plus platinum, platinum monotherapy and CAP) at the expense of using robust methods applied to the synthesis of effectiveness data.

In the base-case results for Analysis 1, paclitaxel monotherapy emerged as the cheapest treatment. When the ICERs were estimated, topotecan was ruled out on the grounds of extended dominance. Hence the options considered in the analysis were paclitaxel and PLDH. The ICER for PLDH compared with paclitaxel was £7053 per QALY in the overall patient population (comprising platinum-sensitive, -refractory and -resistant patients). The ICER was more favourable in the platinum-sensitive group (£5777 per QALY) and less favourable in the platinum-refractory/resistant group (£9555 per QALY). Clearly, the conclusions about cost-effectiveness will depend on the NHS's threshold WTP for additional health gain (in terms of QALYs). Assuming that the NHS is willing to pay between £20,000 and £40,000 per additional QALY, then PLDH appears to be cost-effective compared with topotecan and paclitaxel monotherapy in terms of the overall patient population and the main subgroups considered. These conclusions were robust to alternative cost assumptions and the use of subgroup-specific treatment effects.

The cost-effectiveness results for the base-case analysis were sensitive to the inclusion of trial 30-57. This trial compared paclitaxel with PLDH and provided additional direct evidence information on the relative effectiveness of these two treatments. Incorporating the results of trial 30-57 resulted in less favourable estimates for the ICER for PLDH versus paclitaxel compared with the base-case results. The ICER of PLDH compared with paclitaxel was £20,620 per QALY in the overall patient population, £16,183 per QALY in the platinum-sensitive population and £26,867 per QALY in the platinum-resistant/refractory

population. Using the same range of values to represent the NHS's willingness to pay for an additional QALY (£20,000–40,000), these results suggest that PLDH was still the optimal treatment.

Although the results of Analysis 1 appear most sensitive to the inclusion of trial 30-57, these findings should be interpreted with caution for a number of reasons. First, since trial 30-57 was terminated prematurely, the results have only been reported for a limited follow-up period. This contrasts with the longer term follow-up available from trials 039 and 30-49 used in the base-case analysis. Until comparative follow-up data are available, the findings from trial 30-57 should only be considered provisional. Second, since paclitaxel is now being increasingly used as part of first-line therapy (in combination with platinum), paclitaxel monotherapy may not be considered a relevant comparator for platinum-resistant and -refractory patients. For this patient group, the relevant treatment comparators would be limited to topotecan and PLDH. In our analyses, PLDH has been shown to dominate topotecan in all scenarios considered in Analysis 1.

The results from Analysis 2 explored the cost-effectiveness of the full range of treatment comparators for platinum-sensitive patients. The treatment options considered in this model comprised PLDH, topotecan, paclitaxel monotherapy, CAP, paclitaxel plus platinum and platinum monotherapy. Owing to the less robust approaches that were employed to synthesise the available evidence and the heterogeneity between the different trials, the reliability of these results should therefore be interpreted with caution. Topotecan, paclitaxel monotherapy and PLDH were all dominated by platinum monotherapy (i.e. higher costs and lower QALYs). After excluding these alternatives, the treatments that remained under consideration were platinum monotherapy, CAP and paclitaxel/platinum combination therapy. The ICER for CAP compared with platinum monotherapy was £16,421 per QALY. The ICER for paclitaxel/platinum combination therapy compared with CAP was £20,950 per QALY.

Chapter 6
Discussion

Summary of clinical effectiveness

In total nine RCTs were included in the assessment of clinical effectiveness. In five of these trials, the comparators in both trial arms were used within their licensed indications. In the further four trials identified, one of the trial arms assessed a comparator that was used outside its licensed indication in terms of either cycle length, dosage, route of administration or type of disease. The discussion of the clinical effectiveness of the three comparators assessed in this review, PLDH, topotecan and paclitaxel, will therefore mainly focus on the five trials in which the comparators were used within their licensed indications.

Summary of clinical effectiveness data

Three out of the five trials included participants with both platinum-resistant and platinum-sensitive relapsed advanced ovarian cancer,[24,27,44] and a further two trials included only participants with platinum-sensitive disease.[28,29] The comparators that were assessed in the three trials that included both subtypes of participants were PLDH versus topotecan,[44] topotecan versus paclitaxel[24] and PLDH versus paclitaxel.[27] In the further two trials that included participants with the subtype of platinum-sensitive disease only, the comparators that were assessed were single-agent paclitaxel versus a combination of cyclophosphamide, doxorubicin and cisplatin (CAP)[28] and paclitaxel plus platinum-based chemotherapy versus conventional platinum-based therapy alone.[29]

Trials including participants with platinum-refractory, -resistant and -sensitive disease

PLDH versus topotecan

This trial was a multi-centre open-label comparative trial of good quality. In total, 474 participants were treated with either PDLH 50 mg/m^2 every 28 weeks or topotecan 1.5 mg/m^2/day for five consecutive days every 3 weeks. A total of 239 participants were treated with PDLH and 235 with topotecan. At baseline, 46.5% of the participants were classified as having platinum-sensitive disease and 53.5% as having platinum-resistant disease. Approximately 73% of the included participants had received a paclitaxel and platinum-based combination therapy as first-line treatment.

