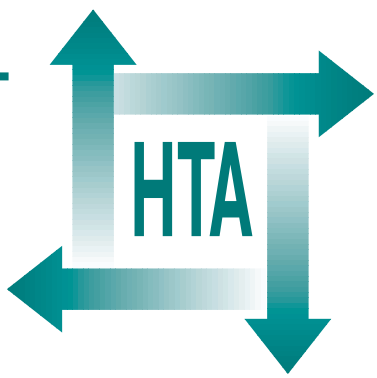
Health Technology Assessment 2002; Vol. 6: No. 23

A systematic review and economic evaluation of pegylated liposomal doxorubicin hydrochloride for ovarian cancer

C Forbes
J Wilby
G Richardson
M Sculpher
L Mather
R Riemsma

Health Technology Assessment
NHS R&D HTA Programme



How to obtain copies of this and other HTA Programme reports.
An electronic version of this publication, in Adobe Acrobat format, is available for downloading free of charge for personal use from the HTA website (http://www.hta.ac.uk). A fully searchable CD-ROM is also available (see below).

Printed copies of HTA monographs cost £20 each (post and packing free in the UK) to both public **and** private sector purchasers from our Despatch Agents.

Non-UK purchasers will have to pay a small fee for post and packing. For European countries the cost is £2 per monograph and for the rest of the world £3 per monograph.

You can order HTA monographs from our Despatch Agents:

– fax (with **credit card** or **official purchase order**)
– post (with **credit card** or **official purchase order** or **cheque**)
– phone during office hours (**credit card** only).

Additionally the HTA website allows you **either** to pay securely by credit card **or** to print out your order and then post or fax it.

Contact details are as follows:

HTA Despatch
c/o Direct Mail Works Ltd
4 Oakwood Business Centre
Downley, HAVANT PO9 2NP, UK

Email: orders@hta.ac.uk
Tel: 02392 492 000
Fax: 02392 478 555
Fax from outside the UK: +44 2392 478 555

NHS libraries can subscribe free of charge. Public libraries can subscribe at a very reduced cost of £100 for each volume (normally comprising 30–40 titles). The commercial subscription rate is £300 per volume. Please see our website for details. Subscriptions can only be purchased for the current or forthcoming volume.

Payment methods

Paying by cheque
If you pay by cheque, the cheque must be in **pounds sterling**, made payable to *Direct Mail Works Ltd* and drawn on a bank with a UK address.

Paying by credit card
The following cards are accepted by phone, fax, post or via the website ordering pages: Delta, Eurocard, Mastercard, Solo, Switch and Visa. We advise against sending credit card details in a plain email.

Paying by official purchase order
You can post or fax these, but they must be from public bodies (i.e. NHS or universities) within the UK. We cannot at present accept purchase orders from commercial companies or from outside the UK.

How do I get a copy of *HTA on CD*?

Please use the form on the HTA website (www.hta.ac.uk/htacd.htm). Or contact Direct Mail Works (see contact details above) by email, post, fax or phone. *HTA on CD* is currently free of charge worldwide.

The website also provides information about the HTA Programme and lists the membership of the various committees.

A systematic review and economic evaluation of pegylated liposomal doxorubicin hydrochloride for ovarian cancer

C Forbes[1*]
J Wilby[1]
G Richardson[2]
M Sculpher[2]
L Mather[1]
R Riemsma[1]

[1] NHS Centre for Reviews and Dissemination and
[2] Centre for Health Economics, University of York, UK

[*] Corresponding author

Competing interests: Mark Sculpher has been a consultant to and received research funding from GlaxoSmithKline. Colleagues at the Centre for Health Economics (not involved in this review) have received research funding from GlaxoSmithKline and Schering-Plough Ltd. The Centre of Health Economics also receives funding from Schering-Plough Ltd for a Research Fellowship.

Published October 2002

This report should be referenced as follows:

Forbes C, Wilby J, Richardson G, Sculpher M, Mather L, Reimsma R. A systematic review and economic evaluation of pegylated liposomal doxorubicin hydrochloride for ovarian cancer. *Health Technol Assess* 2002;**6**(23).

Health Technology Assessment is indexed in *Index Medicus*/MEDLINE and *Excerpta Medica*/EMBASE. Copies of the Executive Summaries are available from the NCCHTA website (see opposite).

NHS R&D HTA Programme

The NHS R&D Health Technology Assessment (HTA) Programme was set up in 1993 to ensure that high-quality research information on the costs, effectiveness and broader impact of health technologies is produced in the most efficient way for those who use, manage and provide care in the NHS.

The research reported in this monograph was commissioned by the HTA Programme on behalf of the National Institute for Clinical Excellence (NICE). Technology assessment reports are completed in a limited time to inform the appraisal and guidance development processes managed by NICE. The review brings together evidence on key aspects of the use of the technology concerned. However, appraisals and guidance produced by NICE are informed by a wide range of sources.

The research reported in this monograph was funded as project number 01/20/01.

The views expressed in this publication are those of the authors and not necessarily those of the HTA Programme, NICE or the Department of Health. The editors wish to emphasise that funding and publication of this research by the NHS should not be taken as implicit support for any recommendations made by the authors.

Criteria for inclusion in the HTA monograph series
Reports are published in the HTA monograph series if (1) they have resulted from work commissioned for the HTA Programme, and (2) they are of a sufficiently high scientific quality as assessed by the referees and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

The editors and publisher have tried to ensure the accuracy of this report but do not accept liability for damages or losses arising from material published in this report.

ISSN 1366-5278

Published by Core Research, Alton, on behalf of the NCCHTA.
Printed on acid-free paper in the UK by The Basingstoke Press, Basingstoke.

T

Contents

Glossary and list of abbreviations

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context, but a glossary is provided for the non-specialist reader. In some cases, usage differs in the literature, but the term has a constant meaning throughout this review.

Glossary*

Advanced ovarian cancer Refers to disease classified as International Federation of Gynaecologists and Obstetricians (FIGO) stages II to IV.

Adverse effect 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 visible illness. An effect may be classed 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/the 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 anti-neoplastic activity. They intercalate with DNA, and thus 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.

CA-125 A cell surface marker found in serum.

Carcinoma A cancerous growth.

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

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

Confidence interval (CI) Quantifies the uncertainty in measurement. Usually reported as 95% CIs, i.e. the range of values within which one can be 95% sure that the true values for the whole population lie.

Cost–benefit analysis (CBA) A form of economic evaluation where both costs and benefits are expressed in the same units, usually monetary units, i.e. all of the health benefits (e.g. disability days avoided, life-years gained, medical complications avoided) are translated into monetary units. This type of analysis is not widely used in the economic evaluation of drugs or technologies, as it is often difficult to determine the cost of health benefits.

Cost-effectiveness analysis (CEA) A form of economic evaluation where costs are expressed in monetary units and effectiveness is expressed in some unit of effectiveness. Units of effectiveness are usually the same as those clinical outcomes used to measure effectiveness in clinical trials or practice. When comparing two interventions, the difference in cost and effectiveness between the two interventions is expressed as an incremental cost-effectiveness ratio, with the difference in cost in the numerator and the difference in effectiveness in the denominator. A particular form of cost-effectiveness is sometimes referred to as

continued

Glossary* *contd*

a cost–utility analysis (CUA), where the measure of effectiveness is typically measured in terms of quality-adjusted life-years (QALYs).

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

Cost-minimisation analysis (CMA) A special form of CEA and the simplest form of economic evaluation. Costs are expressed in monetary units and the patient outcome is assumed to be the same in both/all of the intervention groups evaluated. Thus, the object of this type of analysis is to identify the least expensive alternative.

Cost–utility analysis (CUA) A special form of CEA in which the units of effectiveness are QALYs. CUAs are important in the evaluation of cancer therapies, as such therapies are often associated with potentially serious or intolerable adverse events.

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.

Early ovarian cancer Refers to disease classified as FIGO stage I.

European Organisation for Research and Treatment of Cancer (EORTC) 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 the survival and quality of life (QoL) of patients.

Expected value of perfect information (EVPI) A measure of the cost of uncertainty associated with a given decision problem in terms of health forgone and resource costs. Perfect information through further research would remove this uncertainty and hence the cost of uncertainty is synonymous with the value of perfect information. Often graphically represented over a range of monetary values of society's maximum willingness to pay for an additional unit of health gain. This measure offers an insight into whether the necessary (but not sufficient) conditions are met for additional research to be cost-effective.

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 have an early stage of the disease which has been previously treated with surgery alone but has since relapsed and requires chemotherapy.

Hazard ratio (HR) The hazard (the instantaneous risk of patients experiencing a particular event at a specified time point) associated with one category of patients divided by the hazard of another set of patients. The HR can be estimated at an instant or averaged over an interval.

Heterogeneous Of differing origins or different types.

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

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

Histology The examination of the cellular characteristics of a tissue.

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 CIs.

continued

Glossary* *contd*

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).

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

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.

Lymphocytopenia An abnormally low level of lymphocytes in the blood. Lymphocytes are white cells which help to fight infections within the body and are responsible for producing antibodies.

Measurable lesion A lesion that can be unidimensionally or bidimensionally measured by physical examination, echography, radiography or computed tomography scan.

Meta-analysis The statistical pooling of the results of a collection of related individual studies to increase statistical power and synthesise their findings.

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

Myalgia Muscle pain.

Neuropathy A term that describes any disorder of the neurones or nerves of the body.

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.

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 unknown, but is believed to be a result of microtrauma within the tissue leading to leaky blood vessels.

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

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

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

Platinum-resistant disease Disease that is resistant to first-line platinum-based chemotherapy, as defined by the continuation of tumour growth during treatment, or disease in patients who initially respond to treatment but then relapse within 6 months.

Progressive disease Used to describe a tumour that continues to grow or the development of more metastatic sites.

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

Quality-adjusted life-year (QALY) An index of health gain where survival duration is weighted or adjusted by the patient's QoL during the survival period. QALYs have the advantage of incorporating changes in both quantity (mortality) and quality (morbidity) of life.

Quality-of-Life Questionnaire-C30 (QLQ-C30) A self-administered QoL questionnaire developed by the EORTC for the measurement of health-related QoL. 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

continued

Glossary* *contd*

scores on the symptom scales indicate the presence of more symptoms.

Quality-adjusted time without symptoms or toxicity (Q-TWiST) A quality-adjusted survival methodology used to compare interventions in terms of the period the average patient experiences no symptoms or toxicity. A higher Q-TWiST is desirable.

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.

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

Recurrent/disease-free survival The time from the primary treatment of the cancer to the first evidence of cancer recurrence.

Refractory disease† Disease that has never responded to first-line therapy

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, an RR < 1 means a person is at decreased risk and an RR = 1 means there is no effect on risk at all. An RR = 4.0 suggests the result is about four times as likely to happen, and an RR = 0.4 means it is four times less likely to happen. The RR is expressed with CIs, for example, RR = 3.0 (95% CI, 2.5 to 3.8), which means the result is three times as likely to happen – anything from 2.5 to 3.8 times as likely and 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 is not statistically significant. The chances range from half as likely to happen (0.5 – a decreased chance) to nearly nine times as likely to happen (8.9 – an increased chance).

Remission A period when a cancer has responded to treatment and there are no signs of the tumour or tumour-related symptoms.

Resistant disease† Disease that has responded to first-line therapy but has then relapsed within 6 months of completing treatment.

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, that is, 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 < 25% change in measurable lesions for at least 4–8 weeks with no new lesions appearing.

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

Stomatitis Inflammation/ulceration of the mouth.

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 QoL.

continued

Glossary* *contd*

Hence, utility has been described as a global measure of health-related QoL. Sometimes, utility is only used to refer to preferences (on the 0–1 scale) that are elicited using methods that 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 riskless context.

* Definitions adapted from Beltz and Yee[1] and Lister Sharp and colleagues.[2]
† Definitions from topotecan report by Forbes and colleagues.[3]
‡ Definition provided by Cochrane Collaboration Glossary.

List of abbreviations

BNF	*British National Formulary*
CBA	cost–benefit analysis
CEA	cost-effectiveness analysis
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
CMA	cost-minimisation analysis
CUA	cost–utility analysis
EORTC	European Organisation for Research and Treatment of Cancer
EVPI	expected value of perfect information
FIGO	International Federation of Gynaecologists and Obstetricians
G-CSF	granulocyte-colony stimulating factor
HR	hazard ratio
HRQoL	health-related quality of life
ITT	intention-to-treat
i.v.	intravenous/intravenously
ln	natural log
NA	not applicable
NICE	National Institute for Clinical Excellence
PPE	palmar–plantar erythrodysesthesia
QLQ-C30	Quality-of-Life Questionnaire-C30
QoL	quality of life
QALY	quality-adjusted life-year
Q-TWiST	quality-adjusted time without symptoms or toxicity
RCT	randomised controlled trial
RR	relative risk
SD	standard deviation
SE	standard error
TWiST	time without symptoms or toxicity

Executive summary

Background

Ovarian cancer is the most common gynaecological cancer with an annual incidence of 21.6 per 100,000 in England and Wales. As the early stages of ovarian cancer are often asymptomatic, most cases are not detected until the advanced stages. Consequently, prognosis after diagnosis is poor with 5-year survival in the UK of only about 30%. Paclitaxel and platinum-based (cisplatin/carboplatin) therapy are currently recommended as first-line chemotherapy for ovarian cancer. However, most patients develop resistant or refractory disease eventually requiring second-line therapy. Patients may respond to re-challenge with platinum agents if the treatment-free interval is > 6 months, but an alternative is often required. Topotecan has recently been recommended as one agent to be considered for second-line therapy, and pegylated liposomal doxorubicin hydrochloride is one of five other drugs currently licensed in the UK for use in second-line therapy.

Aims of the review

To examine the clinical effectiveness and cost-effectiveness of intravenous pegylated liposomal doxorubicin hydrochloride (Caelyx®, Schering-Plough Ltd, UK; Doxil®, Alza Corporation, USA) as second-line treatment for advanced ovarian cancer after failure of first-line platinum-based therapy.

Methods

Search strategy

Twenty-three electronic databases, databases of ongoing research and Internet resources were searched from inception to June 2001, and bibliographies of retrieved articles and pharmaceutical company submissions were examined.

Inclusion/exclusion criteria

Two reviewers independently screened all titles/abstracts, and made final decisions to include/exclude studies based on full copies of articles. Any disagreements were resolved through discussion.

Only randomised controlled trials (RCTs) and full economic evaluations comparing pegylated liposomal doxorubicin hydrochloride to non-pegylated liposomal doxorubicin hydrochloride regimens or standard care were included. Only second-line therapy of advanced disease after failure of first-line platinum-based therapy was considered, and the outcomes included were survival, response, symptom relief, quality of life (QoL), adverse events and costs.

Data extraction and quality assessment

Data were extracted by one reviewer and checked by another. Two reviewers, using specified criteria, independently assessed the quality of the clinical effectiveness and economic studies. Any disagreements were resolved through discussion.

Analysis strategy

Due to the limited number of studies included in the review, the outcome data could not be pooled statistically. Clinical effectiveness data were discussed according to outcome. RCTs were discussed separately from Phase II studies. For time to event data, hazard ratios with 95% confidence intervals (CIs) were presented where available. For the remaining outcomes, relative risks were reported or calculated where appropriate and where sufficient data were available, and also presented as forest plots without pooled estimates. Economic data were presented as a summary and critique of the evidence. Additional analysis was undertaken to explore cost-effectiveness more fully, including assessment of assumptions underlying the submitted economic analyses using relevant experts, estimation of differential mean survival duration, presentation of cost-effectiveness acceptability curves, assessment of the sensitivity of cost-effectiveness to possible differences between therapies in health-related QoL (HRQoL) and estimation of the expected value of additional research.

Results

Included studies

Of 143 titles/abstracts screened for relevance, full copies of 53 articles were assessed for inclusion.

Eighteen published papers of two RCTs and six Phase II studies of clinical effectiveness and two economic evaluations were included. Further details of one RCT, three Phase II studies and the economic evaluations were obtained from Schering-Plough Ltd. Overall, one international multicentre RCT comparing pegylated liposomal doxorubicin hydrochloride with topotecan (trial 30-49) was used in the final assessment of clinical effectiveness; and two cost-minimisation analyses based on trial 30-49 were used in the assessment of cost-effectiveness.

Quality of clinical effectiveness data

The RCT (trial 30-49) was of reasonably good quality, although valid intention-to-treat analyses were not used to assess outcome data. The six Phase II studies had several methodological problems and were of a much weaker design. Interpretation of such data requires great caution and the evidence from these studies was, therefore, not included in the final assessment of clinical effectiveness.

Quality of economic evaluations

Trial 30-49 on which both economic analyses were based was of reasonably good quality. The economic analyses used a cost-minimisation design, which was justified by the RCT being designed to show equivalence in overall survival. However, no equivalence in HRQoL was established. Other characteristics of the economic evaluations were generally of high quality.

Assessment of clinical effectiveness

The clinical effectiveness assessment was based on the best available evidence, although this was limited to data from trial 30-49 on 474 participants. Apart from some minor exceptions, there were no significant differences between pegylated liposomal doxorubicin hydrochloride and topotecan in overall survival, median survival, response rate, median time to response, median duration of response and QoL. The only significant differences reported were identified in subgroup analyses (platinum-sensitive disease and disease without ascites), which were of questionable validity, and their relevance to a general advanced ovarian cancer patient population undergoing second-line chemotherapy is unclear. However, significant differences were observed in the incidence of adverse events. Topotecan was associated with increased haematological toxicities (including neutropenia, leukopenia, anaemia and thrombocytopenia), alopecia, nausea and vomiting. Pegylated liposomal doxorubicin hydrochloride increased the incidence of palmar–plantar erythrodysesthesia, stomatitis, mucous membrane disorders and skin rashes.

Assessment of cost-effectiveness

The analysis of costs was thorough in both economic analyses. The company submission showed a mean cost saving from the use of pegylated liposomal doxorubicin hydrochloride of £2657. The mean cost with pegylated liposomal doxorubicin hydrochloride was £9970 (95% CI, £9080 to £10,861) compared with £12,627 (95% CI, £11,527 to £13,727) with topotecan. In the analysis by Smith and colleagues,[4] the mean saving was US$2909 (95% CI, $779 to $3415), approximately £2078, in favour of pegylated liposomal doxorubicin hydrochloride. In both cases, the savings were largely due to lower resource use in the management of adverse events with pegylated liposomal doxorubicin hydrochloride. The fairly extensive sensitivity analysis showed the estimates of differential costs were robust to changes in key parameter values. Further analysis for this report showed that when a full probabilistic cost-effectiveness analysis was undertaken and effectiveness expressed in terms of mean survival duration, there was a high probability that pegylated liposomal doxorubicin hydrochloride is more cost-effective (70–80%). However, the possible differences in HRQoL between the two therapies, reflecting differences in adverse events, may produce quite different cost-effectiveness results when effectiveness is expressed in terms of quality-adjusted life-years (QALYs) – a preferable measure when both length of life and QoL are potentially influenced. Therefore, although pegylated liposomal doxorubicin hydrochloride is very likely to have lower costs than topotecan, its overall cost-effectiveness is unclear.

Conclusions

The main results of this review suggested that there is little RCT evidence for assessment of the effectiveness of pegylated liposomal doxorubicin hydrochloride as second-line therapy for advanced ovarian cancer. Data from only one RCT was included in the final assessment of clinical effectiveness, and only two economic evaluations relevant to the UK NHS were identified and included in the cost-effectiveness assessment.

The evidence suggested that there were no differences between pegylated liposomal doxorubicin hydrochloride and topotecan in the main clinical outcomes. However, significant differences were

observed in the incidence of adverse events. The clinical significance of these findings was not discussed. Overall, the clinical effects of pegylated liposomal doxorubicin hydrochloride could at best be described as modest, however, the only other comparator considered in this review offered no real advantages. If anything, pegylated liposomal doxorubicin hydrochloride offered possible clinical advantages over topotecan due to fewer adverse events.

Based on existing data, pegylated liposomal doxorubicin hydrochloride is less costly than topotecan. When effectiveness was based on survival duration, pegylated liposomal doxorubicin hydrochloride had a high probability of being cost-effective. However, differences between the two therapies are likely to exist in overall HRQoL, which, when expressed in terms of QALYs, could alter these cost-effectiveness results markedly.

Recommendations for research

To provide a clearer picture of clinical effectiveness, further good quality RCTs comparing pegylated liposomal doxorubicin hydrochloride with other licensed and potentially useful (soon to be licensed) second-line chemotherapy agents for ovarian cancer are needed. Such studies should also generate data for cost-effectiveness analysis – the economic results presented here suggest a potentially high value of additional information from further research. At present, it is difficult to make choices between pegylated liposomal doxorubicin hydrochloride and other drugs for second-line ovarian cancer treatment without such direct comparisons.

In view of the timescale required to conduct good quality RCTs and economic evaluations, and the fact that no such ongoing studies were identified, it seems reasonable not to update the current review until findings from such evaluations are available.

Chapter 1

Objectives and background

Objectives of the review

This review aimed to examine the clinical effectiveness and cost-effectiveness of intravenous pegylated liposomal doxorubicin hydrochoride (Caelyx®, Schering-Plough Ltd, Welwyn Garden City, UK; Doxil®, Alza Corporation, Mountain View, CA, USA) for second-line treatment of advanced ovarian cancer, after the failure of platinum-based regimens.