At long-term follow-up, when 90% of the participants had died or were lost to follow-up, PLDH was marginally more effective than topotecan for the outcome of overall survival in the total trial population, HR = 1.216 (95% CI: 1.00 to 1.48). The reduction in the risk of death for participants treated with PLDH was 18% compared with those treated with topotecan. However, the lower boundary of the 95% CI suggests that although the point estimate favours treatment with PLDH, the size of this benefit may be small. Further analysis, which assessed the effectiveness of the two comparators in subgroups of participants classified at baseline as having platinum-sensitive or platinum-resistant disease, indicated that this treatment effect was not consistent across the two subgroups. In the platinum-sensitive disease subgroup there was a more pronounced survival benefit for participants treated with PLDH than those treated with topotecan, HR = 1.432 (95% CI: 1.066 to 1.923). This corresponds to a 30% reduction in the risk of death for the participants treated with PLDH. However, in the platinum-resistant disease subgroup there were no statistically significant differences between the two groups shown for overall survival, HR = 1.069 (95% CI: 0.82 to 1.387). This suggests that any survival benefit observed for PLDH compared with topotecan is limited to participants with platinum-sensitive disease and that the marginally significant benefit observed in the total trial population is driven by the more pronounced benefit observed in this subgroup. For the further outcomes of PFS and response there were no statistically significant differences between the two treatment regimens either in the total trial population or in either of the subgroups. The point estimates for both PFS and response rates favoured PLDH over topotecan but, as all CIs crossed unity, this benefit was not significant.

In terms of the toxicity states reported in the trial, there were three treatment-related deaths due to sepsis in the topotecan group, but no treatment-related deaths observed in the PLDH treatment arm. The incidence of grade 3 toxicities of

stomatitis, PPE, mucous membrane disorder and rash was significantly higher in the PLDH treatment arm compared with the topotecan treatment group. However, there were no significantly higher rates of grade 4 adverse events reported in this group compared with the topotecan arm. The topotecan treatment arm had significantly higher reported rates of grade 3 haematological toxicities (anaemia, leucopenia, neutropenia and thrombocytopenia), alopecia and fever compared with the PLDH treatment group. In addition, grade 4 haematological toxicities were also significantly higher in this group.

Overall summary of the trial

Although the long-term follow-up data from this trial indicated that PLDH is marginally more effective than topotecan in terms of overall survival rates, it appears that this benefit is limited to the subgroup of participants with platinum-sensitive disease. In addition, a number of caveats must be considered when interpreting these trial data. First, at an earlier time of analysis there were no significant differences observed between the two treatment groups in terms of overall survival, although a trend was noticed in favour of treatment with PLDH for platinum-sensitive participants. Second, this trial was not realistically powered to detect differences in the treatment effect between the comparators in subgroups of participants.

Topotecan versus paclitaxel

This trial was a good-quality randomised open-label comparative trial. In total, 112 participants were treated with topotecan and 114 with paclitaxel. The treatment cycle in both of the trial arms was 21 days. At baseline 47% of the participants were classified as having platinum-sensitive disease and 53% as having platinum-refractory disease. None of the participants had received a taxane as part of first-line therapy.

At 4 years postrandomisation there were no statistically significant differences between the two treatment groups in terms of overall survival, TTP, responses rate or response duration. The point estimates for all of these outcomes favoured treatment with topotecan over paclitaxel, but as the CIs for all of the outcomes cross unity this benefit was not statistically significant. There were also no significant differences between the two treatment groups in the subgroups of participants who were classified as having platinum-sensitive or platinum-resistant disease at baseline. There was, however, a significant difference observed in terms of time to response, in favour of paclitaxel. The median time to response was 9.0 weeks in the topotecan group compared with 6 weeks in the paclitaxel group. The results from the *post hoc* analysis of third-line crossover therapy, when participants crossed over to the alternative treatment regime, also showed that there were no significant differences between the two treatment groups in terms of overall survival, TTP or response. This suggests that the two treatment regimens are non-cross-resistant in only a small number of participants, and therefore sequential treatment with these two regimens may not be beneficial in the majority of patients.

In relation to toxicity states, in this trial two participants in the topotecan treatment group died owing to treatment-related toxicity. Both of these deaths were attributed to topotecan-induced sepsis. There were no deaths attributed to paclitaxel-induced myelosuppression. The incidence of grade 3 and 4 haematological toxicities was significantly higher in the topotecan group than the paclitaxel treatment arm, apart from grade 4 anaemia. The only incidence of haematological toxicity that was higher in the paclitaxel group was grade 3 neutropenia. For grade 3–4 non-haematological toxicities, nausea, vomiting, constipation, abdominal pain, fatigue and fever/infection were reported more commonly in the topotecan group. For the paclitaxel group, grade 3–4 alopecia, arthralgia, myalgia and skeletal pain were reported more frequently.

Overall summary of the trial

At a follow-up time of 4 years postrandomisation, there were no significant differences between the two treatment regimens in overall survival, TTP, responses rate or response duration. The point estimates favoured topotecan on all of these outcomes, but remained statistically insignificant. The only outcome that was statistically significant was time to response, which favoured paclitaxel. The incidence of adverse events in both of the treatment arms indicated that topotecan was associated with a higher incidence of haematological toxicities than paclitaxel. There were no significant differences in the number of grade 3–4 non-haematological adverse events reported in both of the trial arms.

PLDH versus paclitaxel

This trial was a reasonably good-quality randomised open-label comparative trial. In total 108 participants were randomised to treatment with PLDH and 108 to paclitaxel. All participants in the trial had received one prior line of platinum-based chemotherapy and were taxane

naïve. However, owing to poor participant accrual it was terminated early when only ~50% of the intended participants had been accrued. For this reason, the trial data were only analysed for the primary outcome of overall survival.

There were no significant differences in overall survival between the two treatment groups. A further analysis of the results for overall survival in the subgroups of participants classified as having either platinum-sensitive or platinum-resistant disease indicated that there were also no significant differences between the two treatment groups in either of these subgroups. The incidence of grade 4 adverse events was relatively low in both treatment arms. At the grade 3 level of toxicity, PPE, ascites, stomatitis and dyspnoea were observed significantly more often in the PLDH group than the paclitaxel group. The only toxicity that occurred significantly more often in the paclitaxel group was alopecia.

Overall summary of the trial
Although there were no significant differences observed between the two treatment groups, it is likely that, owing to the low participant numbers, the trial was significantly underpowered to detect any differences in treatment effect between the two groups. Furthermore, owing to its early termination, the results of the trial are likely to be preliminary and the longer term implications of the relative efficacy of these two comparators are unclear. However, from the available data it appears that paclitaxel has a favourable toxicity profile compared with PLDH.

Trials including participants with platinum-sensitive disease only

Paclitaxel versus CAP

This trial was a relatively small randomised pilot study. In total 47 participants were treated with single-agent paclitaxel 175 mg/m^2 every 21 days and 47 with the combination of cyclophosphamide 500 mg/m^2, doxorubicin 50 mg/m^2 and cisplatin 50 mg/m^2 (CAP) every 21 days. All the participants had previously been treated with two or three chemotherapy regimens that did not include a taxane. The treatment-free interval for all the participants was reasonably long, being 30.2 months in the paclitaxel arm and 38.8 months among the participants receiving CAP.

At a median follow-up of 49 months, after adjusting for prognostic factors, CAP was more effective than paclitaxel for the outcomes of overall survival, HR = 0.58 (95% CI: 0.34 to 0.98), and PFS, HR = 0.60 (5% CI: 0.37 to 0.l97). However, there were no significant differences between the two treatment groups in terms of response. The response rate to CAP was 55% compared with 45% in the paclitaxel treatment arm. The further analysis of third-line crossover therapy, when participants crossed over to the alternative treatment regime, showed that there were no significant differences between the two treatment regimes in terms of response. The analysis of the adverse events that were experienced in both treatment groups showed that CAP was associated with significantly higher rates of grade 3 and 4 haematological toxicity than paclitaxel. It was also associated with significantly higher rates of grade 2 nausea and vomiting. Treatment with paclitaxel was associated with significantly higher rates of alopecia and allergic reactions relative to treatment with CAP.

Overall summary of the trial
The results of this trial suggest that, in platinum-sensitive patients who are taxane naïve, treatment with a platinum-containing regimen at even third-line may be more beneficial than treatment with paclitaxel. However, it should also be noted that the quality of the trial from which these results were obtained is variable. The trial was a small randomised pilot study and therefore the number of participants upon which these results are based is small. This limited sample size makes the point estimate of efficacy imprecise. Furthermore, owing to the trial design that allowed crossover to third-line therapy, the interpretation of the survival data is problematic. Hence it is not possible to draw any firm conclusions regarding the relative efficacy of CAP compared with paclitaxel. Further trials assessing CAP as a comparator in platinum-sensitive patients do, however, seem to be warranted.