Description of the underlying health problem

Ovarian cancer is the most common of the gynaecological cancers with an annual incidence of approximately 21.6 per 100,000 women.[5] In 1996, there were 4580 deaths from the disease in the UK.[6] The value of screening remains the subject of ongoing clinical trials because, due to the often asymptomatic nature of the early stages of disease, many cases of ovarian cancer are not detected until the advanced stages. Consequently, the prognosis after diagnosis is poorer than for other gynaecological cancers and figures suggest that the 5-year survival rate in the UK is only about 30%.[7,8]

There are three main types of ovarian cancer, which are determined by the primary cell types involved. Most cases of ovarian cancer (approximately 80%) are epithelial in origin and the remaining tumours are classified as either germ cell or stromal (sex cord–stromal) tumours.[9] The aetiology of ovarian cancer remains unclear. A genetic basis has been identified for a small number of ovarian tumours and an estimated 5–10% of cases involve women with a family history of breast and/or ovarian cancer.[10,11] However, 90% of ovarian cancers are sporadic in nature, although a link with incessant ovulatory function has been proposed throughout the literature. Suspected risk factors include advancing age, early menarche,[12] late menopause,[12] infertility,[13] the use of fertility drugs,[13,14] the use of talcum powder[15] and lactose intolerance.[15,16] In contrast, a number of factors, including parity,[17] the use of oral contraceptives,[18,19] a history of breast-feeding,[20] tubal ligation[20] and hysterectomy,[20] have been reported to be associated with a decreased risk of ovarian cancer.

Development of ovarian cancer is classified into stages using the International Federation of Gynaecologists and Obstetricians (FIGO) system. During stage I, malignant growth is confined to the ovaries, however, by stage IV, distant metastasis can be identified. In earlier stages of the disease, surgery is used as a first-line intervention, but in many cases the cancer is far too advanced to surgically remove all of the tumour and chemotherapeutic agents are, therefore, used in addition to 'debulking' surgery. Currently, there are three main types of chemotherapy used for the first-line treatment of ovarian cancer: non-platinum agents (e.g. cyclophosphamide, doxorubicin), platinum agents (e.g. cisplatin, carboplatin) and the newly developed taxanes (e.g. paclitaxel).

Patients treated with first-line therapy can be classified into three main groups. Those who respond to treatment for a period greater than 6 months are described as sensitive, those who initially respond to treatment but then relapse within 6 months are known as resistant and those who do not respond at all to first-line therapy are described as refractory. In most cases, even when the initial response to treatment is good, the malignancy will recur or be refractory to chemotherapy. In such cases, second-line chemotherapy may be considered. Among those women who respond, this 'salvage' therapy has a palliative effect and can prolong survival. However, in order to achieve the best possible response during second-line therapy, it is important that the agent used does not share cross-resistance with the first-line agent.

A number of potential prognostic factors, which may also influence survival and response to treatment, have been suggested. These include stage of disease, amount of residual cancer after cytoreductive (debulking) surgery, grade of tumour, performance status, histology and age.[21] The stage of disease at diagnosis has also been suggested to strongly influence overall survival. Serum CA-125 is also a potential prognostic indicator. Raised levels of this tumour marker have been correlated with disease progression. However, CA-125 is not

specific to ovarian tumours and increased levels may also be found with other tumours, such as breast tumours. Overall, the outlook for most ovarian cancer patients at present is poor and there is a need to develop more effective treatments.

Current service provision

Current guidance from the National Institute for Clinical Excellence (NICE) states that "the use of paclitaxel/platinum combination therapy in the treatment of recurrent (or resistant) ovarian cancer (i.e. second-line or salvage therapy) is recommended if the patient has not previously received this drug combination".[22] If, however, the patient has already received both drugs, the combination of paclitaxel and platinum-based therapy in recurrent (or resistant) ovarian cancer is not recommended. The choice of an alternative drug is, therefore, very much dependent on those previously used. Recent guidance from NICE recommends that "topotecan should be considered as one of the options for the second-line (or subsequent) treatment of women with advanced ovarian cancer where the disease is initially resistant or refractory to first-line platinum-based combination therapy or has become resistant after successive courses of platinum-based combination therapy".[23]

Description of pegylated liposomal doxorubicin hydrochloride

Pegylated liposomal doxorubicin hydrochloride is a Stealth® (Schering-Plough Ltd, Welwyn Garden City, UK) liposomal formulation of doxorubicin hydrochloride. Doxorubicin is obtained from *Streptomyces peucetius* var. *caesius* and belongs to the class of drugs known as anthracyclines, a group of antibiotics that have potent antineoplastic activity. They intercalate with DNA and thus adversely affect cell functions that rely on DNA. Furthermore, anthracyclines interact with cell membranes thereby altering their functions and generating hydrogen peroxide and hydroxy radicals, which are highly destructive to cells. In the case of pegylated liposomal doxorubicin hydrochloride, doxorubicin is encapsulated in liposomes that have been pegylated – that is, they have surface-bound methoxypolyethylene glycol. Pegylation protects the liposomes from detection by the body's immune system, which increases the time that they remain in circulation in the blood. Encapsulating doxorubicin in pegylated liposomes enhances drug localisation and concentration in tumour tissues. Overall, this serves to increase the efficacy of the drug and also limits its toxicity by targeting the drug to the tumour. Pegylated liposomal doxorubicin hydrochloride is a relatively new drug that has been licensed for the treatment of AIDS-related Kaposi's sarcoma for a number of years and has recently received approval in the UK (October 2001) for use in the treatment of advanced ovarian cancer.

Current indications for pegylated liposomal doxorubicin hydrochloride

Pegylated liposomal doxorubicin hydrochloride is licensed in the UK for the treatment of patients with advanced ovarian cancer after the failure of a first-line platinum-based chemotherapy regimen.

Summary of current manufacturers' information provided for health professionals[24,25]

Recommended dosage

Intravenous administration at a dose of 50 mg/m^2 once every 4 weeks for as long as the disease does not progress and the patient continues to tolerate the treatment.

Administration should be immediately discontinued in patients who experience early symptoms or signs of infusion reaction. After appropriate premedications (antihistamine and/or short-acting corticosteroid), therapy can be restarted, but at a slower rate. The dose of pegylated liposomal doxorubicin hydrochloride may also be reduced or delayed in patients with adverse events, such as palmar–plantar erythrodysesthesia (PPE), stomatitis and haematological toxicity.[24]

Contraindications

- A history of severe hypersensitivity reactions to the active substance and/or its excipients.
- Pregnancy and breastfeeding.

Special warnings and special precautions for use

All patients routinely receiving pegylated liposomal doxorubicin hydrochloride are recommended to undergo frequent electrocardiogram monitoring and monitoring of left ventricular ejection fraction by echocardiography or preferably by multiple gated arteriography. Where possible injury is detected in association with pegylated liposomal doxorubicin hydrochloride treatment, the benefit of therapy should be weighed against the risk of myocardial injury. Caution should be exercised when treating patients who have been previously

treated with anthracyclines or who have impaired cardiac function.

Adverse events

Myelosuppression is mainly mild, moderate or manageable. The main frequently reported treatment-related adverse events are PPE and stomatitis. Other drug-related adverse events (> 5%) include nausea, asthenia, rash, vomiting, alopecia, constipation, anorexia, mucous membrane disorder, diarrhoea, abdominal pain, fever, paraesthesia, pain, skin discolouration, pharyngitis, dry skin, dyspepsia and somnolence. Clinically significant laboratory abnormalities include increases in total bilirubin and serum creatinine levels.

Unit costs

The net price for a 10 ml vial is £411.30 and for a 25 ml vial is £813.49.[25]

Comparator/alternative technologies

For those patients who require second-line therapy, guidance advises the use of platinum-based therapy, except in cases where such therapy has previously failed. In these cases, a number of other alternative antineoplastic drugs are available, including topotecan, paclitaxel, docetaxel, gemcitabine, etoposide, ifosfamide, tamoxifen, hexamethylmelamine, treosulfan, vinorelbine, oxaliplatin, fluorouracil plus folinic acid, epirubicin and gonadotrophin-releasing hormone agonist (see *Table 1*).[22] Paclitaxel, hexamethylmelamine, treosulfan, carboplatin, pegylated liposomal doxorubicin hydrochloride and topotecan are currently licensed in the UK for the treatment of advanced ovarian cancer where standard platinum-containing therapy (cisplatin or carboplatin) has failed. NICE currently recommends that topotecan should be considered as one of the options for treatment in such circumstances.[23]

TABLE 1 *Potential and existing drugs for second-line/salvage treatment of ovarian cancer*

Drug name (manufacturer)	Mode of action	Administration	Side-effects/toxicity
Carboplatin (Paraplatin®, Bristol-Myers Squibb)	Platinum-based compound. Binds to DNA to form interstrand crosslinks, which prevent DNA replication	400 mg/m^2 as a single i.v. dose administered by a 15–60-minute infusion. Licensed in the UK for advanced ovarian cancer for first-line therapy and second-line therapy after other treatments have failed	Myelosuppression, nephrotoxicity, nausea and vomiting
Docetaxel (Taxotere®, Aventis)	Prevents microtubule assembly and arrests cell division cycles in phases G2 and M	1-hour i.v. infusion after pre-medication with dexamethasone. Not yet licensed in the UK for the treatment of ovarian cancer	Hypersensitivity and fluid retention
Epirubicin (Ellence®, Pharmacia)	Anthracycline antibiotic. Binds to DNA and inhibits nucleic acid synthesis	i.v. administration. Not yet licensed in the UK for the treatment of ovarian cancer	Alopecia, skin rashes, myelo-suppression, nausea/vomiting, mouth sores/ulcers, cardiac problems and diarrhoea
Etoposide (Eposin®, Medac; Etopophos®/Vepesid®, Bristol-Myers Squibb)	Topoisomerase II inhibitor. Inhibits DNA replication	Oral or i.v. administration. Not yet licensed in the UK for the treatment of ovarian cancer	Myelosuppression, alopecia, nausea and vomiting
Fluorouracil (injection non-proprietary, Faulding Pharmaceuticals) plus folinic acid (Refolinon®, Pharmacia)	Antimetabolite. Inhibits the enzyme thymidylate synthase, which blocks DNA synthesis	Oral or i.v. administration. Not yet licensed in the UK for the treatment of ovarian cancer	Neutropenia, thrombo-cytopenia, anaemia, nausea/ vomiting, mouth sores/ulcers and diarrhoea
Gemcitabine (Gemzar®, Eli-Lilly)	Antimetabolite. A nucleoside analogue that incorporates into replicating DNA causing DNA chain termination	30-minute i.v. infusion. Not yet licensed in the UK for the treatment of ovarian cancer	Mild gastrointestinal side-effects, rashes, renal impair-ment, pulmonary oedema and influenza-like symptoms
Gonadotrophin-releasing hormone antagonist Goserelin (Zoladex®, AstraZeneca)	Gonadorelin analogue. Down-regulates gonadotrophin-releasing hormone receptors, thereby reducing the release of gonadotrophins, which, in turn, inhibits androgen and oestrogen production	Subcutaneous injection. Not yet licensed in the UK for the treatment of ovarian cancer	Withdrawal bleeding, fibroid degeneration, ovarian cysts and transient changes in blood pressure
Hexamethylmelamine (Hexalen®, David Bull Laboratories)	Alkylating agent. Damages DNA and interferes with DNA replication	Oral administration. Licensed in the UK for the second-line treatment of ovarian cancer. Often given in combination with other agents, such as cyclo-phosphamide, doxorubicin and, if the patient can tolerate it, cisplatin	Neurotoxicity, myelosuppression, nausea and vomiting
Ifosfamide (Mitoxana®, ASTA Medica)	Alkylating agent. Damages DNA and interferes with DNA replication	i.v. administration. Not yet licensed in the UK for the treatment of ovarian cancer	Neutropenia, anaemia, thrombocytopenia, nausea/vomiting and alopecia
Oxaliplatin (Eloaxtin®, Sanofi-Synthelabo)	Diaminocyclohexane platinum compound	i.v. administration. Not yet licensed in the UK for the treatment of ovarian cancer	Sensory/peripheral neuropathy, bone marrow suppression, nausea/vomiting and diarrhoea

continued

TABLE 1 contd *Potential and existing drugs for second-line/salvage treatment of ovarian cancer*

Drug name (manufacturer)	Mode of action	Administration	Side-effects/toxicity
Paclitaxel (Taxol®, Bristol-Myers Squibb)	Taxane. Promotes microtubule assembly and arrests cell division cycles in phases G2 and M	3–24-hour i.v. infusion after premedication with corticosteroid, antihistamine and histamine H_2-receptor antagonist. Licensed in the UK for metastatic ovarian cancer where standard platinum-containing therapy (cisplatin or carboplatin) has failed	Hypersensitivity, myelosuppression, peripheral neuropathy, cardiac conduction defects with arrhythmias, alopecia and myalgia/arthralgia
Pegylated liposomal doxorubicin hydrochloride (Caelyx®, Schering-Plough Ltd; Doxil®, Alza Corporation)	Anthracycline antibiotic. Binds to DNA and inhibits nucleic acid synthesis	i.v. administration. Received UK approval in October 2001 for the second-line treatment of advanced ovarian cancer	Hand–foot syndrome, stomatitis and neutropenia
Tamoxifen (Nolvadex®, AstraZeneca; Oestrifen®, APS; Emblon®, Berk; Fentamox®, Cox; Tamofen®, Pharmacia; Soltamox®, Rosemont)	Oestrogen receptor antagonist	Oral administration. Not yet licensed in the UK for the treatment of ovarian cancer	Endometrial changes, leukopenia, skin rashes, alopecia, headaches and gastrointestinal disturbances
Topotecan (Hycamtin®, GlaxoSmithKline)	Topoisomerase inhibitor that inhibits DNA replication	i.v. administration. Licensed in the UK for the second-line treatment of ovarian cancer. Recommended by NICE as one of the options to be considered for second-line treatment of platinum-resistant disease	Bone marrow suppression, nausea, alopecia and vomiting
Treosulfan (Treosulfan®, Medac)	Alkylating agent. Damages DNA and interferes with DNA replication	Oral or i.v. administration. Licensed in the UK for the treatment of ovarian cancer	Bone marrow suppression and skin rashes
Vinorelbine (Navelbine®, Burroughs Wellcome)	Vinca alkaloid. Irreversibly inhibits cell division (mitosis) by binding to microtubule protein and inhibiting the formation of mitotic spindles	i.v. administration. Not yet licensed in the UK for the treatment of ovarian cancer	Peripheral/autonomic neuropathy, abdominal pain, constipation, myelosuppression and alopecia

i.v. intravenous/intravenously

Chapter 2
Methods

Search strategy

The following databases were searched for relevant published literature (details of the search strategies are given in appendix 1): BIOSIS, CANCERLIT, Cochrane Controlled Trials Register, Cochrane Database of Systematic Reviews, CINAHL, PubMed, Database of Abstracts of Reviews of Effectiveness, EMBASE, HTA database, HealthStar, Index to Scientific and Technical Proceedings, MEDLINE, NHS EED, Science Citation Index and Office of Health Economics Health Economic Evaluations Database.

Research groups (see appendix 2) identified through searches of the registers were contacted for information about ongoing trials: National Research Register, United Kingdom Coordinating Committee on Cancer Research Register (<http://www.cto.mrc.ac.uk/ukcccr/text_only/search.html>), National Cancer Institute (<http://cancernet.nci.nih.gov/trialsrch.shtml>), National Institute of Health (<http://clinicaltrials.gov/ct/gui/c/r>), CenterWatch Clinical Trials Listing Service (<http://www.centerwatch.com/main.htm>), Current Controlled Trials (<http://www.controlled-trials.com/>), American Society of Clinical Oncology (<http://www.asco.org/>) and National Cancer Institute of Canada (<http://www.ctg.queensu.ca/>).

The following Internet sites were used to conduct a general search to identify background material and additional information: Google (http://www.google.com), Metaeureka (http://www.metaeureka.com/), Altavista (http://uk.altavista.com/), Schering-Plough Ltd (http://www.schering-plough.com/), RxList (http://www.rxlist.com) and the *British National Formulary* (*BNF*) 41 (http://www.bnf.vhn.net/).

In addition, the bibliographies of retrieved articles and industry submissions made to NICE were searched for further studies.

Inclusion and exclusion criteria

Two reviewers independently screened all titles and abstracts. Full paper manuscripts of potentially relevant titles/abstracts were obtained where possible and assessed for inclusion according to the following criteria. Studies that did not fulfil all of the criteria were excluded. The bibliographical details of these excluded studies were listed with the reason for exclusion. Any discrepancies were resolved by consensus and, if necessary, a third reviewer was consulted.

Study design

The following study designs were eligible for inclusion.

- Randomised controlled trials (RCTs) that compared pegylated liposomal doxorubicin hydrochloride-containing regimens with any other second-line treatments (e.g. topotecan and hexamethylmelamine), including combination therapy without pegylated liposomal doxorubicin hydrochloride or best supportive care. (Note, the review assessed the best available evidence for making an informed decision about the use of pegylated liposomal doxorubicin hydrochloride in the NHS (i.e. RCTs), and about its benefits and disbenefits. However, studies using weaker designs, such as non-comparative Phase II studies, were included at the request of NICE. Although summarised in full in the appendices, the data from these studies are only discussed briefly in the main body of the report due to the inherent methodological limitations of using such studies in the assessment of effectiveness.)
- Full economic evaluations that compared two or more options and considered both costs and consequences, including cost-minimisation analyses (CMAs), cost-effectiveness analyses (CEAs), cost–utility analyses (CUAs) and cost–benefit analyses (CBAs).

Interventions

Intravenous pegylated liposomal doxorubicin hydrochloride used alone or in combination with other chemotherapeutic agents as part of the following stages of treatment was eligible for inclusion.

- Second-line therapy (defined as the second chemotherapy regimen administered either as a result of relapse after first-line platinum-

based therapy or immediately following on from first-line platinum-based therapy in patients with progressive or stable disease).
- Salvage therapy (defined as any therapy given in the hope of getting a response when the standard therapy (i.e. platinum-based therapy) had failed. This could overlap with second-line therapy, but could also include therapy given for patients with refractory disease, that is, disease that has never responded to first-line therapy).

Participants

Women with ovarian cancer, encompassing all stages of disease, were included. Where possible, the FIGO system was used to define the stage of disease (see appendix 3). Early ovarian cancer refers to stage I and advanced disease refers to stages II–IV.

Outcomes

Data on the following outcome measures were eligible for inclusion:

- progression-free survival
- overall survival
- response (including complete and partial response)
- quality of life (QoL)
- adverse events as reported in the trials, including haematological toxicity (including neutropenia, thrombocytopenia and anaemia), non-haematological toxicity (including PPE, nausea, diarrhoea, constipation, stomatitis, abdominal pain, fatigue, asthenia, alopecia, anorexia, malaise and hyperbilirubinaemia) and any other adverse events judged to be appropriate
- costs from all reported perspectives.

Data extraction strategy

Data relating to both study design and quality (see appendix 4) were extracted by one reviewer into an Access database, and independently checked for accuracy by a second reviewer. Data from studies with multiple publications were extracted and reported in the appendices. However, only data from the most recent publication were reported in the main body of the report and used in the analyses. This included using data from abstracts or interim reports if the most recent data were only available in these forms. The use of interim data is clearly stated in the text of the report. All of the publications identified as eligible for inclusion were published in English.

Quality assessment strategy

The quality of the individual studies was assessed independently by two reviewers. Disagreements were resolved through consensus and, if necessary, a third reviewer was consulted.

The quality of clinical effectiveness studies was assessed using criteria based on the NHS Centre for Reviews and Dissemination Report No. 4 (see appendix 5).[26] The quality of the cost-effectiveness studies was assessed using a checklist updated from that developed by Drummond and colleagues (see appendix 5).[27] This checklist reflects the criteria for economic evaluations detailed in the methodological guidance developed by NICE.[28] The quality of the clinical effectiveness studies is presented in tables within the text of the report, and the quality of the economic evaluations is presented in table form in appendix 6 and summarised within the text of the report.

Analysis strategy

Effectiveness

Details of the extracted data and quality assessment for each individual study of clinical effectiveness are presented in structured tables and as a narrative description. The possible effects of study quality on the effectiveness data and review findings are discussed. Data are reported separately for each different study design (RCTs and non-comparative Phase II studies) and outcome measure. Where sufficient data were available, treatment effects have been presented in the form of relative risks (RRs) or hazard ratios (HRs) as appropriate. Ideally, survival data have been presented as HRs or median times based on Kaplan–Meier survival curves. However, this was not always possible due to a lack of appropriate data. Where data were not available, RRs and *p*-values have been 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 have also been presented in the form of forest plots, but without pooled estimates.

Due to the small number of studies included in the review and the heterogeneity between the studies (i.e. they compared different 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. For some of the unpublished studies that were identified, no outcome data and, in some cases, little methodological information could be obtained, despite contacting the trialists concerned.

Cost-effectiveness

Details of each published economic evaluation together with a critical appraisal of its quality are presented. Quality has been assessed using a checklist updated from that developed by Drummond and co-workers,[27] and additional commentary is also provided where appropriate. This checklist reflects the criteria for economic evaluations detailed in the methodological guidance developed by NICE.[28]

The costs, effects and cost-effectiveness of the alternative treatment options have been considered based on available studies. Additional analysis was undertaken to explore cost-effectiveness more fully. This included a careful assessment of assumptions underlying the submitted economic analyses using relevant experts, the estimation of differential mean survival duration, the presentation of cost-effectiveness acceptability curves (CEACs) and the estimation of the expected value of additional research.