Paclitaxel in combination with platinum-based chemotherapy versus platinum-based therapy alone (ICON4)

This trial was a good-quality randomised multi-centre parallel trial. In total, 392 participants were randomised to treatment with paclitaxel in combination with platinum-based therapy and 410 to conventional platinum-based therapy alone. Approximately 40% of the participants had received prior chemotherapy with a taxane. In 25% of the participants the treatment-free interval was <12 months and in 75% >12 months.

At a median follow-up of 42 months, paclitaxel and platinum combination was more effective than platinum-based therapy alone for the outcomes of overall survival and PFS. An analysis to assess the

effect of the two different treatment regimens, on both overall survival and PFS in subgroups, indicated that there were no significant differences between the two treatment group in terms of these outcome measures in any of the subgroups explored. This suggests that treatment with the combination of paclitaxel and platinum is beneficial even across a population of patients who are heterogeneous in terms of the number of previous lines of chemotherapy that have been received, their previous exposure to taxanes and their treatment-free interval. However, many of the subgroups were small and therefore may lack the power to detect any realistic differences in treatment effect in these groups. There was no significant difference between the two treatment regimens in terms of response rate but, again, the response rates appeared to favour treatment with the combination therapy. The response rate to paclitaxel plus platinum therapy was 66% compared with 55% for the conventional platinum-based therapy group. In terms of toxicities experienced during the trial, the incidence of grade 2–4 neurological toxicities and alopecia was significantly higher in the paclitaxel plus platinum chemotherapy regimen group compared with the conventional monotherapy arm. However, the rates of haematological toxicity were significantly higher in the conventional platinum chemotherapy group.

Overall summary of the trial

The ICON4/AGO-OVAR-2.2 trial was a good-quality randomised multi-centre trial. However, the trial can be criticised regarding the heterogeneous nature of the patient population that was enrolled into the trial, in terms of the differences in prior therapy and treatment-free interval. A further criticism can be made regarding the treatment received in the platinum-based monotherapy group. Some 33% of participants in this arm were taxane naïve as they had not received a taxane either as part of first-line therapy or within the trial. However, despite these criticisms and the difficulties they present in interpreting the trial results, ICON4 is the first adequately powered trial to evaluate the extent of the benefit of combination paclitaxel and platinum-based therapy relative to platinum-based therapy alone in participants with platinum-sensitive disease.

Overall discussion of clinical effectiveness

This review included five trials that assessed the efficacy and safety of PLDH, topotecan and paclitaxel with both comparators used within their licensed indications, in patients with relapsed advanced ovarian cancer. The evidence base from these trials is heterogeneous in terms of the trial quality, comparators assessed and the patient populations. Although it is clearly recognised that response to prior platinum-based chemotherapy is a continuum, the results from the trials will be compared in relation to the two subgroups of participants, those with platinum-sensitive disease and those with platinum-resistant disease. This is because the clinical issues that need to be addressed in these two patient populations are different owing to the differing prognosis in terms of potential tumour chemo-responsiveness and overall survival within each of these groups.

Platinum-resistant disease subgroup

Three trials included participants who were classified at baseline as having platinum-resistant disease.[19,22,24] However, only overall survival data were available for the trial of PLDH versus paclitaxel.[27] The median survival, median PFS and overall response rate data for the platinum-resistant subgroups of participants from these three trials are summarised in *Table 68*.

Table 68 shows that there were no substantial differences in the median survival rates across the three trials, with these ranging from 36.7 to 54.3 weeks. The most favourable median survival time was observed for the paclitaxel treatment arm within the trial of PLDH versus paclitaxel, at 54.3 weeks.[27] This trial was conducted in participants who were taxane naïve. In terms of response rate, it can again be observed from the data that there were no substantial differences in terms of response rates across the three trials, with these ranging from 6.7 to 13.3%. The most favourable response rate was observed for topotecan, within the trial of topotecan versus paclitaxel, at 13.3%.[24,25]

Overall, from the summary data of the three trials that included participants with platinum-resistant disease, it can be observed that there was a low probability of response to treatment with PLDH, topotecan or paclitaxel. Response rates varied from 6.7 to 13.3%. Likewise, there was little difference between the three comparators in relation to overall survival, with median survival times varying from 36.7 to 54.3 weeks. Given the low survival times and response rates observed in these trials, and the different toxicity profiles of PLDH, topotecan and paclitaxel, it appears that the crucial issues to be addressed when choosing a second-line treatment for patients who have platinum-resistant disease would be the

TABLE 68 *Summary of the median survival, progression-free survival and response rates for participants with platinum-resistant disease*

Reference	Drug	*n*	Median survival (weeks)	Overall response rate (%)	Median PFS (weeks)	Taxane at first-line therapy	Treatment-free interval
Trial 30-49[44]	PLDH	130	38.3	11.5 (95% CI: 6.0 to 17.0)	9.1	74% received taxane first-line	54% relapsed within 6 months
	Topotecan	125	42.1	7.2 (95% CI: 2.7 to 11.7)	13.6	72% received taxane first-line	53% relapsed within 6 months
Trial 039[24,25]	Topotecan	60	NA	13.3	NA	Taxane naive	53% relapsed within 6 months
	Paclitaxel	59	NA	6.7	NA	Taxane naive	53% relapsed within 6 months
Trial 30-57[27]	PLDH	64	36.7	NA	NA	Taxane naive	NA
	Paclitaxel	67	54.3	NA	NA	Taxane naive	NA

NA, not available.

maintenance of QoL and the control of symptoms and toxicity. Further factors that would therefore need to be considered would be the cost-effectiveness of the three comparators, the ease of administration and patient choice in terms of the potential toxicities they were prepared to undergo. It can also be suggested that these patients may benefit from being included in clinical trials of new drugs.

Platinum-sensitive disease subgroup

All five trials included participants who were classified at baseline as having platinum-sensitive disease.[24,27–29,44] Again, however, only overall survival data were available for the trial of PLDH versus paclitaxel.[27] These five trials were reasonably heterogeneous in terms of the prior chemotherapy regimens that participants had received and the treatment-free interval of the trial participants. The differences in the treatment-free intervals of the participants between the trials may be particularly pertinent when assessing the differences observed in the median survival times and overall response rates of these trials. A summary of the median survival times, PFS times and the overall response rates for the platinum-sensitive participants who were assessed in the five trials is summarised in *Table 69*.

As can be seen, there was a considerable difference in the median survival times observed across the five trials, with these ranging from 65.4 to 156 weeks. It is problematic, however, to compare indirectly the results of the different trial arms owing to the heterogeneity of the prior chemotherapy regimens that participants had received and also the differences in the treatment-free intervals between the trials. The differences in the overall survival rates between the trials do suggest, however, that there are large potential differences in relation to overall survival in this patient population, and therefore the choice of treatment may make a substantial difference. It can be suggested from the results of the two trials that compared combination chemotherapy with a single agent regimen, that treatment with a platinum-based combination therapy is superior to treatment with a single agent. However, no inferences can be drawn regarding the relative efficacy of paclitaxel–platinum combination therapy and CAP, as both of these regimens were compared with different monotherapies, and the treatment-free intervals of the participants in these trial populations differed considerably.

In terms of treatment with a single-agent therapy, again the median survival times varied substantially across the trials, ranging from 65.4 weeks for the PLDH treatment arm, in the trial that compared PLDH and paclitaxel,[27] to 116 weeks in the single-agent paclitaxel arm, in the trial that compared CAP and paclitaxel. However, it is difficult to compare the results of these trials as the treatment-free interval and first-line therapy that participants had received differed considerably across the trials. It can be stated, however, that PLDH was significantly more beneficial in terms of overall survival than topotecan, although this is based on a subgroup analysis. In a second trial that directly compared topotecan and paclitaxel, there were no significant

TABLE 69 *Summary of the median survival, progression-free survival and response rates for participants with platinum-sensitive disease*

Reference	Drug	*n*	Median survival (weeks)	Overall response rate (%)	Median PFS (weeks)	Taxane at first-line therapy	Treatment-free interval
Trial 30-49[44]	PLDH	109	107.9	29.4 (95% CI: 20.8 to 37.9)	27.3	74% received taxane first-line	54% relapsed within 6 months
	Topotecan	110	70.1	28.2 (95% CI: 19.8 to 36.6)	22.7	72% received taxane first-line	53% relapsed within 6 months
Trial 039[24,25]	Topotecan	52	NA	28.8	NA	Taxane naive	53% relapsed within 6 months
	Paclitaxel	55	NA	20.0	NA	Taxane naive	53% relapsed within 6 months
Trial 30-57[27]	PLDH	44	65.4	NA	NA	Taxane naive	NA
	Paclitaxel	41	75.7	NA	NA	Taxane naive	NA
Cantu *et al.*[28]	Paclitaxel	47	116	45	40	Taxane naive	136 weeks
	CAP	47	156	55	70	Taxane naive	175 weeks
ICON and AGO Collaborators[29]	Paclitaxel and platinum combination	392	130	66	54	41% received taxane first-line	25% ≤ 12 months; 75% >12 months
	Platinum alone	410	108	54	40	39% received taxane first-line	25% ≤ 12 months; 75% >12 months

NA, not available.

differences between the two comparators in terms of overall survival. In a further trial, that compared PLDH with paclitaxel in a head-to-head comparison, the limited data available suggested there were no significant differences in overall survival between the two treatment arms.