Chapter 3
Results

Quantity of research available

A total of 143 titles and abstracts were identified and screened for relevance. Fifty-three full paper copies of articles were examined in further detail and assessed for inclusion in the review (see *Figure 1*).

Excluded studies

Of the 53 articles examined in further detail, a total of 35 were excluded from the review.

Seventeen of the articles were literature reviews and background papers. The remaining publications were excluded for the following reasons: seven did not use a suitable study design (i.e. RCT or Phase II study),[29–35] three were not original reports of relevant studies but were non-systematic reviews,[36–38] two did not consider pegylated liposomal doxorubicin hydrochloride as an intervention,[39,40] five presented no relevant outcome data[11,41–44] and the final study did not focus on ovarian cancer patients.[45] Details of these studies

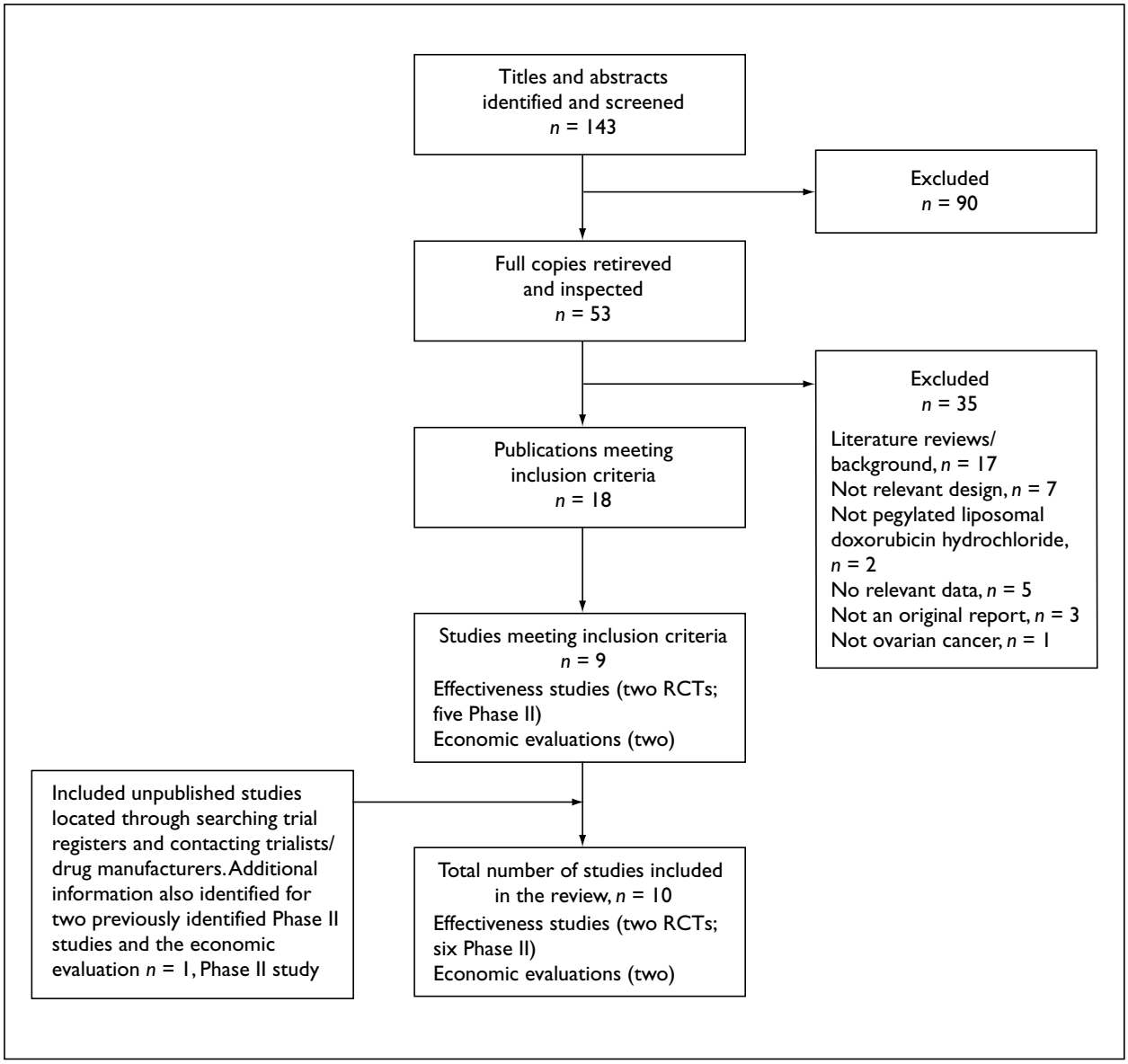


FIGURE 1 *Summary of study identification, retrieval and inclusion/exclusion*

and the reasons for their exclusion are given in appendix 7.

Included studies

Of the ten studies that met the criteria for inclusion in the review, eight were clinical effectiveness studies (two RCTs (see *Table 2*[46–49]) and six Phase II studies (see *Table 3*[50–59])) and two economic evaluations (see *Table 4*[1,47,48]). One of the RCTs was only described in minimal detail and because of a lack of outcome data it was not ultimately possible to consider this trial.

RCTs

The two effectiveness studies were identified as trial 30-49 (474 participants) and trial 30-57, both sponsored by Schering-Plough Ltd. Trial 30-49 compared pegylated liposomal doxorubicin hydrochloride with topotecan. Details of the final trial analysis were available in published form and a full trial report was included as part of a company submission.[47] Both of these sources of information have been used in this report.

Trial 30-57 compared pegylated liposomal doxorubicin hydrochloride with paclitaxel. Very few details about this trial were available, although brief details about the design of the trial were available in abstract form.[49] Due to the early termination of the trial (due to paclitaxel being adopted as a first-line therapy), no outcome data regarding the effectiveness of pegylated liposomal doxorubicin hydrochloride were available, even after contacting the sponsoring company directly.

Both of the studies were international multicentre Phase III RCTs evaluating intravenous pegylated liposomal doxorubicin hydrochloride (50 mg/m^2/day as a 1-hour infusion every 28 days) in advanced epithelial ovarian carcinoma (FIGO stage III/IV). In both cases, patients had undergone prior first-line platinum-based chemotherapy, which had failed. It was not clear in either trial whether participants had also undergone other alternative forms of therapy in addition to chemotherapy. In terms of the clinical outcomes, trial 30-49 reported data relating to response rate, survival, time to response, time to progression, duration of response, QoL and adverse events. As previously stated, outcome data for trial 30-57 were not available and this trial is, therefore, not discussed further in this report. Further details of trial 30-49 are given in appendix 8.

Phase II studies

Of the six Phase II studies identified, all were non-comparative, two were sponsored by Sequus (now Schering-Plough Ltd) and two by Alza Corporation (Schering-Plough Ltd in Europe). The remaining two Phase II studies were conducted in Europe for which only a few interim details of the studies were available in the form of published abstracts, and the source of sponsor was not stated in either case. Attempts were made to contact the trial researchers for further information, but no replies were received.

Of the four company-sponsored studies, all involved multiple study sites (three in the USA (studies 30-22, 30-47 and Israel and colleagues) and one in Europe (study 30-47E)). All of the studies had reached the stage of completion and details of two of the studies were published in full (studies 30-22[51] and 30-47[55]). The interim data from the remaining study was published in abstract form only (Israel and colleagues[57]). Data concerning the remaining study (study 30-47E) were only available in an unpublished report submitted by Schering-Plough Ltd.[56] All of the Phase II studies included participants

TABLE 2 *Summary of clinical effectiveness studies (RCTs) included in the review*

Study	Status and source	Study design	Comparators
30-49 (Schering-Plough Ltd)	Completed. Interim results published as an abstract.[46] Final results submitted by Schering-Plough Ltd[47] and published in part[48]	Phase III, multicentre open-label RCT; 474 participants analysed	Pegylated liposomal doxorubicin hydrochloride (50 mg/m^2/day as a 1-hour infusion every 28 days) versus topotecan (1.5 mg/m^2/day as a 30-minute infusion every day for 5 days consecutively every 21 days)
30-57 (Schering-Plough Ltd)	Terminated due to use of paclitaxel for first-line treatment. No outcome data published or available from the company. Brief design details provided in abstract form[49]	Phase III, multicentre open-label RCT	Pegylated liposomal doxorubicin hydrochloride (50 mg/m^2/day as a 1-hour infusion every 28 days) versus paclitaxel 175 mg/m^2/day as a 3-hour infusion every 21 days

TABLE 3 *Summary of clinical effectiveness studies (Phase II studies) included in the review*

Study	Status and source	Study design
30-22 (Sequus, now Schering-Plough Ltd)	Completed. Interim results published as an abstract.[50] Final results published[51]	Two USA sites (September 30 1994–June 30 1997). 35 women with Karnofsky performance status ≥ 50% (European Cooperative Oncology Group performance status ≤ 2) who had progressive ovarian cancer after treatment with either cisplatin or carboplatin and paclitaxel or at least one platinum-based and paclitaxel-based regimen. Median age = 65 years (range 46–78); median Karnofsky performance status = 80% (range 60–100); largest lesion ≥ 5 cm = 13/35 (37%); FIGO stage III–IV = 31/35 (89%); ≥ 6 months interval since last treatment = 6/35 (17%); serous histology = 25/35 (71%); poorly differentiated/ non-specified tumour = 31/35 (89%)
30-47 (Alza Corporation (Schering-Plough Ltd in Europe))	Completed. Interim results published as abstracts.[52–54] Final results reported in company report from Schering-Plough Ltd[55]	24 USA sites (up until May 15 1999). 123 participants with locally advanced or metastatic epithelial ovarian cancer following the failure of at least two but no more than three prior cytotoxic chemotherapeutic regimens. Median Karnofsky performance status = 90%; median age = 61 years (range 34–85); median prior drug-free interval = 1.5 months (range not stated); 50/122 (41%) were refractory to platinum and paclitaxel (double refractory), 67/122 (55%) were refractory to platinum, paclitaxel and topotecan (triple refractory), 117/122 (96%) were in the combined refractory population (double and triple); median CA-125 level = 290.25 U/ml (range 7–46594), mean CA-125 level = 1569.35 U/ml; number of prior chemotherapy regimens: one = 13/122 (10.7%), two = 63/122 (51.6%), three = 46/122 (37.7%)
30-47E (Alza Corporation (Schering-Plough Ltd in Europe))	Completed. Unpublished. Final results submitted by Schering-Plough Ltd[56]	14 European sites (October 1996–May 1999). 62 participants with histologically proven advanced or metastatic epithelial ovarian cancer that was refractory to platinum- and taxane-based chemotherapy; treated with at least two but no more than three prior chemotherapy regimens; Karnofsky performance status ≥ 60%; aged ≥ 18 years. Median age = 53 years (range 22–80); median Karnofsky performance status = 90% (range not stated); median prior drug-free interval = 2.6 months (range not stated); 32/62 (52%) refractory to platinum and paclitaxel (double refractory), 11/62 (18%) refractory to platinum, paclitaxel and topotecan (triple refractory); median CA-125 level = 680 U/ml (range 7–31990); baseline lesion ≥ 5cm in one dimension = 30/62 (48.4%)
Israel *et al.* (Sequus, now Schering-Plough Ltd)	Completed. Interim results published as an abstract[57]	Two USA sites. 63 participants of whom 48/63* (76%) had confirmed measurable or assessable recurrent or metastatic epithelial ovarian cancer and had a Karnofsky performance status ≥ 60%, having failed at least one prior cisplatin-based therapy. More than two prior chemotherapy regimens = 27/48 (56%); platinum resistant = 44/48 (91.7%); bulky disease (≥ 5 cm) = 12/21 (57%); serous histology = 32/48 (66.7%). Age and Karnofsky performance status data were only given for the population as a whole and not just the ovarian cancer patients
Linardou *et al.*† (Hellenic Cooperative Oncology Group)	Ongoing. Interim results published as an abstract[58]	Multicentre, European? No further details available. 35 participants with platinum-resistant recurrent ovarian cancer, all of whom had previously received paclitaxel. Median Eastern Cooperative Oncology Group performance status = 1; median age = 66 years (range 28–77); median number of prior chemotherapy regimens per patient = 3.0 (range 1–7); median treatment-free interval = 2 months

continued

***TABLE 3* contd** *Summary of clinical effectiveness studies (Phase II studies) included in the review*

Study	Status and source	Study design
Cervantes *et al.* [†] (Unknown)	Ongoing. Interim results published as an abstract[59]	Multicentre, European? No further details available. 18 participants with WHO performance status < 3 and histologically confirmed ovarian carcinoma showing resistance or progression after cisplatin treatment. Median age = 60 years (range 32–78); serous histology = 14/18 (77.8%); ≥ 3 lesions = 13/18 (72.2%); largest lesion > 5 cm = 8/18 (44.4%); median number of previous treatments = 2 (range 2–5); ascites present = 6/18 (33.3%); median WHO performance status = 2 (range 0–2); median time from last treatment = 2 months (range not stated)

[*] *The remaining 15 participants had other gynaecological cancers (cervical, endometrial, vaginal) and are not discussed in this summary*
[†] *Authors contacted for further information, but no response received*

TABLE 4 *Summary of economic evaluations included in the review*

Study	Status and source	Study design	Comparators
30-49 (Schering-Plough Ltd)	Single trial (30-49 Schering-Plough Ltd)[47,48]	Phase III, multicentre open-label RCT; 474 participants analysed. The economic study was a CMA with the assumption of equivalence in effects based on the results from the clinical study of pegylated liposomal doxorubicin hydrochloride (versus topotecan) trial	Pegylated liposomal doxorubicin hydrochloride (50 mg/m^2/day as a 1-hour infusion every 28 days) versus topotecan (1.5 mg/m^2/day as a 30-minute infusion for 5 days consecutively every 21 days)
Smith *et al.*, 2001[4]	As above. This is a paper submitted for publication based on trial 30-49	As above	As above

with ovarian cancer that had failed previous platinum-based regimens. However, the specific detailed inclusion and exclusion criteria for participants and their overall baseline characteristics varied between the individual studies, as did the dose regimens in some cases. Further details of the individual studies are reported in appendix 9.

Economic evaluations

Both evaluations identified were based on the single RCT 30-49, and, as such, they are both multicentre and multinational. Both are CMAs and assume equivalence of the two drugs based on survival duration. No equivalence in health-related QoL (HRQoL) was established. Although the studies are based, in part, on non-UK patients, attempts were made to adjust some aspects of the resource costs to reflect NHS practice. Further details of the individual economic evaluations are reported in appendix 10.

Quality of research available

The quality of the clinical effectiveness studies and economic evaluations was assessed using the checklists described in appendix 5.

Quality of clinical effectiveness studies

RCTs

Details of trial 30-49 were published as a final report and a full trial report was obtained from Schering-Plough Ltd.[47] In addition, the company provided specific information relating to three of the quality criteria on request.

Participants in trial 30-49 were judged using a comprehensive list of criteria (all of which appeared to be reasonable) to assess their suitability for inclusion in the trial. In addition, no other co-existing treatments, apart from those administered in the management of adverse events, were identified. Overall, 474 participants were considered eligible

and were subsequently randomised into two treatment groups (239 to pegylated liposomal doxorubicin hydrochloride and 235 to topotecan). Information supplied on request from Schering-Plough Ltd stated that a truly random computerised method was used, with participants stratified according to platinum sensitivity and the presence or absence of bulky disease. This process was carried out centrally and was, therefore, sufficiently concealed to avoid bias through possible tampering at the study site. In addition, the two study groups appeared to be comparable in terms of the six potentially important factors outlined in the quality assessment, which suggested that the randomisation process was successful. The six factors were identified by the external review panel as being potentially important factors in determining a patient's response to treatment.

Differences in the two treatment regimens (pegylated liposomal doxorubicin hydrochloride was administered once over 1 hour every 4 weeks and topotecan was administered over 30 minutes on 5 days consecutively every 3 weeks) made it impossible to blind participants and their carers to their intervention assignment. Of more concern is the fact that the trial reports and a recent European Public Assessment Report of trial 30-49 suggested that those individuals that assessed the treatment responses were not blinded to the intervention assignment.[60] Blinding is not important for outcomes, such as survival, where death is a clear outcome, but if the assessor is not blinded for response outcomes the outcomes may be biased. Knowledge of the drug under assessment may lead to the assessor providing a more or less favourable outcome as compared with the true effect. This is particularly important in the case of ovarian cancer where the assessment of response to therapy is notoriously difficult. According to Schering-Plough Ltd, the treatment responses were reviewed by an independent body subsequent to the completion of the trial, however, this information was not yet available at the time of this report.

In order to get a view of the study findings that is more indicative of clinical practice, it is important to carry out an intention-to-treat (ITT) analysis. In such an analysis, all of the participants randomised to take part in the trial are included according to their original intervention assignment, regardless of whether they subsequently dropped out of the trial or received an alternative treatment. The study report stated that an ITT analysis was performed. However, 481 participants were randomised to take part in the trial and the ITT analysis only includes 474 participants, and it was, therefore, effectively not a true ITT analysis. The seven participants missing from the final analysis were lost prior to the start of treatment. Since further details regarding the reason and intervention assignment of these participants was not provided, it was not possible to reassess the study outcomes in terms of a true ITT analysis. Consequently, the ITT analysis reported by the trialists has been used in this review, but this should be interpreted with some degree of caution in view of the issues described above.

Overall, the trial would seem to be of reasonably good quality, with the only major issues for concern being the failure to conduct a true ITT analysis and the lack of blinding of assessors to treatment allocation. A summary of the quality of trial 30-49 is presented in *Table 5*. In addition, further details of study 30-49 and its quality are reported in appendix 8.

Phase II studies

The six Phase II studies included in the review were all non-comparative. These trials, therefore, only examined patients treated with pegylated liposomal doxorubicin hydrochloride and did not use a no treatment or alternative treatment control group. This made the findings difficult to interpret in terms of the true clinical effectiveness of pegylated liposomal doxorubicin hydrochloride, as the studies were open to a number of potential biases and confounding effects. Consequently, the findings of the studies, in terms of clinical outcomes, may not have been solely attributable to the effects of the drug.

All of the studies clearly reported their aims, which were, in every case, to determine the effectiveness and safety of pegylated liposomal doxorubicin hydrochloride. The primary aim of Phase II studies is to determine whether a drug has activity and if it is safe to use. However, as has already been discussed, a non-comparative design is not the best design to use to determine the actual clinical effectiveness of a drug. In terms of the aims of this review and its assessment of clinical effectiveness, alternative studies using a controlled design, preferably RCTs, were required to make an assessment based on good quality evidence.

The six studies varied in the number of participants recruited from 18 to 123. Only three of the studies (30-22, 30-47E and Cervantes and colleagues[59]) provided information about the six factors identified by the external review panel as being potentially important in determining a patient's response

TABLE 5 *Quality of effectiveness studies (RCTs)*

Quality criteria	30-49 Schering-Plough Ltd[46–48]
Was the method used to assign participants to the treatment groups really random?	Yes*
Was the allocation of treatment concealed?	Yes*
Was the number of participants who were randomised stated?	Yes
Were details of baseline comparability presented in terms of treatment-free interval, disease bulk, number of previous regimens, age, histology and performance status?	Yes
Was baseline comparability achieved for treatment-free interval, disease bulk, number of previous regimens, age, histology and performance status?	Yes
Were the eligibility criteria for study entry specified?	Yes
Were any co-interventions identified that may have influenced the outcomes for each group?	No
Were the outcome assessors blinded to the treatment allocation?	No*
Were the individuals who were administered the intervention blinded to the treatment allocation?	No
Were the participants who received the intervention blinded to the treatment allocation?	No
Was the success of the blinding procedure assessed?	NA
Were ≥ 80% of the participants originally included in the randomisation process, followed up in the final analysis?	Yes
Were the reasons for any withdrawals stated?	Yes
Was an ITT analysis included?	Partially†

* *Additional information requested, but not yet available, from Schering-Plough Ltd*

† *The study reported that an ITT analysis was performed. However, this analysis did not include all of the participants originally randomised to take part in the trial and was, therefore, not a true ITT analysis*

Yes, item adequately addressed; No, item not adequately addressed; Partially, item partially addressed; Unclear, unclear or not enough information; NA, not applicable

to treatment. This made it difficult to assess the disease status of the participants and the likely heterogeneity within the study population. In the majority of instances, the trials appeared to have followed up participants for a sufficiently long period, that is, until death. However, this was difficult to confirm in two studies because both were based on abstracts with minimal data and information about the studies concerned.[58,59] Only two of the studies appeared to have used statistical methods to justify the sample size (studies 30-22 and 30-47). One additional study stated that a predetermined target number of participants had been recruited, but failed to provide any further information regarding how this was achieved (study 30-47E). The remaining studies failed to report any justification for the sample sizes used or to indicate whether the numbers were sufficient to show clinically statistically significant effects.

The importance of using independent assessments of treatment responses has already been discussed with regard to RCTs, and the same applies to Phase II non-comparative study designs. All six studies failed to state whether independent assessments were performed. Similarly, there was a lack of information regarding a number of other important issues, including compliance with the study protocol/treatment regimen and the occurrence of untoward effects that could influence the study findings. In all cases, this may have been due to poor or limited reporting (in the case of abstracts), or, alternatively, it may have reflected true weaknesses in the studies. Consequently, the findings of the studies should be interpreted with great caution.