Within this group of women with advanced ovarian cancer it appears that prolongation of PFS and overall survival, and also the maintenance of QoL and symptom control, can be realistic treatment objectives. Based on the results of these trials, it appears that combination chemotherapy either with paclitaxel in combination with a platinum-based therapy or CAP may be beneficial compared with monotherapy alone. However, combination therapy can also be associated with a higher incidence of toxicity compared with single-agent therapy, and therefore may not be a suitable treatment option for some patients. In terms of treatment with single-agent therapy, there appears from the limited evidence available to be an indication that PLDH is more effective than topotecan. This is, however, based on the data from a subgroup analysis of one trial and therefore the evidence base is very limited. Furthermore, as there are no trials that have directly compared PLDH with a single-agent platinum compound, it is not possible to comment on whether treatment with a different chemotherapeutic compound is more beneficial than treatment with a platinum-based chemotherapeutic regimen in platinum-sensitive patients.

Summary of cost-effectiveness

Four published studies met the inclusion criteria for the cost-effectiveness review. In addition, separate submissions were received from BMS, GSK and Schering-Plough Ltd. The published studies and manufacturers' submissions were assessed and a new model was developed to address the limitations identified in these sources and to provide a direct comparison of the full range of possible strategies that are relevant to the NHS. The model explored a range of uncertainties and sources of variability that were not fully addressed in existing data sources.

An integral component of the model was the use of Bayesian approaches to synthesise effectiveness data from a series of mixed and indirect treatment comparisons. This approach provides an analytical framework to incorporate evidence in situations where there exist both direct head-to-head evidence and indirect evidence relative to a common comparator. It allows consideration of

the complete evidence base and facilitates a direct comparison of the full range of treatment strategies. Clearly, when indirect evidence is used to estimate treatment effects it is not possible to rule out the introduction of bias, and the results should be interpreted accordingly. The approach is, however, based on only a few additional assumptions over standard meta-analysis.

The evidence reported from ICON4 (platinum plus paclitaxel and platinum alone) provided no evidence on the relationship between these comparators and any of the other treatments under consideration. In order to incorporate the results of this trial into the model, it was necessary to break randomisation in order to obtain estimates of the relative treatment effect. Consequently, although it was possible to make direct comparisons amongst the full range of treatment strategies, this was at the expense of a less robust estimate for the effectiveness data. Furthermore, systematic searches for all possible comparators were not undertaken. Hence there may be additional indirect evidence on the effectiveness of these comparators that could be considered alongside the evidence reviewed in this report.

In addition, the model presented here has several potential limitations that need to be considered in conjunction with the main results. First, although the model made adjustments for the QoL of patients according to different disease states (e.g. PFS and disease progression), no separate adjustments could be made to reflect the impact of the different treatments in terms of adverse events reported during the treatment period. No utility estimates were identified which could be used to reflect the different types and severity grades of the various adverse events reported in each of the trials. Consequently, it is not possible to assess the robustness of the model results to this aspect. The lack of suitable utility data emphasises the need for this data to be an integral part of future trials.

Second, in the absence of patient-level data, it was not possible to conduct a detailed analysis of the resource use and costs associated with the management of adverse events. Although several patient-level costing studies were identified as part of the review of existing cost-effectiveness evidence, these analyses were restricted to a comparison between topotecan and PLDH. In order to adopt a consistent approach to the full range of comparators considered in the model, it was necessary to use the aggregated data reported in the trials. Furthermore, the analysis was restricted to severity grades 3–4 owing to a lack of data reported on the less severe toxicities in some of the trials. Although this approach provided a common basis on which to compare the different treatments, this method is likely to underestimate the overall costs (since we cannot account for patients who have had more than one adverse event of the same type and severity) and also may not adequately capture the true differences in costs between the treatments. Indeed, a comparison between our own results and those reported by Smith and colleagues[50] and the submission by Schering-Plough highlights that the differences in total costs relate mainly to the costs of managing adverse events. Both Smith and colleagues and Schering-Plough estimated that the additional costs of managing adverse events for patients receiving topotecan compared with PLDH ranged between £2593 and £2909. In contrast, using the aggregate data reported in the trials, our model estimated this difference to be only £1289.