With regards to the analysis of the study data, all studies quoted at least some absolute values, but few provided an adequate description of statistical analyses used or the statistical significance of their findings. In addition, only two studies appeared to use survival analyses to interpret time to event data (i.e. survival, time to response, etc.). This made it difficult to assess the validity of the findings. In addition, as with RCTs, it is important that all participants recruited to the trial are included in the final analysis (i.e. that an ITT analysis is conducted), and only three studies reported what appeared to be true ITT analyses (studies 30-22, 30-47E and Cervantes and

co-workers[59]). One additional study reported an ITT analysis, but, because not all the original trial participants were included in the analysis, it was not a true ITT analysis (study 30-47). One other study that included participants with other forms of gynaecological cancers reported that a number of participants were dropped from the final analysis.[57] However, it was not reported whether these individuals had ovarian cancer and it was, therefore, unclear whether the analysis presented was a true ITT analysis or not.

Overall, the Phase II studies represent a lower level of evidence in terms of clinical effectiveness in comparison with the RCTs. All had a number of design issues (most notably the lack of a control group), which made them very vulnerable to bias. In addition, it was difficult to assess the effect of other factors that may have potentially affected the treatment outcomes. Issues related to specific studies and differences between the studies in terms of dose regimens and baseline population differences suggests that data from these studies should be treated with great caution. Consequently, only a limited discussion of the findings of these studies has been included in the report. Instead, the clinical effectiveness assessment focused on the much higher-quality (although limited) evidence from RCT 30-49. A summary of the quality of the Phase II studies is presented in *Table 6*. In addition, further details of the Phase II studies and their quality are reported in appendix 9.

Quality of economic evaluations

The economic analyses provided in both of the papers were based on trial 30-49. This trial was assessed in the quality of clinical effectiveness studies section on page 14 and was of reasonably good quality. The economic analyses assumed equivalence of outcomes between the two drugs, which may have been a conservative assumption in the face of the trends in favour of pegylated liposomal doxorubicin hydrochloride from the clinical trial. However, given the incidence of adverse events, which differ between pegylated liposomal doxorubicin hydrochloride and topotecan, equivalence in terms of quality-adjusted life-years (QALYs) had not been established or justified. It may have been the case that those adverse events that had a higher incidence in patients randomised to pegylated liposomal doxorubicin hydrochloride (e.g. PPE) had HRQoL effects which, when valued in terms of QALYs together with all other adverse events and survival duration, made the assumption of equivalence in terms of health outcomes unsafe. CUAs would, therefore, have been preferable study designs. Furthermore, the use of CMAs has the effect of removing an important source of uncertainty (in effectiveness), which should ideally have been incorporated into the analyses. These limitations may have jeopardised the safety of the key conclusions of the analyses. Sensitivity analyses were undertaken to assess the robustness of the results to sources of uncertainty, in particular the extent to which clinical practice in the trial was generalisable to the NHS (e.g. management of adverse events). A summary of the quality of the economic evaluations is presented in appendix 6, and further details of the evaluations are reported in appendix 10.

Adherence to NICE technical guidance

Both reported economic evaluations took the perspective of an NHS/third-party payer. NICE technical guidance advises an NHS and Personal Social Services decision maker. Few costs, which were likely to differ between the treatment options, occurred outside the hospital, and, therefore, the NHS perspective was adequate. CMAs would be consistent with NICE guidance as long as trial 30-49 had safely demonstrated equivalence in health outcomes. As argued above, this seemed to be the case in terms of overall survival, but not in terms of HRQoL. CUAs would have, therefore, been preferable. The timeframe was reasonable given the short life expectancy of these patients. Other comparators could have been included in addition to topotecan (particularly as the evidence for the latter was limited). The study was carried out internationally, and resource use was estimated locally from expert panels. There could be some concern that the UK-based data were actually data from several countries within Europe (although the UK made up the largest contributor of patients into the trial). Clinical data were presented showing the effectiveness results of the equivalence trial, but did not form part of the economic analyses. Resource use and costs were handled appropriately, while discounting was not appropriate. Incremental costs were presented, however, incremental effects were not appropriate for cost-minimisation. Uncertainty in cost data was dealt with and confidence intervals (CIs) around mean costs were presented. Uncertainty in the effectiveness data was not accounted for because the effects of the two drugs were assumed to be the same. An assessment of budgetary impact was provided, and the potential equity issues were discussed.

TABLE 6 *Quality of effectiveness studies (Phase II studies)*

Quality criteria	30-22[50,51]	30-47[52-55]	30-47E[56]	Israel *et al.*[57]	Linardou *et al.*[58]	Cervantes *et al.*[59]
Were the study participants adequately described (age, treatment-free interval, histology, performance status, number of previous regimens, disease bulk)?	Yes	Yes*	Yes	Yes	No	Yes
Did the researchers clearly state their aims?	Yes	Yes	Yes	Yes	Yes	Yes
Was a control group used?	No	No	No	No	No	No
Should a control group have been used?	Yes	Yes	Yes	Yes	Yes	Yes
Was the study design the best design to address the researchers' aims?	No	No	No	No	No	No
Were the participants followed up over a sufficiently long period of time?	Yes	Yes	Yes	Yes	Unclear	Not stated
Was an adequate sample size used (i.e. did the authors justify the size statistically)?	Yes†	Yes	Unclear	Not stated	Not stated	Not stated
Were the outcome measures likely to be valid (e.g. were the assessors blinded or was independent verification used)?	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated
Was compliance with the study treatment monitored and discussed?	Yes†	Yes*	Yes	Not stated	Not stated	Not stated
Were any relevant outcomes not assessed?	Yes	Yes	Yes	Yes	Yes	Yes
Were the statistical methods used described adequately?	Yes†	Yes*	Yes	Yes	No	No
Did any untoward events happen during the trial, which could have affected the findings?	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated
Did the researchers use a survival analysis where appropriate?	Yes†	Yes*	Yes	Yes	Not stated	Not stated
Were all participants accounted for in the analysis (i.e. was an ITT analysis used)?	Yes	No‡	Yes	Unclear	No	Yes
Were the basic data described adequately (e.g. absolute numbers quoted)?	Yes	Yes	Yes	Yes	Yes	Yes
Was the statistical significance of the findings reported (e.g. *p*-values, 95% CIs)?	Partially†	Yes	Yes	No	No	No
Could any other factors have affected the outcomes (e.g. patient characteristics, etc.)?	Yes	Yes	Yes	Yes	Yes	Yes
Were null findings interpreted appropriately?	Yes	Yes	Yes	Yes	Yes	Yes
Were important effects overlooked?	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear

* *Additional information obtained from the full trial report supplied by Schering-Plough Ltd*[55]
† *Additional information obtained on request from Schering-Plough Ltd*
‡ *The authors stated that an ITT analysis was performed, but this was not in fact a true ITT analysis because not all randomised participants were included in the analysis*

Yes, item adequately addressed; No, item not adequately addressed; Partially, item partially addressed; Unclear, unclear or not enough information; NA, not applicable

Assessment of clinical effectiveness

The following section describes the clinical effectiveness data from trial 30-49 (Schering-Plough Ltd) and the six Phase II studies (30-22, Schering-Plough Ltd; 30-47, Schering-Plough Ltd; 30-47E, Schering-Plough Ltd; Israel and colleagues[57]; Linardou and co-workers[58] and Cervantes and colleagues[59]). This section of the report, as outlined in the methods section, aimed to assess the clinical effectiveness of pegylated liposomal doxorubicin hydrochloride using the best-quality evidence available, that is, RCTs. Consequently, this section of the report focuses on trial 30-49 and, for reasons related to the quality issues previously discussed, only a brief discussion of the Phase II study data is included.

Trial 30-49 gathered data relating to six main outcomes and each outcome is discussed separately. The Phase II studies focused on only three main outcomes: response, survival and the incidence of adverse events. Due to the obvious heterogeneity between the Phase II studies (i.e. differences in treatment regimens and the characteristics of the study populations), it was not possible to pool the data from these studies.

Assessment of clinical effectiveness using trial 30-49

RRs were calculated for the data relating to response rate, adverse events and QoL where absolute numbers were quoted. Where appropriate, the RR data has also been presented in the form of forest plots. The study did not present RR data, and if the CIs crossed the line of no effect (i.e. 1), the RR estimate was considered not to be statistically significant (p-values ≤ 0.05 were considered statistically significant). No comments have been made about the clinical significance of the findings and this issue was not addressed in the trial reports for 30-49.

The remaining outcomes (overall survival, median survival time, time to response, time to progression and response duration) all involve what is termed survival data or time to event data. These types of data require special consideration and statistical analysis in the form of Kaplan–Meier estimates, survival curves and HRs. All of these statistical methods take into account the fact that the outcome of interest may never be observed over the period of follow-up (i.e. observations may be censored) and that, throughout the follow-up period, individuals will be lost to the analysis.

Kaplan–Meier survival curves for the main time to event outcomes (i.e. survival and time to progression) were given in the trial reports for 30-49 and these have been reproduced in this report by kind permission of the manufacturers, Schering-Plough Ltd.[47] HRs were also clearly reported, although only for the main time to event data, with 90% CIs instead of the usual 95% CIs. In the interim data for trial 30-49, 91.6% CIs were quoted. No explanation for the change in CIs was given although both sets of CIs were available for a small number of effects and, where available, these have been quoted. However, the main findings of the trial were based on the 90% CIs. In order to present the data in more usual form, the 90% CIs were converted to 95% CIs using the following formula:

$$\ln 95\%\ \text{lower CI} = \ln \text{HR} - [1.96 \times (\ln \text{of HR} - \ln \text{of lower 90\% CI})/1.645]$$

$$\ln 95\%\ \text{upper CI} = \ln \text{HR} + [1.96 \times (\ln \text{of HR} - \ln \text{of lower 90\% CI})/1.645]$$

where ln is the natural log and 1.645 is the z-value for 90%. The ln 95% CIs values were then converted back to 95% CIs.

For certain outcomes, such as survival and time to progression, a number of subgroup analyses were reported in the trials. Such subgroup analyses can be informative, but can also be very much open to bias. Where such analyses involve small numbers of participants, as was the case in the trial reported in this review, the significance of the findings should be interpreted with great caution. It is likely with such a large number of subgroups with small numbers of participants that what appeared to be statistically significant results were in fact purely the result of chance because such statistical tests have reduced power in these circumstances. However, the results of the various subgroup analyses have been reported in the following assessment of clinical effectiveness taking into account the aforementioned caveats. In addition, where an apparently statistically significant difference in effect was observed, a statistical test for interaction was performed in order to assess whether there was a statistically significant interaction between the subgroup characteristic and the outcome of interest. This was achieved by calculating a value for delta (Δ) with 95% CIs and p-values as follows:

Δ = ln HR of significant subgroup – ln HR of other subgroup

SE of $\Delta = \sqrt{((\text{SE of ln HR of significant subgroup})^2 + (\text{SE of ln HR of other subgroup})^2)}$

$p = \Delta / \text{SE of } \Delta$

Lower 95% CI = $\Delta - (\text{SE of } \Delta \times 1.96)$

Upper 95% CI = $\Delta + (\text{SE of } \Delta \times 1.96)$

where SE is the standard error. A statistically significant delta suggests that there is a significant interaction between the subgroup and the outcome.

Where possible, only ITT data have been presented in this report. However, as has been previously discussed in the quality of clinical effectiveness studies section on page 14, true ITT analyses were not performed despite claims by the authors that ITT data were presented. ITT analyses should include all patients initially involved in the randomisation procedure and patients should be analysed according to the groups to which they were originally assigned rather than the groups they were finally assigned to. Analyses should also include all dropouts and withdrawals that may have occurred. In this respect, they give a more conservative estimate of clinical effects that more closely resemble effects observed in clinical practice. Seven participants were missing from the final analyses of trial 30-49 that were lost prior to the start of treatment. Further details regarding the reason and intervention assignment of these participants were not provided and it was, therefore, not possible to reassess the study outcomes in terms of a true ITT analysis. Consequently, the ITT analysis reported by the trialists was used. This should be borne in mind when interpreting the findings of the trial. Further details of trial 30-49 and its outcomes are reported in appendix 8.

Survival

Survival is usually defined as the time from randomisation until death. However, survival time was not defined in trial 30-49, although the median survival times were appropriately based on Kaplan–Meier estimates (see *Table 7*) and derived from the accompanying survival curves (see *Figure 2*). No statistically significant differences in survival were reported for pegylated liposomal doxorubicin hydrochloride versus topotecan. This is reflected in the Kaplan–Meier curve (*Figure 2*), which shows little overall difference between the curves for the two drugs. A small difference is observed in the later stages of the curves, but this corresponds to a period where few participants remain in the analysis (i.e. > 600 days after randomisation).

Trial 30-49 also performed a subgroup analysis (using Cox regression) according to a variety of potentially important baseline patient characteristics, including age, Karnofsky performance status, drug-free interval after first-line therapy, the presence or absence of bulky disease, platinum sensitivity and the presence or absence of ascites. These data are shown in *Table 8*. However, as has already been discussed, subgroup analyses can be very unreliable and misleading, particularly where the groups only contain small numbers of participants as in this instance. Therefore, the following analyses should be treated with great caution.

Only one of the differences was significant as indicated by the CIs of the HR. This favoured pegylated liposomal doxorubicin hydrochloride over topotecan with respect to patients with platinum-sensitive disease (108.0 versus 71.1 weeks; HR = 1.720, 95% CI, 1.145 to 2.585). An interaction test showed that $\Delta = 0.256$ (95% CI, 0.151 to 1.155), $p = 0.011$, suggesting that there was a statistically significant interaction between platinum sensitivity and survival (i.e. a difference of the treatment differences observed in the subgroups), and consequently the observation that pegylated liposomal doxorubicin hydrochloride is more effective than topotecan in this group of patients may be of interest.

Taking into account all of the above baseline factors in the regression analysis, the adjusted HR (1.073, CI not stated) for overall median survival time was similar to the unadjusted HR (1.121, 95%

TABLE 7 *Summary of survival data based on ITT analyses for pegylated liposomal doxorubicin hydrochloride versus topotecan*[47]

Outcome	Pegylated liposomal doxorubicin hydrochloride	Topotecan	*p*-value	HR
Median survival time (weeks) based on Kaplan–Meier estimates	60.0	56.7	0.34	1.121 (95% CI, 0.886 to 1.419)

* *95% CIs were estimated from the original 90% CIs (quoted by the authors of the trial report) using the formula on page 19*

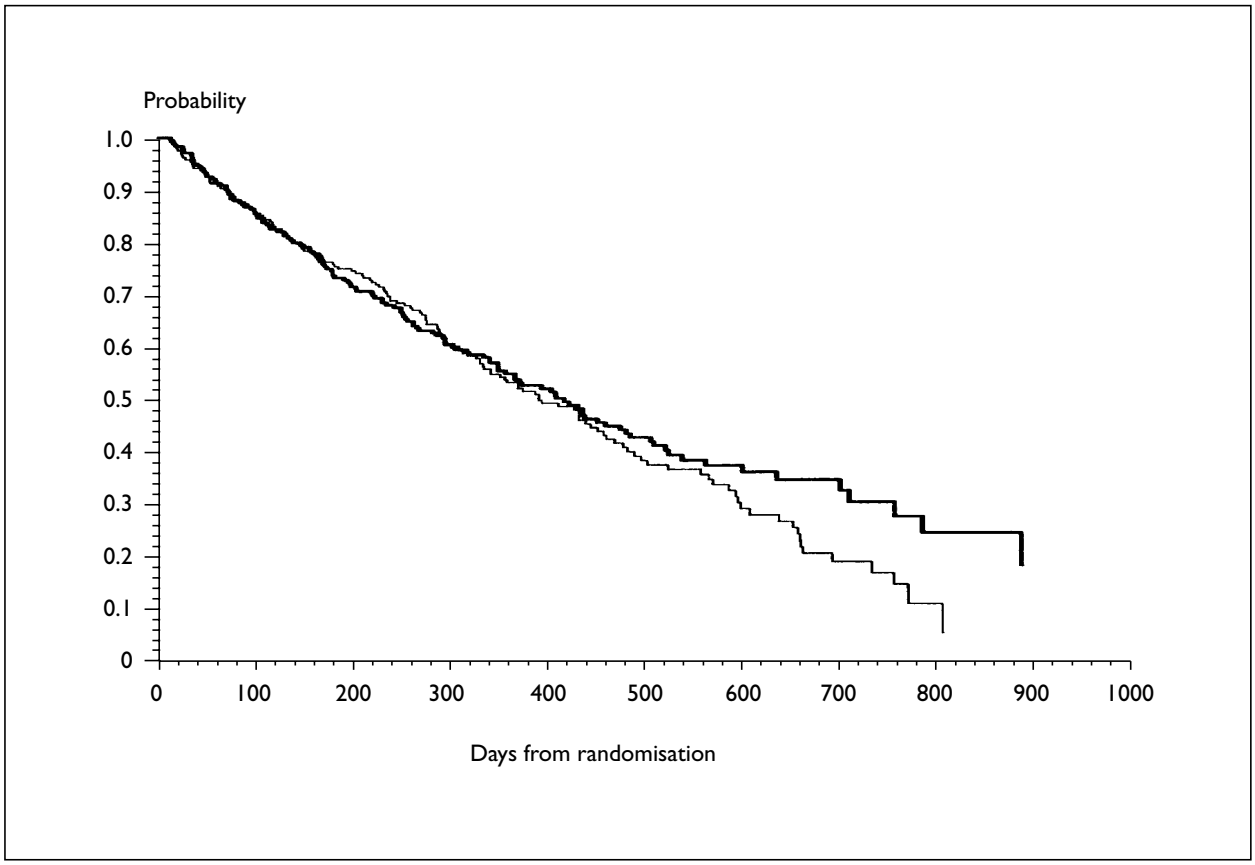


FIGURE 2 *Kaplan–Meier survival curves for pegylated liposomal doxorubicin hydrochloride versus topotecan for overall survival of the ITT population (reproduced with kind permission of Schering-Plough Ltd[47]).* ▬ *, pegylated liposomal doxorubicin hydrochloride;* ——*, topotecan*

CI, 0.886 to 1.419). The statistical significance of this adjusted HR was not stated, although, considering the significance of the unadjusted HR, it was likely to be non-significant. However, the adjusted HR did suggest that the general findings with regard to survival time were not significantly influenced by the identified baseline factors.

Response rate (including complete and partial response)

Response rates can be a very subjective endpoint, particularly when the assessor is not independent or blinded to the intervention assignment, as was initially the case in trial 30-49. Subsequently, the response outcomes for trial 30-49 were subjected to independent assessment. The revised figures were requested from Schering-Plough Ltd but were not available at the time of this review.

A responder was defined as a patient with at least a durable (complete or partial) response. A durable response was the patient's maximum confirmed response. A complete response 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 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.

Figure 3 shows the data relating to the incidence of complete, partial and total responses for trial 30-49 (pegylated liposomal doxorubicin hydrochloride versus topotecan).[47,48] RR data suggest that there are no statistically significant differences between pegylated liposomal doxorubicin hydrochloride and topotecan with respect to the number of complete, partial and total responses (see *Figure 3*).

Response rate data were also presented according to the baseline response of the patients to first-line platinum therapy, that is, whether patients were platinum sensitive or refractory (see *Figure 4*). This is thought to be an important factor in determining patients' response to treatment and their survival. *Figure 4* shows that there were no statistically significant differences between pegylated liposomal doxorubicin hydrochloride and topotecan in terms of response rates (complete, partial or total) for any of the groups of patients in trial 30-49.

TABLE 8 *Summary of subgroup analyses (using Cox regression) of survival data based on baseline characteristics for pegylated liposomal doxorubicin hydrochloride versus topotecan*[47]

Subgroup (baseline)	Pegylated liposomal doxorubicin hydrochloride (*n* = 239)	Topotecan (*n* = 235)	HR (95% CI)*
Age < 65 years	Median = 62.7 weeks (156/239)	Median = 56.3 weeks (138/235)	1.143 (95% CI, 0.844 to 1.548)
Age ≥ 65 years	Median = 58.1 weeks (83/239)	Median = 62.1 weeks (97/235)	1.008 (95% CI, 0.684 to 1.485)
Karnofsky performance status < 80	Median = 19.6 weeks (39/239)	Median = 20.6 weeks (37/235)†	0.847 (95% CI, 0.500 to 1.435)
Karnofsky performance status ≥ 80	Median = 66.0 weeks (200/239)	Median = 65.7 weeks (194/235)†	1.147 (95% CI, 0.876 to 1.501)
≤ 6 months drug-free interval after first-line therapy	Median = 35.6 weeks (102/239)	Median = 39.4 weeks (109/235)	1.017 (95% CI, 0.738 to 1.402)
> 6 to ≤ 18 months drug-free interval after first-line therapy	Median = 74.7 weeks (107/239)	Median = 70.1 weeks (94/235)	1.126 (95% CI, 0.766 to 1.655)
> 18 months drug-free interval after first-line therapy	Median = 112.1 weeks (30/239)	Median = 94.4 weeks (32/235)	1.782 (95% CI, 0.681 to 4.662)
Bulky disease present	Median = 53.7 weeks (111/239)	Median = 49.0 weeks (111/235)	1.093 (95% CI, 0.691 to 1.511)
Bulky disease absent	Median = 74.7 weeks (128/239)	Median = 66.1 weeks (124/235)	1.154 (95% CI, 0.819 to 1.627)
Sensitive to platinum	Median = 108.0 weeks (109/239)	Median = 71.1 weeks (111/235)	1.720 (95% CI, 1.145 to 2.585)
Refractory to platinum	Median = 35.6 weeks (130/239)	Median = 41.3 weeks (124/235)	0.895 (95% CI, 0.668 to 1.199)
Ascites present	Median = 28.1 weeks (77/239)	Median = 39.4 weeks (65/235)†	0.982 (95% CI, 0.665 to 1.450)
Ascites absent	Median = 77.0 weeks (162/239)	Median = 63.9 weeks (168/235)†	1.330 (95% CI, 0.975 to 1.814)

* *95% CIs were calculated from the original 90% CIs (quoted by the authors of the trial report) using the formula on page 19*
† *Data taken from the study report. Discrepancies in the total number of participants in each group may be due to missing patient data*

Time to response

Time to response was considered a secondary and not a primary outcome measure in trial 30-49 and limited data were, therefore, reported. Data were expressed as the median time to response, although no exact definition of the outcome measure was provided. A summary of the time to response data is presented in *Table 9*. The data were not reported in the form of HRs and survival curves. However, no significant difference in median time to response was reported between pegylated liposomal doxorubicin hydrochloride and topotecan in trial 30-49, as indicated by *p*-values.