Third, although the impact of patient heterogeneity was explored in a series of subgroup analyses, it was not possible to undertake separate analyses for platinum-refractory and -resistant patients. Consequently, the results for these patients were presented by combining data from the two groups. Although the base-case results for the main analysis indicated that PLDH was cost-effective for the overall patient population and for the combined group of platinum-resistant and -refractory patients, these results may not hold when considering the platinum-refractory group in isolation.

Fourth, in order to estimate mean survival times from the estimated hazards, it was necessary to assume that the survival data were approximately exponential (i.e. a constant hazard) in form. In the absence of patient-level data, it is difficult to establish the validity of this assumption or to determine whether alternative distributional forms would be more appropriate (e.g. Weibull). However, since overall survival times in this patient population were relatively short, it is unlikely that alternative assumptions would significantly impact on the results presented here.

Finally, the analysis presented here does not directly consider the impact of treatments provided as part of third-line and subsequent therapies. It is possible that the differences observed in the various trials may be partly confounded by the different therapies received after second-line drugs. For example, patients

receiving PLDH as second-line therapy might have received topotecan as third-line therapy, but the same pathway may not be possible for patients receiving topotecan as second-line drug. In other words, differences in the long-term results could also depend on treatments received after the second-line therapies.

Although the economic model presented here has a number of potential weaknesses, it does represent the most comprehensive comparison of topotecan, paclitaxel and PLDH in advanced ovarian cancer. The analysis conducted here also helps to reiterate the need for a formal comparison, via an RCT, of all the treatments considered, in particular the comparison between paclitaxel in combination with platinum therapy, topotecan, PLDH and paclitaxel monotherapy in platinum-sensitive patients.

Chapter 7
Conclusions

Clinical effectiveness

Trials including participants with platinum-refractory, -resistant and -sensitive disease

PLDH versus topotecan

- PLDH was marginally more effective than topotecan in terms of overall survival in the total trial population that included both participants with platinum-resistant and -refractory disease. That is, the point estimate favoured treatment with PLDH but the lower boundary of the 95% CIs suggests that the size of this benefit may be very small.
- The overall survival benefit from treatment with PLDH compared with topotecan was most pronounced in the platinum-sensitive subgroup of participants. For participants with platinum-refractory disease there was no statistically significant difference in overall survival between the PLDH and topotecan treatment groups.
- There were no statistically significant differences between the PLDH and topotecan groups in terms of PFS, response or QoL.
- The rates of grade 3 stomatitis, PPE, mucous membrane disorder and rash were significantly higher in the PLDH treatment arm.
- In the topotecan arm, the rates of grade 3 and 4 haematological toxicities and grade 3 alopecia and fever were significantly higher.

Topotecan versus paclitaxel

- There were no statistically significant differences between the two treatment groups in terms of overall survival, TTP, response rate or response duration. The point estimates for all of these outcomes favoured treatment with topotecan over paclitaxel, but these differences were not statistically significant. However, there was a significant difference between the two treatment groups in terms of time to response. This difference favoured paclitaxel.
- After crossover to third-line therapy, there were no statistically significant differences between the two groups on any of the effectiveness outcomes assessed.
- Treatment with topotecan was associated with significantly more grade 3 and 4 haematological toxicities compared to paclitaxel. In addition, rates of grade 3 and 4 nausea, vomiting, constipation, abdominal pain, asthenia, fatigue and fever/infection were significantly higher in this group.
- Treatment with paclitaxel was associated with significantly more grade 3 and 4 alopecia, arthralgia, myalgia and skeletal pain compared with topotecan treatment.

PLDH versus paclitaxel

- In relation to overall survival, there were no significant differences between treatment with PLDH or paclitaxel.
- Treatment with PLDH was associated with significantly more grade 3 PPE, ascites, stomatitis and dyspnoea compared with treatment with paclitaxel.
- Treatment with paclitaxel was associated only with a higher incidence of grade 3 alopecia.

Trials including participants with platinum-sensitive disease only

Paclitaxel versus CAP

- CAP was more effective than paclitaxel in terms of both PFS and overall survival. However, there were no significant differences between the two treatment regimens in terms of response.
- The incidence of grade 3 and 4 haematological toxicities and grade 2 nausea and vomiting was significantly higher in the CAP treatment arm.
- Treatment with paclitaxel was associated with significantly higher rates of alopecia and allergic reactions relative to treatment with CAP.