Duration of response

Duration of response is usually defined as the time from the initial documented response to the first sign of disease progression. Progression is defined as a > 25% increase in a single measurable lesion, reappearance of measurable disease, clear worsening of evaluable disease, appearance of any new lesions, including brain metastases, even if there was response outside of the brain or significant worsening of a condition presumed to be related to the malignancy. Trial 30-49 failed to supply an exact definition of the duration of response, but values were expressed in the form of a median time. Again, few data

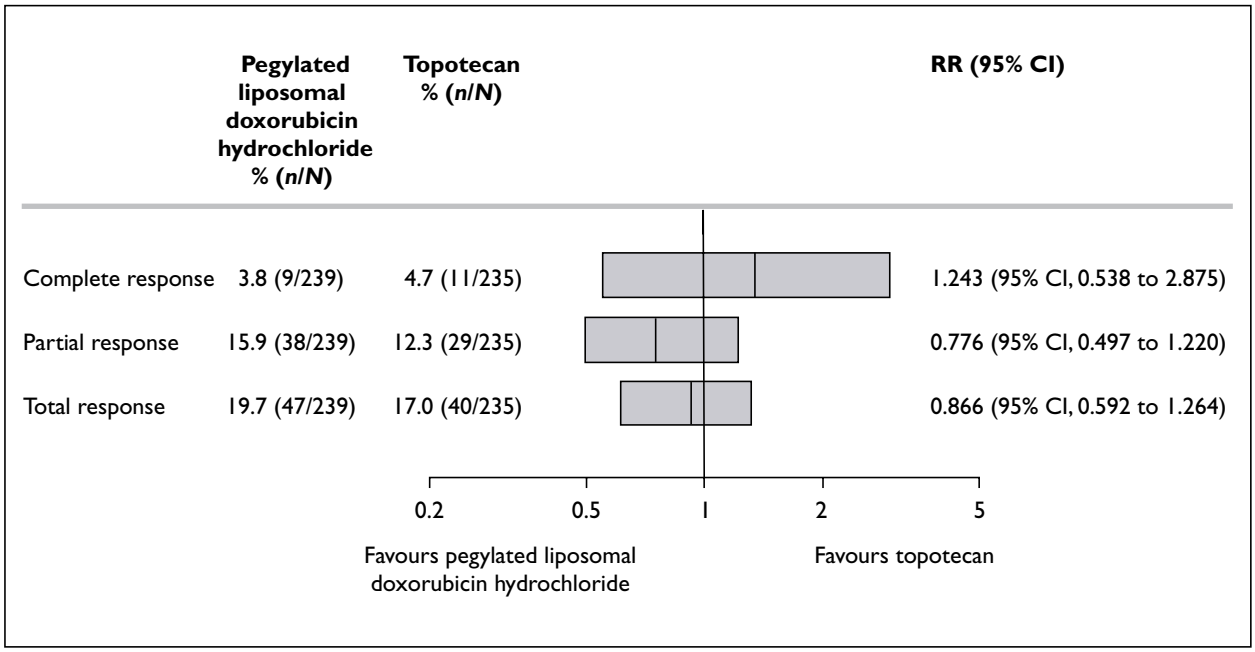


FIGURE 3 *RRs for response rates for pegylated liposomal doxorubicin hydrochloride versus topotecan based on ITT analyses*[47]

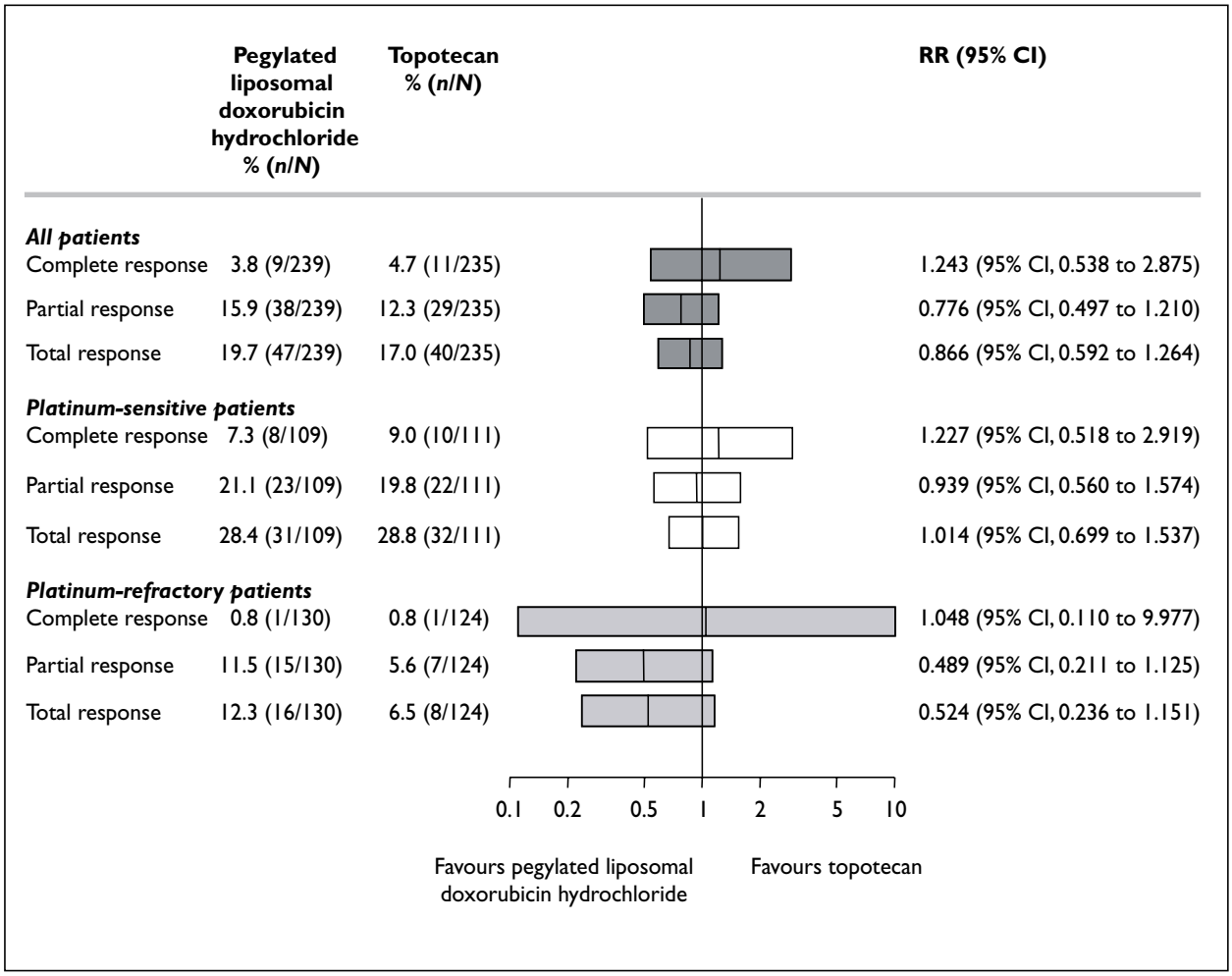


FIGURE 4 *RRs for response rates for pegylated liposomal doxorubicin hydrochloride versus topotecan subgroup analysis (baseline platinum sensitivity)*[47]

TABLE 9 *Summary of time to response data for pegylated liposomal doxorubicin hydrochloride versus topotecan*[47]

Outcome	Pegylated liposomal doxorubicin hydrochloride	Topotecan	*p*-value (log-rank test)	HR
Median time to response (weeks) based on Kaplan–Meier estimates	8.1 (range 4.0–28.4)	8.1 (range 5.6–44.1)	0.448	Not stated

TABLE 10 *Summary of duration of response for pegylated liposomal doxorubicin hydrochloride versus topotecan*[47]

Outcome	Pegylated liposomal doxorubicin hydrochloride	Topotecan	*p*-value (log-rank test)	HR
Median duration of response (weeks) based on Kaplan–Meier estimates	30.1 (*n* = 47; range 5.0–90.4)	25.7 (*n* = 40; range 7.0–55.1)	0.891	Not stated

TABLE 11 *Summary of time to progression data for pegylated liposomal doxorubicin hydrochloride versus topotecan based on ITT analyses*[47]

Outcome	Pegylated liposomal doxorubicin hydrochloride	Topotecan	*p*-value (log-rank test)	HR
Median time to progression (weeks) based on Kaplan–Meier estimates	16.1 (*n* = 239)	17.0 (*n* = 235)	0.095	1.176 (95% CI, 0.972 to 1.423)*

* *95% CIs were calculated from the original 90% CIs (quoted by the authors of the trial report) using the formula on page 19*

were presented as this was not considered a major outcome. A summary of the duration of response data is presented in *Table 10*. The data were not presented in the form of survival curves and HRs. However, *p*-values indicated that no statistically significant difference was observed between pegylated liposomal doxorubicin hydrochloride and topotecan in trial 30-49 with regards to the median duration of response.

Time to progression

Time to progression was reported in terms of median time to progression and was considered to be a major outcome measure in trial 30-49. Again, no specific definition of the outcome measure was provided. Usually, time to progression is defined as the time from randomisation until the development of progressive disease (progression as defined above) or the administration of an alternative therapy. A summary of the median time to progression data is presented in *Table 11*.

No statistically significant differences in time to progression were observed between pegylated liposomal doxorubicin hydrochloride and topotecan as judged by the reported *p*-value and 95% CIs shown in *Table 11*. Trial 30-49 also performed a subgroup analysis (using Cox regression) according to a variety of potentially important baseline patient characteristics, including age, Karnofsky performance status, drug-free interval after first-line therapy, the presence or absence of bulky disease, platinum sensitivity and the presence or absence of ascites. These data are shown in *Table 12*. Such subgroup analyses can be very unreliable and misleading, particularly where the groups only contain small numbers of participants, as in this instance. Therefore, the following analyses should be treated with great caution.

The only statistically significant differences in time to progression between pegylated liposomal doxorubicin hydrochloride and topotecan were reported in the absence of ascites (22.4 versus 19.1 weeks, respectively; HR = 1.295, 95% CI, 1.026 to 1.635) and the platinum-sensitive disease (28.8 versus 23.3 weeks, respectively; HR = 1.349, 95% CI, 1.018 to 1.788) subgroups. Both results appeared to favour pegylated liposomal doxorubicin hydrochloride over topotecan. However, as has already been stressed, these findings should be interpreted with caution and the calculated interaction (i.e. a measure of how independent the result is) showed that $\Delta = 0.254$ (95% CI, –0.129 to 0.638), $p = 0.194$ for the presence of platinum-sensitive disease and $\Delta = 0.331$ (95% CI, –0.093 to 0.755), $p = 0.126$ for the absence of ascites, suggesting that neither platinum sensitivity nor ascites were significantly associated with time

to progression. The observed differences between topotecan and pegylated liposomal doxorubicin hydrochloride are, therefore, unlikely to be of any clinical interest.

Taking into account all of the above baseline factors in the regression analysis, the adjusted HR (1.177, CI not stated) for overall median time to progression was similar to the unadjusted HR (1.176, 95% CI, 0.972 to 1.423). The statistical significance of this adjusted HR was not stated, but does suggest that the general findings with regards to time to progression were not significantly influenced by the identified baseline factors.

QoL

QoL was assessed using the European Organisation for Research and Treatment of Cancer (EORTC) QoL questionnaire-C30 (QLQ-C30). This questionnaire is self-administered and designed to measure HRQoL. It 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), in addition to six questions on 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 increased presence of symptoms.

TABLE 12 *Subgroup analysis of time to progression for pegylated liposomal doxorubicin hydrochloride versus topotecan (Cox regression analysis)*[47]

Subgroup	Pegylated liposomal doxorubicin hydrochloride	Topotecan	HR (95% CI)*
Age < 65 years	Median = 17.3 weeks (156/239)	Median = 16.1 weeks (138/235)	1.190 (95% CI, 0.932 to 1.520)
Age ≥ 65 years	Median = 14.7 weeks (83/239)	Median = 18.3 weeks (97/235)	1.147 (95% CI, 0.835 to 1.575)
Karnofsky performance status score < 80	Median = 7.6 weeks (39/239)	Median = 10.1 weeks (37/235)†	0.867 (95% CI, 0.523 to 1.438)
Karnofsky performance status score ≥ 80	Median = 18.7 weeks (200/239)	Median = 19.1 weeks (194/235)†	1.157 (95% CI, 0.939 to 1.426)
≤ 6 months drug-free interval after first-line therapy	Median = 8.1 weeks (102/239)	Median = 13.4 weeks (109/235)	1.095 (95% CI, 0.815 to 1.470)
> 6 to ≤ 18 months drug-free interval after first-line therapy	Median = 21.1 weeks (107/239)	Median = 18.7 weeks (94/235)	1.170 (95% CI, 0.874 to 1.566)
> 18 months drug-free interval after first-line therapy	Median = 41.4 weeks (30/239)	Median = 32.6 weeks (32/235)	1.530 (95% CI, 0.832 to 2.812)
Bulky disease present	Median = 13.1 weeks (111/239)	Median = 15.7 weeks (111/235)	1.143 (95% CI, 0.863 to 1.151)
Bulky disease absent	Median = 18.7 weeks (128/239)	Median = 18.3 weeks (124/235)	1.206 (95% CI, 0.929 to 1.565)
Sensitive to platinum	Median = 28.8 weeks (109/239)	Median = 23.3 weeks (111/235)	1.349 (95% CI, 1.018 to 1.788)
Refractory to platinum	Median = 9.4 weeks (130/239)	Median = 13.6 weeks (124/235)	1.046 (95% CI, 0.807 to 1.356)
Ascites present	Median = 9.0 weeks (77/239)	Median = 14.6 weeks (65/235)†	0.930 (95% CI, 0.653 to 1.325)
Ascites absent	Median = 22.4 weeks (162/239)	Median = 19.1 weeks (168/235)†	1.295 (95% CI, 1.026 to 1.635)

* *95% CIs were calculated from the original 90% CIs (quoted by the authors of the trial report) using the formula on page 19*
† *Data taken from the study report. Discrepancies in the total number of participants in each group may be due to missing patient data*

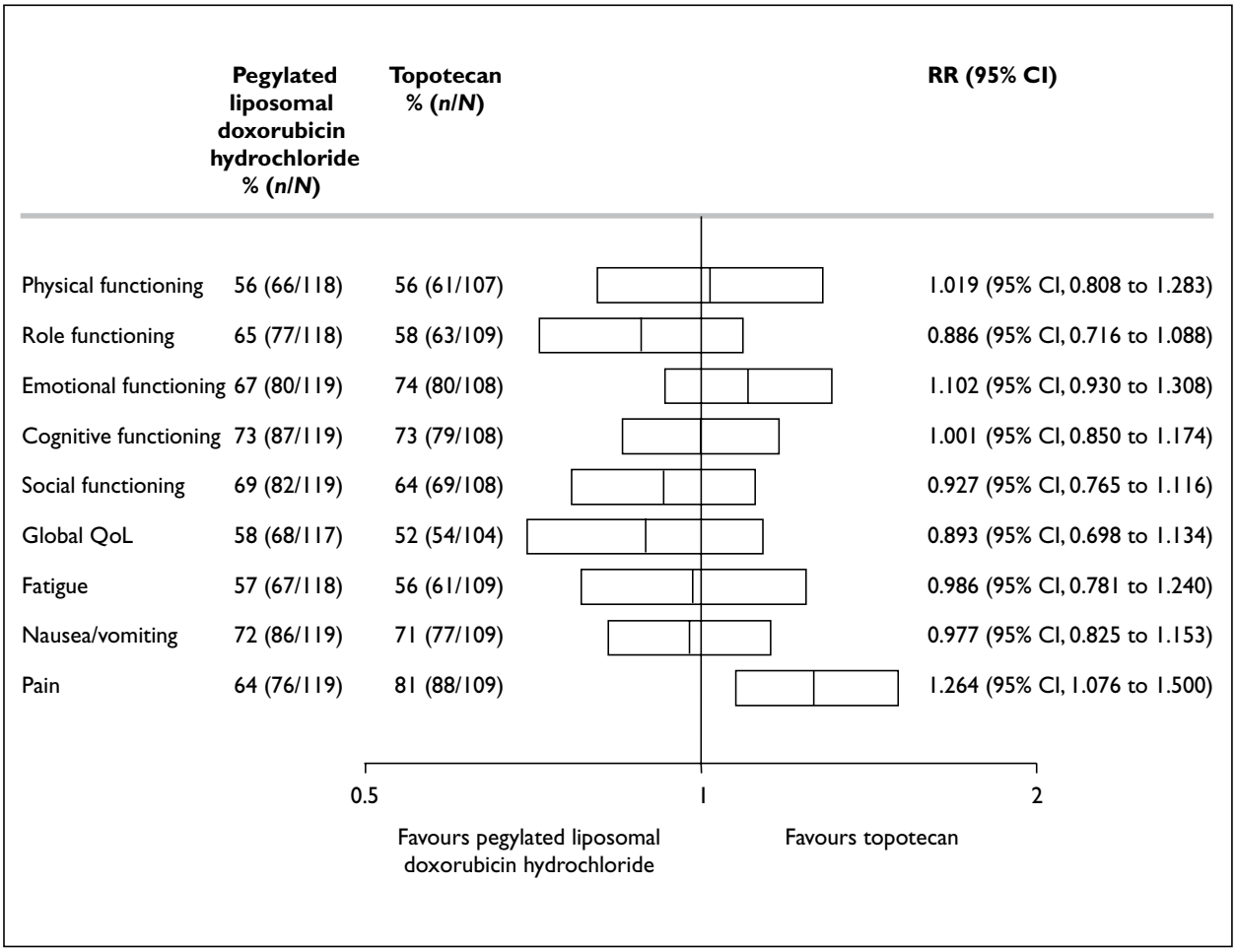


FIGURE 5 *RRs of number of patients with a maintained or improved QoL score at 12-week follow-up for pegylated liposomal doxorubicin hydrochloride versus topotecan (based on number of patients remaining) – all patients*

Assessments were made at baseline and at the start of each treatment cycle until 24 weeks of follow-up. Due to the difference in cycle length of the two drug regimens (topotecan was administered every 3 weeks and pegylated liposomal doxorubicin hydrochloride every 4 weeks), the first time point at which data could be gathered from the two study groups was week 12. At this point, 50% or fewer patients in either group provided QoL data. Again, scores were awarded for each of the individual QoL parameters and, in this case, the data analysed overall and in terms of baseline platinum sensitivity (i.e. platinum-resistant and platinum-sensitive patients). However, the scores for the single QoL questions (dyspnoea, sleep disturbance, appetite loss, constipation, diarrhoea and financial impact) were not presented.

At 12-week follow-up, 23.4% (55/235) of topotecan patients versus 28.5% (68/239) of pegylated liposomal doxorubicin hydrochloride patients had improved or stable global QoL scores and 20.4% (48/235) of topotecan patients versus 20.5% (49/239) of those on pegylated liposomal doxorubicin hydrochloride had worsened global QoL scores (based on ITT data). Neither of these observations were statistically significant (RR = 0.823, 95% CI, 0.605 to 1.122 and RR = 0.966, 95% CI, 0.700 to 1.418, respectively).

The numbers of patients with maintained or improved scores for each of the subscales dependent on their platinum sensitivity at baseline is shown in *Figures 5–7*. The corresponding RRs were calculated and are also shown in *Figures 5–7*. The number of patients (all patients) with a maintained or improved pain subscale at 12 weeks showed a statistically significant difference in favour of topotecan (RR = 1.264, 95% CI, 1.076 to 1.500; see *Figure 5*). The number of platinum-sensitive patients with a maintained or improved pain subscale at 12 weeks also showed a statistically significant difference in favour of topotecan (RR = 1.542, 95% CI, 1.211 to 2.023; see *Figure 6*). However, the clinical relevance of this observation was

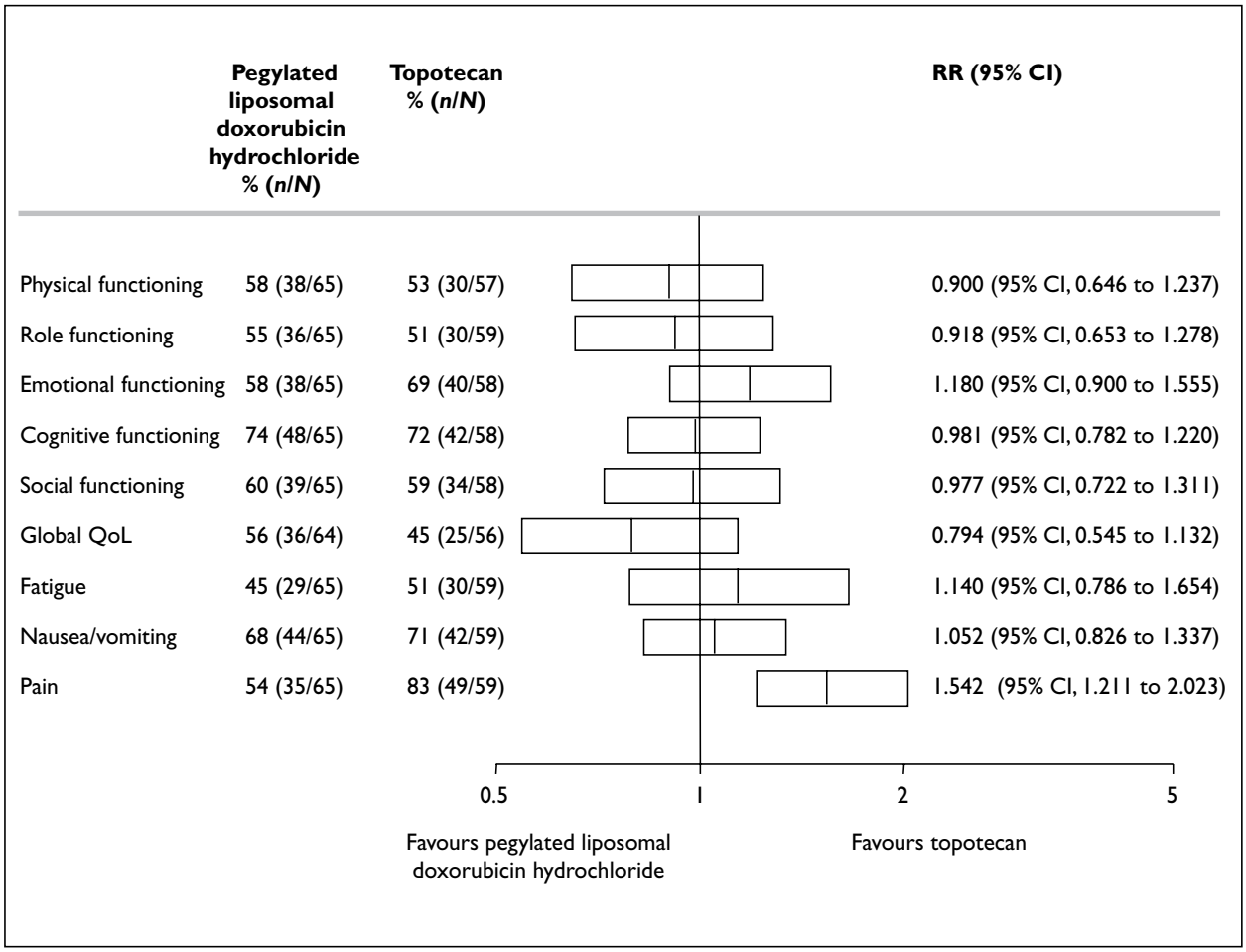


FIGURE 6 *RRs of number of patients with a maintained or improved QoL score at 12-week follow-up for pegylated liposomal doxorubicin hydrochloride versus topotecan (based on number of patients remaining) – platinum-sensitive patients*

unclear. Overall, there was little difference between the two drugs in terms of patient QoL, as measured using the QLQ-C30.

Quality-adjusted survival analysis

Treatments may vary not only in terms of their effect on survival duration, but also in terms of their effect on QoL. Quality-adjusted survival analysis is an approach that compares treatments taking into account both the QoL and quantity of life of a patient.[61–66] For study 30-49, a widely-used quality-adjusted survival methodology, quality-adjusted time without symptoms or toxicity (Q-TWiST) was used to compare pegylated liposomal doxorubicin hydrochloride and topotecan.[67]

Time without symptoms or toxicity (TWiST) is, as it states, the period of time during which the average patient experiences no symptoms or toxicity, and a higher TWiST is desirable. *Figure 8* shows the overall survival curve for each treatment group partitioned into the three health states: toxicity (time a patient reported a grade 3 or higher toxicity), progression (time from relapse until death or 15 months following randomisation, whichever occurred first) and TWiST (time a patient was not in progression or toxicity). The areas between the consecutive curves represent the average time patients spent in each particular health state.

The graphs in *Figure 8* were provided by Schering-Plough Ltd in the final company submission.[67] According to the graph, there is no overlap between the regions of TWiST and progression, indicating that the definition of progression required an occurrence (or recurrence) of symptoms. Therefore, progression without symptoms was not taken into account. Instead of progression-free survival, it would have been better if they called this symptom-free survival. Both the final company submission and the individual trial report for 30-49 were searched, but the company's definition of progression-free survival was not found.

Compared to topotecan, pegylated liposomal doxorubicin hydrochloride has smaller toxicity and

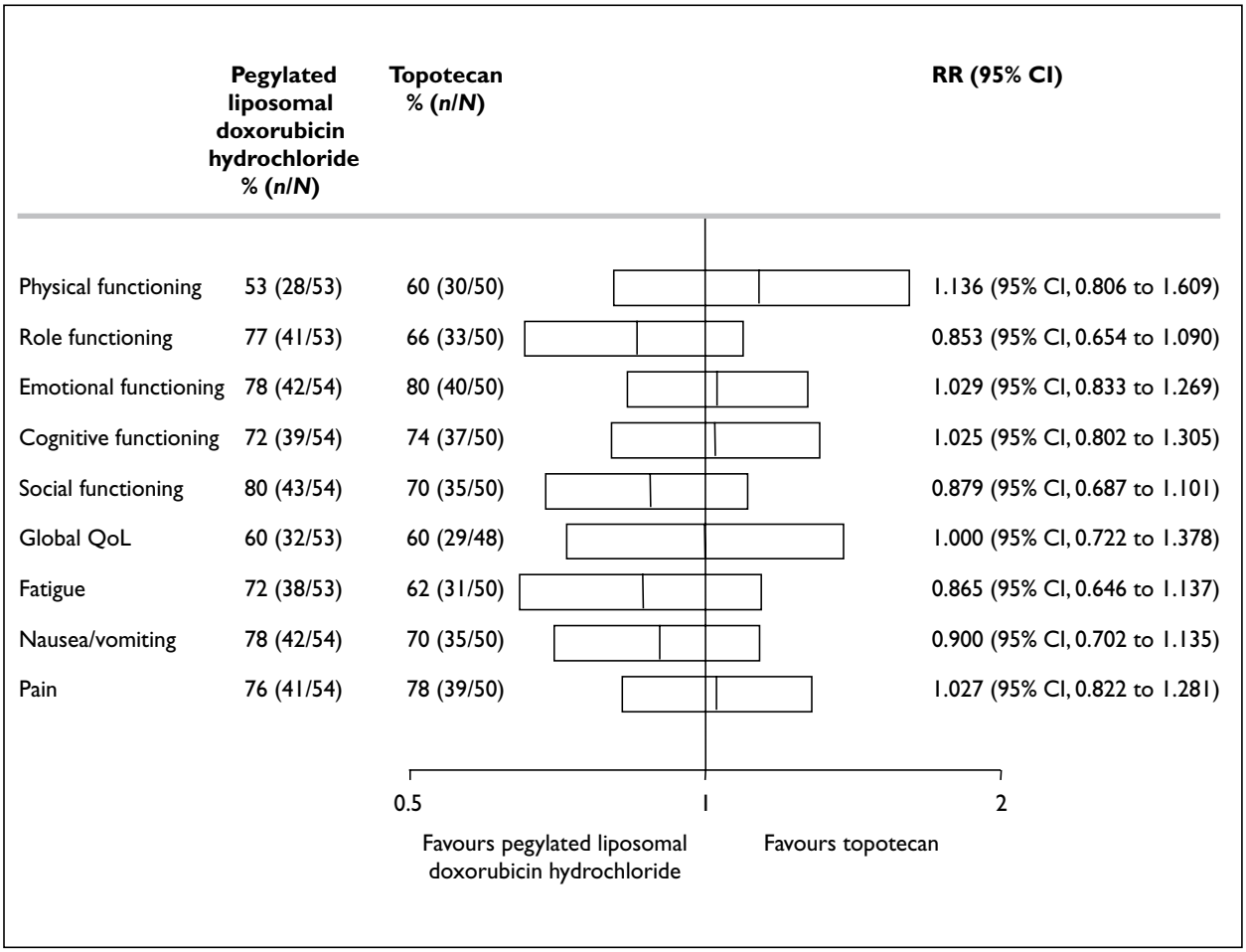


FIGURE 7 *RRs of number of patients with a maintained or improved QoL score at 12-week follow-up for pegylated liposomal doxorubicin hydrochloride versus topotecan (based on number of patients remaining) – platinum-resistant patients*

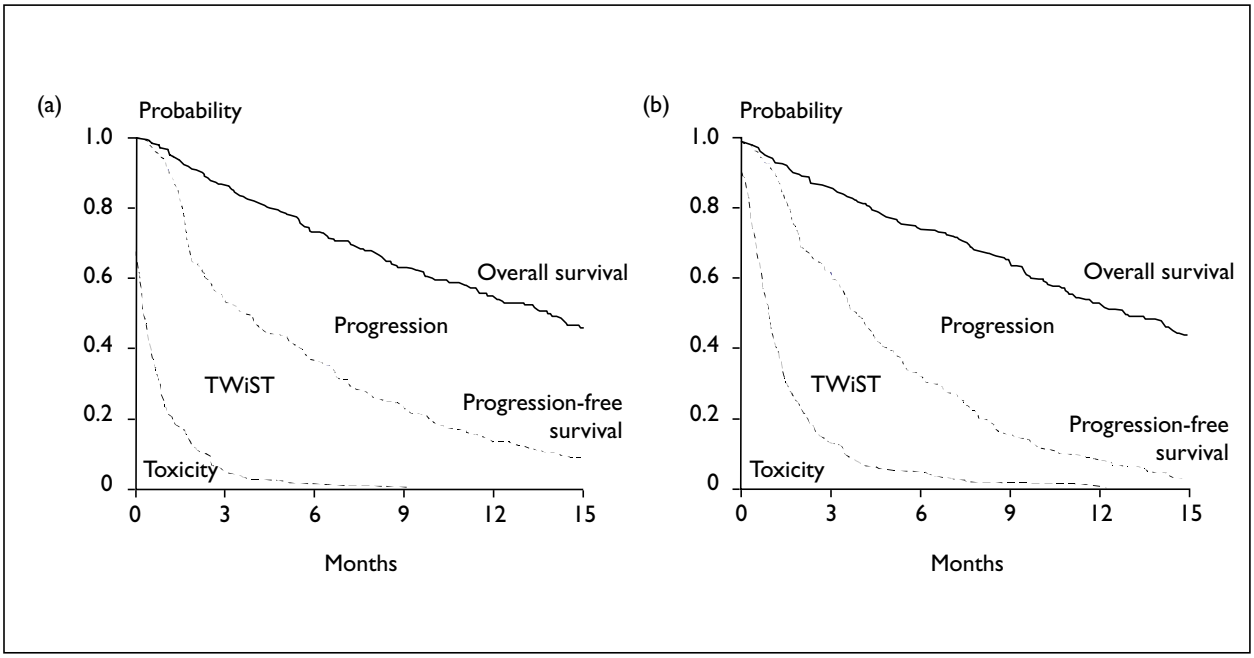


FIGURE 8 *Q-TWiST survival analysis: partitioned survival curves (study 30-49) of (a) pegylated liposomal doxorubicin hydrochloride and (b) topotecan*[67]

progression regions, while the TWiST region is noticeably larger. In other words, patients treated with pegylated liposomal doxorubicin hydrochloride spent more time in the good health state of TWiST and less time in the poor health states of toxicity and progression compared to topotecan-treated patients. The average times in these three health states for the two treatment groups and their differences are presented in *Table 13*.

Q-TWiST combines the toxicity, TWiST and progression areas into a single measure by summing the time spent in these health states weighted by their relative importance (which are referred to as 'utilities'). These 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 toxicity and progression penalised treatments for toxicity and disease progression periods.

Figure 9 shows that for all combinations of the utility values, Q-TWiST would always favour pegylated liposomal doxorubicin hydrochloride. Moreover, this difference was statistically significant in the area below the line in *Figure 9*. Pegylated liposomal doxorubicin hydrochloride provides both lower treatment toxicity and better treatment effect compared to topotecan, and thus improved Q-TWiST.

Overall, the Q-TWiST analysis suggested that although the overall survival was similar for pegylated liposomal doxorubicin hydrochloride and topotecan, when QoL outcomes, such as toxicity and progression, were also taken into account pegylated liposomal doxorubicin hydrochloride had advantages over topotecan. However, the

TABLE 13 *Time (in months) spent in the three health states and their differences (study 30-49)*[67]

Health states	Pegylated liposomal doxorubicin hydrochloride	Topotecan	Difference
Toxicity	0.84	1.54	–0.70 (95% CI, –1.04 to –0.36)
TWiST	4.65	3.51	1.14 (95% CI, 0.46 to 1.82)
Progression	5.07	5.53	–0.46 (95% CI, –1.31 to 0.39)

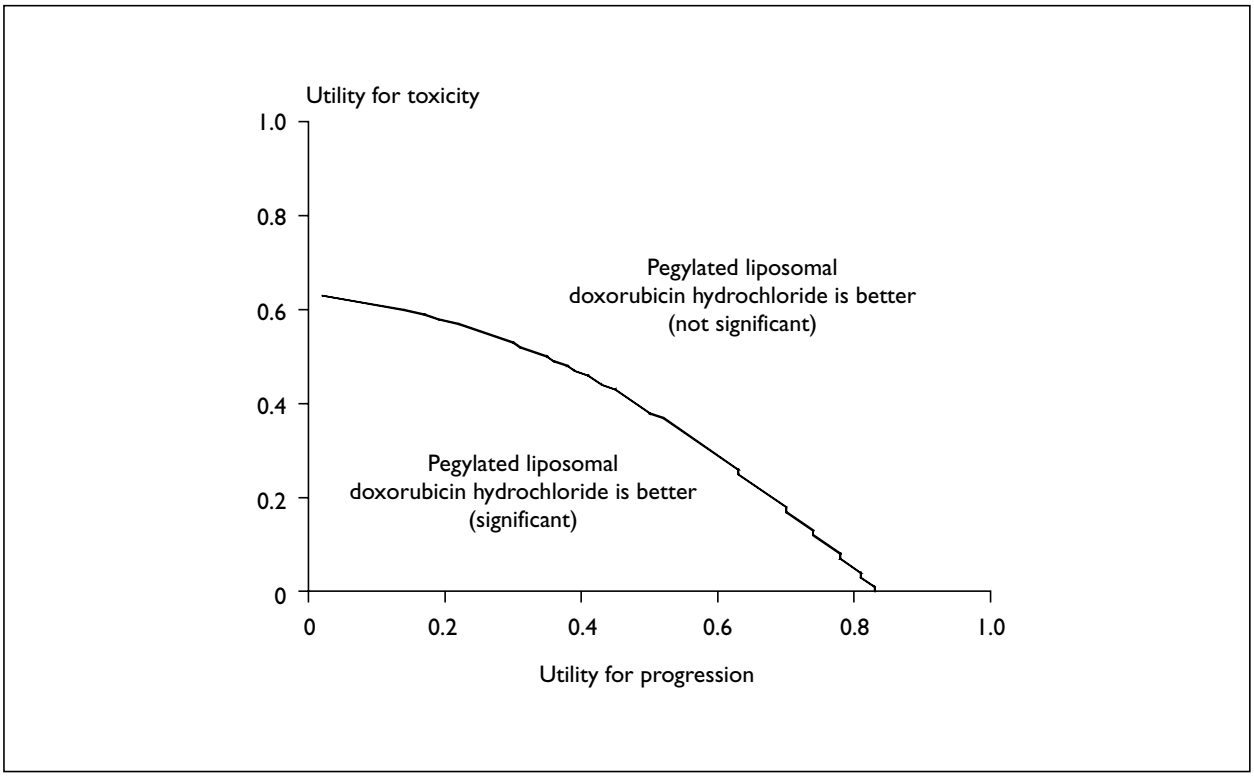


FIGURE 9 *Q-TWiST threshold utility analysis (study 30–49)*[67]

Q-TWiST analysis included a major assumption that may not be justified, namely that a day with toxicity was valued the same (in terms of utility) whatever the type of adverse event the patient was experiencing. For example, if the adverse event of PPE, which had a higher incidence with pegylated liposomal doxorubicin hydrochloride, resulted in a greater decrement in utility than other adverse events, then pegylated liposomal doxorubicin hydrochloride patients may have experienced lower Q-TWiST than topotecan patients. A full analysis of quality-adjusted survival should weight patients' QoL according to the actual health states they experience, including the period without either toxicity or progression when QoL may still be less than perfect. The use of QALYs is similar to Q-TWiST, although the utilities are often based on public valuations rather than those of patients, and a broader array of health states would usually be considered than solely toxicity and progression.

Adverse events

Extensive data on adverse events were gathered in trial 30-49. However, only those treatment-related effects experienced by at least 10% of patients are discussed. Data presented are based on the ITT population as defined by the study. The trial did not report the data in terms of RRs and thus where absolute numbers of patients suffering from an effect were reported, these data have been used to calculate RRs with 95% CIs.

A number of adverse events were reported for both pegylated liposomal doxorubicin hydrochloride and topotecan.[46,47] The adverse events for pegylated liposomal doxorubicin hydrochloride were as previously reported in the *BNF*. The major toxicity was PPE. This condition is 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 unknown, but is believed to be a result of microtrauma within tissue leading to leaky blood vessels.

The main toxic effects of topotecan centred on haematological problems, such as neutropenia, thrombocytopenia and anaemia. All of these conditions relate to the reduction of specific blood cells (neutrophils, thrombocytes and red blood cells/erythrocytes, respectively) within the body, and affect the body's ability to fight infection, coagulate blood and carry oxygen, respectively. In contrast, haematological adverse events were mild/moderate in pegylated liposomal doxorubicin hydrochloride-treated patients.

Overall, in trial 30-49, 16% (39/239) of patients treated with pegylated liposomal doxorubicin hydrochloride and 12% (29/235) of patients treated with topotecan discontinued treatment due to adverse events (RR = 0.756, 95% CI, 0.485 to 1.175). Two patients treated with topotecan died as a result of treatment-related adverse events in the form of grade 3/4 neutropenia. No treatment-related deaths were recorded in those patients treated with pegylated liposomal doxorubicin hydrochloride. *Table 14* and *Figure 10* show further details of the adverse events experienced in the two study groups.

Table 14 and *Figure 10* show that the main toxicities associated with pegylated liposomal doxorubicin hydrochloride were PPE, stomatitis, mucous membrane disorders and skin rashes, of which PPE and stomatitis represented the greatest problems. The incidences of PPE (49 versus 1%; RR = 0.017, 95% CI, 0.005 to 0.063) and stomatitis (40 versus 15%; RR = 0.375, 95% CI, 0.265 to 0.525) were significantly higher in the pegylated liposomal doxorubicin hydrochloride-treated patients than in those treated with topotecan. PPE was classed as severe in 23% of patients treated with pegylated liposomal doxorubicin hydrochloride and severe stomatitis was experienced by 8% of the patients. The steps taken to manage these effects were not stated. The incidences of mucous membrane disorders (14 versus 3%; RR = 0.216, 95% CI, 0.099 to 0.466) and skin rashes (24 versus 8%; RR = 0.316, 95% CI, 0.192 to 0.514) were also significantly higher in patients treated with pegylated liposomal doxorubicin hydrochloride than in those treated with topotecan.