Paclitaxel in combination with platinum-based chemotherapy versus platinum-based therapy alone

- Paclitaxel in combination with platinum-based chemotherapy was more effective than platinum monotherapy in relation to both PFS and overall survival.
- There were no significant differences between the groups treated with paclitaxel in combination with platinum and platinum monotherapy for the outcomes of response rate or overall QoL.
- Treatment with paclitaxel in combination with platinum was associated with significantly higher rates of grade 2–4 neurological toxicity and alopecia.

- Treatment with platinum monotherapy was associated with significantly higher rates of haematological toxicity.

Overall conclusions

Participants with platinum-resistant disease

For participants with platinum-resistant disease, there was a low probability of response to treatment with PLDH, topotecan or paclitaxel. Furthermore, there was little difference between the three comparators in relation to overall survival. The comparators did, however, differ considerably in their toxicity profiles. Given the low survival and response rates it appears that the maintenance of QoL, control of symptoms and toxicity are paramount in this patient group. As the three comparators differed significantly in terms of their toxicity profiles, patient and physician choice is also an important element that should be addressed when decisions are made regarding second-line therapy. It can also be suggested that this group of patients may benefit from being included in further clinical trials of new drugs.

Participants with platinum-sensitive disease

For participants with platinum-sensitive disease, there was a considerable range of median survival times observed across the trials. The results of the trials that compared combination therapy with single-agent therapy suggest that treatment with combination therapy may be more beneficial than treatment with a single-agent chemotherapeutic regimen. In terms of single-agent compounds, the evidence suggests that PLDH is more effective than topotecan. Evidence from a further trial that compared PLDH and paclitaxel suggests that there is no significant difference between these two comparators. The three comparators did, however, differ significantly in terms of their toxicity profiles across the trials. Although treatment with PLDH may therefore be more beneficial than that with topotecan, patient and physician choice as to the potential toxicities associated with each of the comparators, and patients' ability and willingness to tolerate these, are of importance.

Cost-effectiveness

- The model developed by the University of York TAR team sought to assess the cost-effectiveness of intravenous formulations of topotecan monotherapy, PLDH monotherapy and paclitaxel used alone or in combination with a platinum-based compound for the second-line or subsequent treatment of advanced ovarian cancer.
- The model considered two main analyses and several alternative scenarios, owing to the difficulties encountered in obtaining robust estimates using a consistent approach in the methods of evidence synthesis. Analysis 1 was restricted to a comparison of topotecan, PLDH and paclitaxel monotherapies. Analysis 2 explored the cost-effectiveness of PLDH, topotecan, paclitaxel monotherapy, CAP, paclitaxel plus platinum and platinum monotherapy in platinum-sensitive patients.

The following conclusions are possible assuming that the NHS is willing to pay up to £20,000–40,000 per additional QALY:

- PLDH appears to be cost-effective compared with topotecan and paclitaxel monotherapy in terms of the overall patient population and the main subgroups considered.
- The cost-effectiveness results for the base-case analysis were sensitive to the inclusion of trial 30-57. Incorporating the results of trial 30-57 gave less favourable estimates for the ICER for PLDH versus paclitaxel monotherapy, compared with the base-case results. Although the ICER of PLDH compared with paclitaxel monotherapy was less favourable, PLDH was still cost-effective compared with topotecan and paclitaxel monotherapy.
- For platinum-sensitive patients, the combination of paclitaxel and platinum appears to be cost-effective.

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Contribution of authors

Caroline Main (Research Fellow) was the lead reviewer responsible for writing the protocol, study selection, data extraction, validity assessment and writing the final report. Laura Bojke (Research Fellow) was involved in the cost-effectiveness section, writing the protocol, study selection, data extraction, development of the economic model and report writing. Susan Griffin (Research Fellow) was involved in the cost-effectiveness section, writing the protocol, study selection, data extraction, development of the economic model and report writing. Gill Norman (Research Fellow) was the second reviewer involved in the clinical-effectiveness section, and was involved in study selection, data extraction, validity assessment and writing the final report. Marco Barbieri (Research Fellow) was involved in the cost-effectiveness section, responsible for the review and reanalysis of the company submissions. Lisa Mather (Information Officer) devised the search strategy and carried out the literature searches, and wrote the search methodology sections of the report. Dan Stark (Senior Lecturer in Oncology and Honorary Consultant in Medical Oncology) provided input at all stages, commented on various drafts of the report and contributed to the discussion section of the report. Stephen Palmer (Senior Research Fellow) provided input at all stages, commented on various drafts of the report and had overall responsibility for the cost-effectiveness section of the report. Rob Riemsma (Reviews Manager) provided input at all stages, commented on various drafts of the report and had overall responsibility for the clinical-effectiveness section of the report.

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Conflicts of interest

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