The most common treatment-related adverse events associated with topotecan in trial 30-49 were haematological toxicities (neutropenia, anaemia, thrombocytopenia and leukopenia), nausea/vomiting and alopecia, as described previously. All of these toxicities were significantly more frequent and more severe in topotecan-treated patients than in patients treated with pegylated liposomal doxorubicin hydrochloride: neutropenia (81 versus 35%; RR = 2.313, 95% CI, 1.938 to 2.793), anaemia (72 versus 36%; RR = 2.022, 95% CI, 1.6383 to 2.453), thrombocytopenia (65 versus 13%; RR = 4.987, 95% CI, 3.576 to 7.048), leukopenia (63 versus 36%; RR = 1.742, 95% CI, 1.441 to 2.122), nausea (54 versus 36%;

TABLE 14 *RRs of treatment-related adverse events for pegylated liposomal doxorubicin hydrochloride versus topotecan based on the ITT populations (observed in ≥ 10% of patients)*[47]

Adverse effect	Pegylated liposomal doxorubicin hydrochloride	Topotecan
Leukopenia (all grades)	87/239 (36%)	149/235 (63%)
Neutropenia (all grades)	84/239 (35%)	191/235 (81%)
Thrombocytopenia (all grades)	31/239 (13%)	152/235 (65%)
Anaemia (all grades)	85/239 (36%)	169/235 (72%)
Alopecia (all grades)	38/239 (16%)	115/235 (49%)
Stomatitis (all grades)	95/239 (40%)	35/235 (15%)
PPE (all grades)	117/239 (49%)	2/235 (1%)
Nausea (all grades)	85/239 (36%)	127/235 (54%)
Vomiting (all grades)	58/239 (24%)	81/235 (35%)
Fatigue (all grades)	Not stated	Not stated
Constipation (all grades)	33/239 (14%)	58/235 (25%)
Diarrhoea (all grades)	28/239 (12%)	49/235 (21%)
Fever (all grades)*	28/239 (12%)	49/235 (21%)
Asthenia (all grades)	75/239 (31%)	104/235 (44%)
Arthralgia (all grades)	Not stated	Not stated
Myalgia (all grades)	Not stated	Not stated
Neuropathy (all grades)	Not stated	Not stated
Paraesthesia (all grades)	Not stated	Not stated
Abdominal pain (all grades)	20/239 (8%)	29/235 (12%)
Skeletal pain (all grades)	Not stated	Not stated
Flushing (all grades)	Not stated	Not stated
Mucous membrane disorder (all grades)	33/239 (14%)	7/235 (3%)
Anorexia (all grades)	26/239 (11%)	32/235 (14%)
Skin rash (all grades)	58/239 (24%)	18/235 (8%)
Dyspnoea (all grades)	Not stated	Not stated
Headache (all grades)	Not stated	Not stated
Back pain (all grades)	Not stated	Not stated
Urinary tract infections (all grades)	Not stated	Not stated
Pain (all grades)	Not stated	Not stated
Dyspepsia (all grades)	Not stated	Not stated
Anxiety (all grades)	Not stated	Not stated
Coughing (all grades)	Not stated	Not stated
Haematuria (all grades)	Not stated	Not stated
Upper respiratory tract infections (all grades)	Not stated	Not stated
Hypokalaemia	Not stated	Not stated

* *Excludes reports of the verbatim term febrile neutropenia*

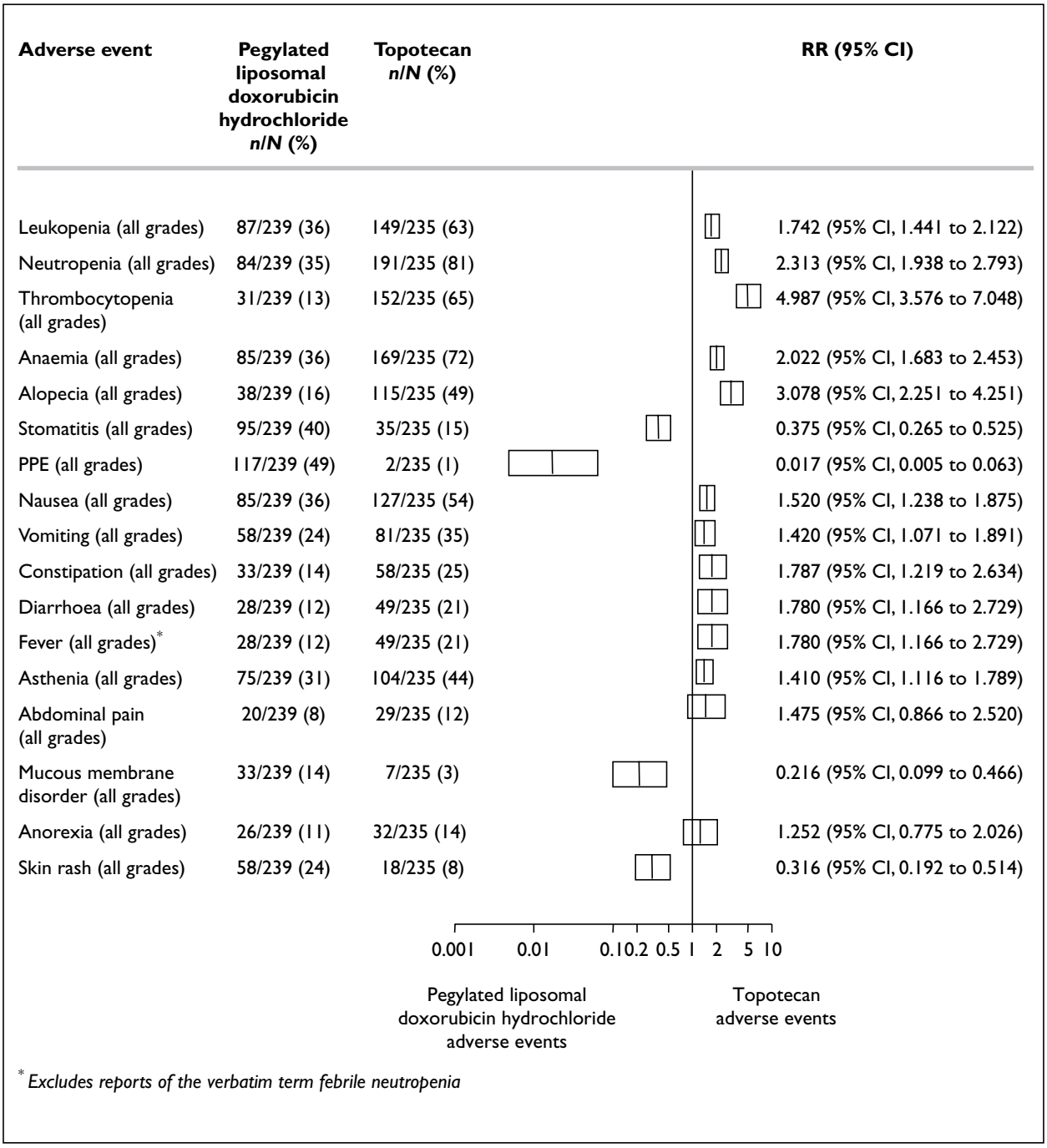


FIGURE 10 *RRs of treatment-related adverse events for pegylated liposomal doxorubicin hydrochloride versus topotecan based on the ITT population (observed in ≥ 10% of patients)*[47]

RR = 1.520, 95% CI, 1.238 to 1.875), vomiting (35 versus 24%; RR = 1.420, 95% CI, 1.071 to 1.891) and alopecia (49 versus 16%; RR = 3.078, 95% CI, 2.251 to 4.251). Of patients in the topotecan group, 29.1 and 57.8% required granulocyte-colony stimulating factor (G-CSF) and transfusions, respectively, compared with 4.6 and 14.9% of the pegylated liposomal doxorubicin hydrochloride group. In addition, constipation, diarrhoea, fever and asthenia were also significantly more frequent in the topotecan group.

Assessment of clinical effectiveness (Phase II studies)

The following section briefly presents the clinical data from the Phase II studies of pegylated liposomal doxorubicin hydrochloride. These data focus on the assessment of response, survival and adverse events. None of the studies considered patient QoL, which is an important outcome in studies of second-line cancer treatments. One study mentioned such an assessment in its aims, but failed to present any outcome data.[55]

The methodological problems associated with these studies limit the usefulness of the data with regards to assessing the true clinical effectiveness of the drug and hence the findings have not been discussed in detail. Further details of the Phase II studies are presented in appendix 9.

Survival

Survival data were reported in five of the six Phase II studies (see *Table 15* for further details). The studies varied in whether they presented data in terms of overall survival, progression-free survival or both. Two of the studies did not base their data on a true ITT analysis and, therefore, these findings should be treated with additional caution.[55,57] One other study was only based on interim data.[58] In addition, only three studies (30-22, 30-47 and 30-47E) reported how survival was measured, and it is, therefore, unclear if the outcome measures were, in fact, equivalent and if they were subject to standard practice. The three studies in question measured overall survival from the point of first study drug administration to death. However, this may have introduced bias because the period between study entry and drug administration was likely to have varied between patients. Consequently, the disease status of patients may have altered from when they entered the study and had their baseline characteristics measured.

The reported median progression-free survival varied between 13 weeks (3.0 months) and 44.9 weeks (10.4 months) and the median overall survival varied between 25.1 weeks (5.8 months) and 47.6 weeks (11.0 months). The wide variation in reported survival is likely to reflect the methodological issues surrounding non-comparative Phase II studies and the fact that the studies varied in terms of their treatment regimens and study populations, and possibly their definitions of survival.

Response

All of the six Phase II studies reported response as a primary outcome measure and presented data in terms of complete, partial and total responses (see *Table 16* for further details). Only three of the studies (30-22, 30-47E and Cervantes and colleagues) used a true ITT analysis based on complete data and only four provided adequate definitions for the response outcomes (30-22, 30-47, 30-47E and Israel and colleagues). Four of the studies (30-22, 30-47, 30-47E and Israel and co-workers) also reported the median duration of response, three (30-22, 30-47 and 30-47E) reported median time to response and two (30-47 and 30-47E) reported median time to progression. All of these outcomes were based on Kaplan–Meier survival analyses, although all of the studies concerned failed to present their findings in terms of HRs with 95% CIs. The

TABLE 15 *Survival data from Phase II studies*

Study	Drug regimen	Median survival data (ITT)	
		Progression-free	Overall
30-22[50,51]	50 mg/m^2 every 3 weeks as a 1-hour i.v. infusion	5.7 months*	11 months (range 1.5–21)*
30-47[55]	50 mg/m^2 every 4 weeks as a 1-hour i.v. infusion for ≥ six cycles	314 days (range 8–824; 44.9 weeks;* not true ITT)	Not reported
30-47E[56]	50 mg/m^2 every 4 weeks as a 1-hour i.v. infusion for ≥ six cycles	Not reported	176 days (range 1–531; 25.1 weeks)*
Israel *et al.*[57]	50 mg/m^2 i.v. over 1 hour every 4 weeks until progression or unacceptable toxicity (note, second cycle was given after a 3-week interval, but all subsequent cycles were given at 4-week intervals)	3 months (range 0.25–18; evaluable population only)	10 months (range 0.25–33; evaluable population only)
Linardou *et al.*[58] (interim data only)	45 mg/m^2 by 1-hour i.v. infusion once every 28 days for a total of six cycles, unless disease progression or unacceptable toxicity (median = three cycles per patient)	Not reported	5 months (range 1–18+)
Cervantes *et al.*[59]	50 mg/m^2 every 3 weeks for a median number of three cycles (range 2–10) per person	Not reported	Not reported

* *Measured from first dose of study drug*

TABLE 16 *Response data from Phase II studies*

Study	Drug regimen	Response data
30-22[50,51]	50 mg/m^2 every 3 weeks as a 1-hour i.v. infusion	Based on ITT:* Complete response: 1/35 (2.9%) Partial response: 8/35 (22.9%) Total response: 9/35 (25.7%) Median time to response = 5.5 months (range 2–8) Median response duration = 6 months (range 3.6–16)
30-47[55]	50 mg/m^2 every 4 weeks as a 1-hour i.v. infusion for ≥ six cycles	Based on ITT as reported by authors, but not a true ITT:* Complete response: 1/122 (0.8%) Partial response: 15/122 (12.3%) Total response: 16/122 (13.1%, 95% CI, 7.1 to 19.1) Median time to response = 106 days (range 23–230; 15.1 weeks) Median response duration = 285 days (range 45–338; 40.7 weeks) Median time to progression = 142 days (range 5–528; 20.3 weeks) There was also separate analysis for platinum-refractory patients (see appendix 9 for further details)
30-47E[56]	50 mg/m^2 every 4 weeks as a 1-hour i.v. infusion for ≥ six cycles	Based on ITT:* Complete response: 0/62 (0%) Partial response: 4/62 (6.5%, 95% CI, 0.3 to 12.6) Total response: 4/62 (6.5%, 95% CI, 0.3 to 12.6) Median time to progression = 81 days (range 1–399; 11.6 weeks) Median time to response = 57 days (range 53–120; 8.1 weeks) Median response duration = 124 days (range 114–280; 17.7 weeks)
Israel *et al.*[57]	50 mg/m^2 i.v. over 1 hour every 4 weeks until progression or unacceptable toxicity (note, second cycle was given after a 3-week interval, but all subsequent cycles were given at 4-week intervals)	Response data not based on an ITT analysis, but only those with measurable disease (n = 21):* Complete response: 1/21 (4.8%) Partial response: 3/21 (14.3%) Total response: 4/21 (19.0%); RR = 19% (CI not reported) Median response duration = 4.5 months (range 3–12)
Linardou *et al.*[58] (interim data only)	45 mg/m^2 by 1-hour i.v. infusion once every 4 weeks for a total of six cycles unless disease progression or unacceptable toxicity (median = three cycles per patient)	Based on ITT, but only interim data: Complete response: 0/35 (0%) Partial response: 2/35 (5.7%) Total response: 2/35 (5.7%)
Cervantes *et al.*[59]	50 mg/m^2 every 3 weeks for a median number of three cycles (range 2–10) per person	Based on ITT: Complete response: 0/18 (0%) Partial response: 1/18 (5.5%) Total response: 1/18 (5.5%)

* *Response defined*

reported response rates varied between 5.5 and 25.7%. In a similar manner to the wide variation in survival, the wide variation in response is likely to reflect the methodological issues surrounding non-comparative Phase II studies and the fact that the studies varied in terms of their treatment regimens and study populations. Another important issue with regards to response data relates to whether an independent assessor carried out the response assessments. None of the six studies provided any information about this and thus the findings should be treated with additional caution in view of the possibility of assessment bias.

Adverse events

All of the six Phase II studies presented some data relating to the toxicity of pegylated liposomal doxorubicin hydrochloride. However, only limited data were available in two of the studies, which were based on abstracts.[58,59] See *Tables 17* and *18* for further details. Complete data regarding the total number of participants experiencing adverse

TABLE 17 *Withdrawals due to adverse events and drug-related deaths reported in Phase II studies (ITT)*

Study	Total number of participants experiencing drug-related adverse events	Withdrawals due to drug-related adverse events	Drug-related deaths
30-22[50,51]	32/35 (91.4%)*	2/35 (5.7%)*	No deaths*
30-47[55]	116/122 (95.1%)*†	13/122 (10.7%)*†	3/122 (2.5%)*†
30-47E[56]	59/62 (95.2%)	4/62 (6.5%)	No deaths
Israel *et al.*[57]	Not stated	1/48 (2%)‡	None reported
Linardou *et al.*[58] (interim data only)	Not stated	Not stated	None reported
Cervantes *et al.*[59]	Not stated	Not stated	None reported

* *Additional information obtained on request from Schering-Plough Ltd*
† *Not based on a true ITT analysis*
‡ *Unclear if this patient had ovarian cancer, as the trial included 63 patients in total, only 48 of whom had ovarian cancer (the remainder had other gynaecological cancers)*

TABLE 18 *Adverse events data from Phase II studies (experienced by ≥ 10% of participants)*

Adverse event	Participants experiencing adverse event (%) for all grades of events*					
	30-22[50,51]	**30-47**[55]	**30-47E**[56]	**Israel *et al.***[57]	**Linardou *et al.***[58] **(interim data only)**	**Cervantes *et al.***[59]
Anaemia	12/35 (34.3%)†	53/122 (43.4%)	12/62 (21.0%)	7/204 cycles (3.4%)‡	2/35 (5.7%)‡	No data
Leukopenia	18/35 (51.4%)†	52/122 (42.6%)	11/62 (17.7%)	17/204 cycles (8.3%)‡	No data	No data
PPE	30/35 (85.7%)†	48/122 (39.3%)	19/62 (30.6%)	No data	1/35 (2.8%)‡	No data
Neutropenia	18/35 (51.4%)†	48/122 (39.3%)	No data	19/204 cycles (9.3%)‡	1/35 (2.8%)‡	No data
Nausea	13/35 (37.1%)†	47/122 (38.5%)	25/62 (40.3%)	2/204 cycles (1.0%)‡	No data	No data
Asthenia	21/35 (60.0%)†	47/122 (38.5%)	13/62 (21.0%)	No data	No data	No data
Stomatitis	20/35 (57.1%)†	40/122 (32.8%)	18/62 (29.0%)	5/204 cycles (2.5%)‡	No data	No data
Rash	15/35 (42.9%)†	37/122 (30.3%)	12/62 (19.4%)	3/204 cycles (1.5%)‡	No data	No data
Mucous membrane disorder	4/35 (11.4%)†	26/122 (21.3%)	No data	No data	No data	No data
Vomiting	9/35 (25.7%)†	24/122 (19.7%)	21/62 (33.9%)	1/204 cycles (1.0%)‡	No data	No data
Anorexia	4/35 (11.4%)†	19/122 (15.6%)	7/62 (11.3%)	No data	No data	No data
Diarrhoea	6/35 (25.7%)†	15/122 (12.3%)	No data	No data	No data	No data
Thrombo-cytopenia	4/35 (11.4%)†	15/122 (12.3%)	No data	8/204 cycles (3.9%)‡	2/35 (5.7%)‡	No data
Alopecia	7/35 (20.0%)†	14/122 (11.5%)	No data	No data	No data	No data
Fatigue	No data	No data	No data	11/204 cycles (5.3%)‡	No data	No data
Skin discolouration	11/35 (31.4%)†	No data	No data	No data	No data	No data
Gastritis	8/35 (22.9%)†	No data	No data	No data	No data	No data
Fever	4/35 (11.4%)†	No data	No data	No data	No data	No data
Exfoliative dermatitis	6/35 (17.1%)†	No data	No data	No data	No data	No data
Infection	No data	No data	No data	3/204 cycles (1.5%)‡	No data	No data

* *See appendix 9 for further details of individual grades of events*
† *Additional data supplied by Schering-Plough Ltd on request*
‡ *Only grade III/IV events considered*

events, the total number of withdrawals due to drug-related adverse events and the number of drug-related adverse events were only available in three of the studies (30-22, 30-47 and 30-47E). Only two of the studies reporting sufficient data were based on true ITT analyses (30-22 and 30-47E). Two of the studies (Cervantes and co-workers and Linardou and co-workers) were only based on abstracts, and the reporting of adverse events data was, therefore, limited.

Only three deaths were reported related to the administration of pegylated liposomal doxorubicin hydrochloride and these were all reported in one study with 122 participants (30-47). Withdrawals due to drug-related adverse events varied from 2 to 10.7% and overall numbers of participants experiencing drug-related adverse events varied from 91.4 to 95.2%. Overall, the findings of the Phase II adverse events data reflected that found in trial 30-49. The most common adverse events included PPE and stomatitis, as reported in trial 30-49. In addition, nausea, asthenia and haematological toxicities, including anaemia, leukopenia and neutropenia, were also frequently reported.

Summary of effectiveness data

Although two RCTs were identified (trials 30-49 and 30-57, both sponsored by Schering-Plough Ltd), data were only available for trial 30-49. This trial included 474 participants and compared pegylated liposomal doxorubicin hydrochloride with topotecan. In addition, six non-comparative Phase II studies involving pegylated liposomal doxorubicin hydrochloride were also identified (see appendix 9). However, these only offered limited poorer-quality evidence on which to base an assessment of clinical effectiveness. Hence, this report focused on the limited but better-quality evidence available from trial 30-49. A summary of best-quality evidence (RCT) of clinical effectiveness is shown in *Table 19*.

In terms of the findings from trial 30-49, there was no clear evidence of any major statistically significant differences between pegylated liposomal doxorubicin hydrochloride and topotecan for median survival, response rate, median time to response, median duration of response and QoL. The only apparently statistically significant differences were observed in the subgroup analyses. However, the validity of these analyses is questionable given the small numbers of patients involved. Tests of interaction were performed for the three statistically significant differences that were observed in the subgroup analyses. However, only one was associated with a statistically significant interaction between the subgroup characteristic and the effectiveness outcome. This significant finding related to the improvement in survival of platinum-sensitive patients treated with pegylated liposomal doxorubicin hydrochloride versus topotecan. However, this significant interaction was not borne out for the subgroup analyses. Pegylated liposomal doxorubicin hydrochloride did show a significantly greater response as compared with topotecan for platinum-sensitive patients and those without ascites, for the outcome of time to progression, but the interaction tests were not statistically significant. Therefore, it is unlikely that the findings of the subgroup analyses for any of the outcomes were of any real significance.

Statistically significant differences were observed for one of the QoL subscale scores, although only 50% of patients were able to supply QoL data. Significantly more patients in the topotecan group compared with the pegylated liposomal doxorubicin hydrochloride group had a maintained or improved pain score at 12-week follow-up for all patients (81 versus 64%, respectively; RR = 1.264, 95% CI, 1.076 to 1.500) and platinum-sensitive patients (83 versus 54%, respectively; RR = 1.54, 95% CI, 1.211 to 2.023). However, the clinical relevance of these differences is not clear.

Q-TWiST analysis suggested that pegylated liposomal doxorubicin hydrochloride had quality-adjusted survival advantages over topotecan. However, the Q-TWiST analysis included a major assumption that may not have been justified, namely that a day with toxicity was valued the same (in terms of utility) whatever the type of adverse event the patient was experiencing. The analyses were also based on data that were not patient-reported.

Although statistically significant differences were not found in terms of the main effectiveness outcomes, differences were apparent in terms of treatment-related adverse events. Statistically significant differences were observed between pegylated liposomal doxorubicin hydrochloride and topotecan. Patients treated with pegylated liposomal doxorubicin hydrochloride suffered from a significantly-increased incidence of PPE (49 versus 1%; RR = 0.017, 95% CI, 0.005 to 0.063), stomatitis (40 versus 15%; RR = 0.375, 95% CI, 0.265 to 0.525), mucous membrane disorders (14 versus 3%; RR = 0.216, 95% CI, 0.099 to 0.466) and skin rashes (24 versus 8%; RR = 0.316, 95% CI, 0.192 to 0.514) compared with patients treated with topotecan.

TABLE 19 *Summary of best-quality evidence (RCT) of clinical effectiveness*

Outcome	Result
Survival	No statistically significant differences except for the platinum-sensitive disease subgroup, which favoured intervention (108.0 versus 71.1 weeks; HR = 1.720, 95% CI, 1.145 to 2.585; Δ = statistically significant)
Response rate	No statistically significant differences; HR = 1.121 (95% CI, 0.886 to 1.419)
Time to response	No statistically significant differences; difference in median values $p = 0.448$
Duration of response	No statistically significant differences; difference in median values $p = 0.891$
Time to progression	No statistically significant differences except for the platinum-sensitive disease and the absence of ascites subgroups, which favoured intervention. However, the Δ values for these interactions were not statistically significant
QoL	***Favoured topotecan over pegylated liposomal doxorubicin hydrochloride*** Number of patients (all patients) with a maintained or improved pain subscale score at 12 weeks: 81% with control versus 64% with intervention (RR = 1.264, 95% CI, 1.076 to 1.500) Pain subscale score in platinum-sensitive patients: 83% with control versus 54% with intervention (RR = 1.54, 95% CI, 1.211 to 2.023)
Q-TWiST	***Favoured pegylated liposomal doxorubicin hydrochloride over topotecan*** Time (months) spent in toxicity: 1.54 with control versus 0.84 with intervention (difference = –0.70, 95% CI, –1.04 to –0.36) Time (months) spent in TWiST: 3.51 with control versus 4.65 with intervention (difference = 1.14, 95% CI, 0.46 to 1.82) Time (months) spent in progression: 5.53 with control versus 5.07 with intervention (difference = –0.46, 95% CI, –1.31 to 0.39)
Adverse events	The following were reported as statistically significant ***Favoured pegylated liposomal doxorubicin hydrochloride over topotecan*** Neutropenia: 81% with control versus 35% with intervention (RR = 2.313, 95% CI, 1.938 to 2.793) Anaemia: 72% with control versus 36% with intervention (RR = 2.022, 95% CI, 1.683 to 2.453) Thrombocytopenia: 65% with control versus 13% with intervention (RR = 4.987, 95% CI, 3.576 to 7.048) Leukopenia: 63% with control versus 36% with intervention (RR = 1.742, 95% CI, 1.441 to 2.122) Alopecia: 49% with control versus 16% with intervention (RR = 3.078, 95% CI, 2.251 to 4.251) Nausea: 54% with control versus 36% with intervention (RR = 1.520, 95% CI, 1.238 to 1.875) Vomiting: 35% with control versus 24% with intervention (RR = 1.420, 95% CI, 1.071 to 1.891) ***Favoured topotecan over pegylated liposomal doxorubicin hydrochloride*** PPE: 1% with control versus 49% with intervention (RR = 0.017, 95% CI, 0.005 to 0.063) Stomatitis: 15% with control versus 40% with intervention (RR = 0.375, 95% CI, 0.265 to 0.525) Mucous membrane disorders: 14% with control versus 3% with intervention (RR = 0.216, 95% CI, 0.099 to 0.466) Skin rashes: 24% with control versus 8% with intervention (RR = 0.316, 95% CI, 0.192 to 0.514)

In contrast, topotecan administration was more commonly associated with haematological toxicities compared with pegylated liposomal doxorubicin hydrochloride, including neutropenia (81 versus 35%; RR = 2.313, 95% CI, 1.938 to 2.793), leukopenia (63 versus 36%; RR = 1.742, 95% CI, 1.441 to 2.122), anaemia (72 versus 36%; RR = 2.022, 95% CI, 1.683 to 2.453) and thrombocytopenia (65 versus 13; RR = 4.987, 95% CI, 3.576 to 7.048). Alopecia (49 versus 16%; RR = 3.078, 95% CI, 2.251 to 4.251), nausea (54 versus 36%; RR = 1.520, 95% CI, 1.238 to 1.875) and vomiting (35 versus 24%; RR = 1.420, 95% CI, 1.071 to 1.891) were also more common with topotecan than with pegylated liposomal doxorubicin hydrochloride.

In summary, there was no clear evidence from trial 30-49 of major differences in clinical effectiveness between pegylated liposomal

doxorubicin hydrochloride and topotecan, although there appeared to be statistically significant differences between the drugs in terms of their adverse events.

The findings of the non-comparative Phase II studies appeared to show that pegylated liposomal doxorubicin hydrochloride has some effect in patients with ovarian cancer, and the adverse events reflected the findings of the RCT. Reported response rates varied between 5.5 and 25.7%, median progression-free survival varied between 13 weeks (3.0 months) and 44.9 weeks (10.4 months) and median overall survival varied between 25.1 weeks (5.8 months) and 47.6 weeks (11.0 months). However, any findings from such studies should be treated with great caution. The large ranges in effect reflected the differences in the study populations and the fact that the evidence from such small non-comparative studies is very weak. The studies suffered from a number of methodological issues, which have been discussed previously, and, consequently, these findings are of little interest to the assessment of clinical effectiveness reported in this review.

Assessment of cost-effectiveness

Description of the published analyses

The assessment of cost-effectiveness was based on two articles using a similar approach and data from the same clinical trial (30-49).[1,47,48,67] This trial was an RCT designed to show equivalence in overall survival between topotecan and pegylated liposomal doxorubicin hydrochloride. As the majority of the clinical outcomes showed no significant difference between the two drugs, a CMA was adopted. Both studies considered only the costs occurring within the treatment period and assumed that similar levels of resources were utilised outside the timeframe of their analysis. Although the economic evaluations were based on the same RCT and adopted very similar methods, they exhibited some differences. These included the costing of adverse events in general and the cost of treating neutropenia in particular. The overall mean cost per patient of treating adverse events in the company submission was estimated as £3362, while in the analysis by Smith and colleagues[4] it was US$3919 (or £2799), a reduction of £563. Although other costs changed slightly, this lower cost of adverse events was largely due to the reduction in the cost of treating neutropenia from £893 to £540. The cost of treating nausea and vomiting was also considerably lower in the Smith and co-workers analysis (£213 per person compared with £355 per person in the company submission).[4]

The company submission also used less resource use data from the trial relating to the treatment of adverse events. Expert panel data were used to estimate resource use in the company submission, while the analysis by Smith and co-workers[4] used actual amounts recorded in the clinical trial. The greater use of trial data is likely to strengthen the analysis, but this depends, in part, on the extent to which resource use data in the trial are representative of practice in the UK.

The paper by Smith and colleagues[4] compared the cost of pegylated liposomal doxorubicin hydrochloride with topotecan in trial 30-49. The analysis considered the cost of the drugs themselves together with the cost of drug administration, including the cost of specialist visits and outpatient attendances where relevant. The costs associated with the management and treatment of adverse events were also estimated, including the cost of medication and any hospitalisation associated with the adverse event. The amount of each study drug was recorded as part of the clinical trial, although assumptions were made about the resource use associated with the administration of the drug (for instance, a specialist visit at the start of each cycle).

Some treatments that were directly linked to an adverse event could be costed using data extracted from the clinical trial, for example, platelet transfusion for thrombocytopenia. However, this was not always feasible, and an expert panel was employed to estimate resource use (including estimates of length of stay) associated with some adverse events. The expert panel consisted of oncologists from the UK and USA, who gave differing values for the UK and USA presumably reflecting differences in clinical practice. No details were provided of the numbers involved in the expert panel or of the breakdown between UK and USA specialists. In addition, there was no description of how the estimates were attained.

Unit costs were derived from commonly used sources within the UK. However, the costs of care for the UK analysis employed resource use data taken from all European patients. Although the UK provided the largest group of patients in the trial, large differences in clinical practice between the UK and the rest of Europe could have impacted on the results. The use of expert opinion to supplement the economic data was acknowledged as a weakness in the design, but the

authors stated that, because over 83% of the costs were collected from the trial data, the potential for bias was limited. In all the cost analyses, 95% CIs around the difference in means were presented. The appropriateness of assuming normality was checked using the bootstrap method.

The authors concluded that in both the UK and USA analyses, pegylated liposomal doxorubicin hydrochloride was significantly less costly than topotecan. The estimate for the UK was that pegylated liposomal doxorubicin hydrochloride had a mean cost per patient of US$2909 (approximately £2078) lower than topotecan.

The analysis forming part of the company submission compared the cost of pegylated liposomal doxorubicin hydrochloride with topotecan in the UK only.[67] This evaluation used the same cost components as the paper by Smith and colleagues[4] – namely, study drug, drug administration and management of adverse events. As with the analysis performed by Smith and co-workers,[4] expert opinion was used to supplement economic data from the clinical trial. In this instance, the experts were from the main UK recruiting centre for the clinical trial. Details of the numbers involved or affiliations of the panel were not provided. The experts were used to derive estimates of resource use associated with drug administration (an outpatient visit at the start of each cycle plus one visit for each dose) and the local treatment patterns for each of the adverse events. However, although not explicit in this paper, it was clear that European and UK patients were treated as synonymous because the numbers in this analysis were identical to those used by Smith and colleagues.[4]

The sensitivity analysis in the company submission reported an extreme case scenario where the resources used were varied to favour topotecan. The results were still significantly in favour of pegylated liposomal doxorubicin hydrochloride, although it should be noted that the costs of treating neutropenia were still high (which favours pegylated liposomal doxorubicin hydrochloride) even in the extreme analysis (and higher than the base-case estimate of the cost of treatment of neutropenia from the analysis by Smith and colleagues[4]).

The results of the costing exercise (see *Table 20*) showed that pegylated liposomal doxorubicin hydrochloride was significantly less costly than topotecan and that this result was robust to a variety of extreme case analyses. Pegylated liposomal doxorubicin hydrochloride had a mean cost of £9970 (95% CI, £9080 to £10,861) and topotecan had a mean cost of £12,627 (95% CI, £11,527 to £13,727). As these CIs do not overlap, pegylated liposomal doxorubicin hydrochloride was statistically significantly less expensive than topotecan based on standard rules of inference.

The authors concluded that pegylated liposomal doxorubicin hydrochloride is a dominant therapy as it was associated with lower costs and similar (or better) outcomes when compared with topotecan.

Additional analysis – methods

The methodology described below was based on estimates derived from the cost analyses presented in the company submissions. Patient level data were not available. The results of these analyses and the assumptions employed within the analyses were, therefore, constrained by the summary statistics presented in the CMA.

A number of aspects of the economic evaluations reviewed here were identified that indicated that additional analysis was warranted.

1) Although the assumption of equivalent overall survival duration was justifiable on the basis of the trial design and its results, the use of a CMA effectively assumes away uncertainty in survival duration. Hence, the uncertainty in cost-effectiveness is not fully represented in a

TABLE 20 *Mean cost per person (in £ sterling) for topotecan and pegylated liposomal doxorubicin hydrochloride*

Authors	Mean cost per person (95% CI, where reported)		Difference in means (95% CI, where reported)
	Pegylated liposomal doxorubicin hydrochloride	Topotecan	
Company submission[67]	£9,970 (95% CI, £9,080 to £10,861)	£12,627 (95% CI, £11,527 to £13,727)	£2,657
Smith *et al.*[4]	£9,998	£12,076	£2,078 (95% CI, £556 to £2,439)

CMA. Although this is usually not a problem if the economically preferred intervention is based on mean costs and mean effects, the cost-minimisation approach fails to describe all uncertainty to decision makers and limits the opportunity to estimate the potential cost-effectiveness of additional research. It was, therefore, decided to reintroduce a measure of survival duration into the analysis and undertake a full CEA, relating differential mean costs to differential mean survival duration. A fully stochastic analysis was developed. Uncertainty in mean costs was characterised as a log-normal distribution based directly on the results reported in the Smith and co-workers paper.[4] Uncertainty in mean survival duration was also characterised as a log-normal; other distributions, such as the Weibull distribution, could not be used as patient level data would be required to generate the scale and shape parameters. Monte Carlo simulation was used to propagate uncertainty in these inputs and to generate a graphical representation of uncertainty in differential costs and life-years on a cost-effectiveness plane.[68] CEACs[69] were then used to present the probability that pegylated liposomal doxorubicin hydrochloride was more cost-effective than topotecan for a range of maximum values the NHS might be willing to pay for an additional life-year in these patients.

2) The survival data presented in the clinical details of 30-49 did not provide an estimate of mean overall survival. Instead, median survival duration was reported. If a full CEA was to be undertaken, it was necessary to take the data presented on median overall survival duration together with some explicit assumptions to estimate mean overall survival durations together with their variances in the two arms of the trial. This involved the assumption that overall survival followed an exponential distribution, which implied a fixed hazard rate. Appendix 11 provides full details of how mean survival durations and their variances were estimated.
3) In common with most economic evaluations, the analyses reviewed here required a series of analytical decisions and assumptions. The general methods adopted in the study were reviewed in the quality of economic evaluations section on page 17. To further assess whether these decisions and assumptions were reasonable, the advice of a group of relevant experts, including clinicians, trialists and pharmacists, was sought. Details of this group are provided in the acknowledgements on page 51.
4) As referred to earlier, the choice of a CMA was based on the equivalence shown in survival duration in trial 30-49. However, the trial did not provide any basis for assuming equivalence in overall HRQoL. In terms of QALYs, therefore, conclusions about the cost-effectiveness of the two interventions may have been different. For this reason, a sensitivity analysis was undertaken to explore what relative magnitude of HRQoL (expressed as relative overall utilities on the standard 0–1 scale) might cause the conclusions of the CEA based on life-years to alter.
5) To guide decisions about further research in the area, the potential cost-effectiveness of additional research was estimated in terms of the expected value of perfect information (EVPI).[70] Based on the distribution of costs and life-years described above, EVPI is equivalent to the cost of uncertainty. The latter is the probability of making a wrong decision multiplied by the cost and life-years implications of that wrong decision.

Additional analysis – results

Overall survival

Table 21 details the estimates of mean survival duration in the two arms of the trial under the assumption that survival follows an exponential distribution. Unlike the two economics papers, reported survival from trial 30-49 was based on the population of evaluable patients rather than on ITT analysis.

Thus, mean survival favoured pegylated liposomal doxorubicin hydrochloride over topotecan. The mean difference in survival was 0.12 years and, consistent with the clinical review, this difference was not statistically significant.

TABLE 21 *Mean overall survival (evaluable population)*

	Pegylated liposomal doxorubicin hydrochloride (*n* = 207)	**Topotecan (*n* = 209)**
Mean survival (years)	1.91 (95% CI, 1.55 to 2.27)*	1.79 (95% CI, 1.47 to 2.11)*

* *Based on 2.5 and 97.5 percentiles from the simulated distributions*

Use of the expert panel to test the assumptions employed in the economic analysis

A summary of the expert panel comments is as follows.

- It was generally considered that topotecan was an appropriate comparator, certainly for the UK where it is very commonly used, and that the perspective of the NHS was appropriate.
- The major adverse events were included in the analysis, although one expert felt that cardiotoxicity might have been considered.
- One comment regarding complications was that patient groups felt that although there were more complications with topotecan than pegylated liposomal doxorubicin hydrochloride, PPE is particularly unpleasant and that it is, therefore, very difficult to say whether one or other drug is better in terms of adverse events/side-effect profile.
- In terms of the cost of the drug, this could be influenced by the level of wastage. In theory, these drugs are single use and could, therefore, be subject to a large amount of wastage. The clinical trial only recorded the amount each patient received, not how much was used. While topotecan is used more often and is, therefore, likely to be associated with a higher volume of waste, pegylated liposomal doxorubicin hydrochloride is considerably more expensive and could be associated with a higher level of waste in monetary terms.
- As regards the treatment of complications, neutropenia is unlikely to be treated in the UK and would probably have no resource use associated with management or treatment.

CEA

Base-case results

Based on the mean survival duration detailed in the overall survival section on page 40 and the mean costs from Smith and colleagues,[4] pegylated liposomal doxorubicin hydrochloride is a dominant intervention – improved mean survival duration (0.12 life-years) and lower mean cost (£2657). This is consistent with the results of the CMAs in the two papers in the review.

However, the full uncertainty in both mean differential survival duration and mean differential costs needs to be considered. The incremental cost-effectiveness plane in *Figure 11* shows 10,000 combinations of costs and effects generated in the Monte Carlo simulation. The figure shows that most of the points fall in the bottom right hand quadrant where pegylated liposomal doxorubicin

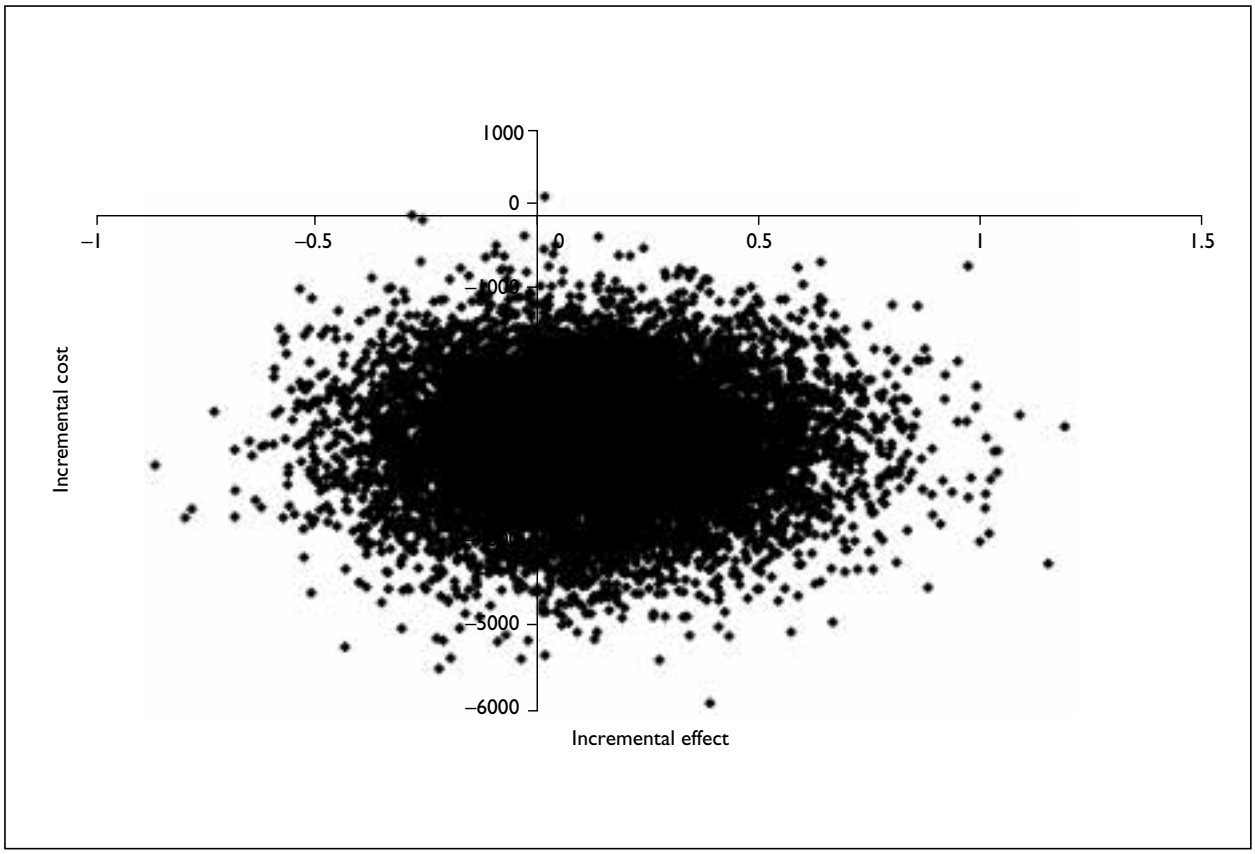


FIGURE 11 *Incremental cost-effectiveness plane*

hydrochloride is both more effective and less expensive.

Figure 12 shows a CEAC, which details the probability that pegylated liposomal doxorubicin hydrochloride is the optimal choice of intervention, compared to topotecan, over a range of maximum values that the NHS may be willing to pay for an additional life-year. At low values (where benefits in terms of increased survival are not highly valued), then the less costly option has a higher probability of being cost-effective. At a value of £30,000 per life-year gained, pegylated liposomal doxorubicin hydrochloride has a probability of 80% of being more cost-effective than topotecan.

Sensitivity analysis

Three sensitivity analyses were undertaken.

1) The expert panel identified the costs associated with the treatment of neutropenia as a possible overestimate in the economic analysis performed as part of the two papers in the review. As a result, the CEA was undertaken excluding the costs of treatment of neutropenia completely. This is an extreme analysis favouring topotecan. The results showed that the model was robust to excluding the costs of neutropenia. For example, for a value of an additional life-year of £30,000, pegylated liposomal doxorubicin hydrochloride had a probability of being more cost-effective than topotecan of 74% compared to a base-case probability of 80%.
2) It is possible that there may have been correlation between the mean costs and mean survival durations in the Monte Carlo simulation that was not incorporated into the base-case analysis. Therefore, the simulations were re-run with perfect positive correlation between mean costs and mean effects. Again, the results were robust to this change. With a maximum value for an additional life-year of £30,000, pegylated liposomal doxorubicin hydrochloride had a probability of 79% of being more cost-effective than topotecan (compared with the base case of 80%).
3) The base-case analysis considered only differences in overall survival between the groups and not differences in quality-adjusted survival (QALYs). The clinical trial provided no information on HRQoL to enable the calculation of QALYs. Threshold analysis has, therefore, been used to indicate the relative QoL values (on the 0–1 utility scale) that would be required to change the conclusions of the CEA. Two thresholds were used. The first was the value that would be required for topotecan to be shown to

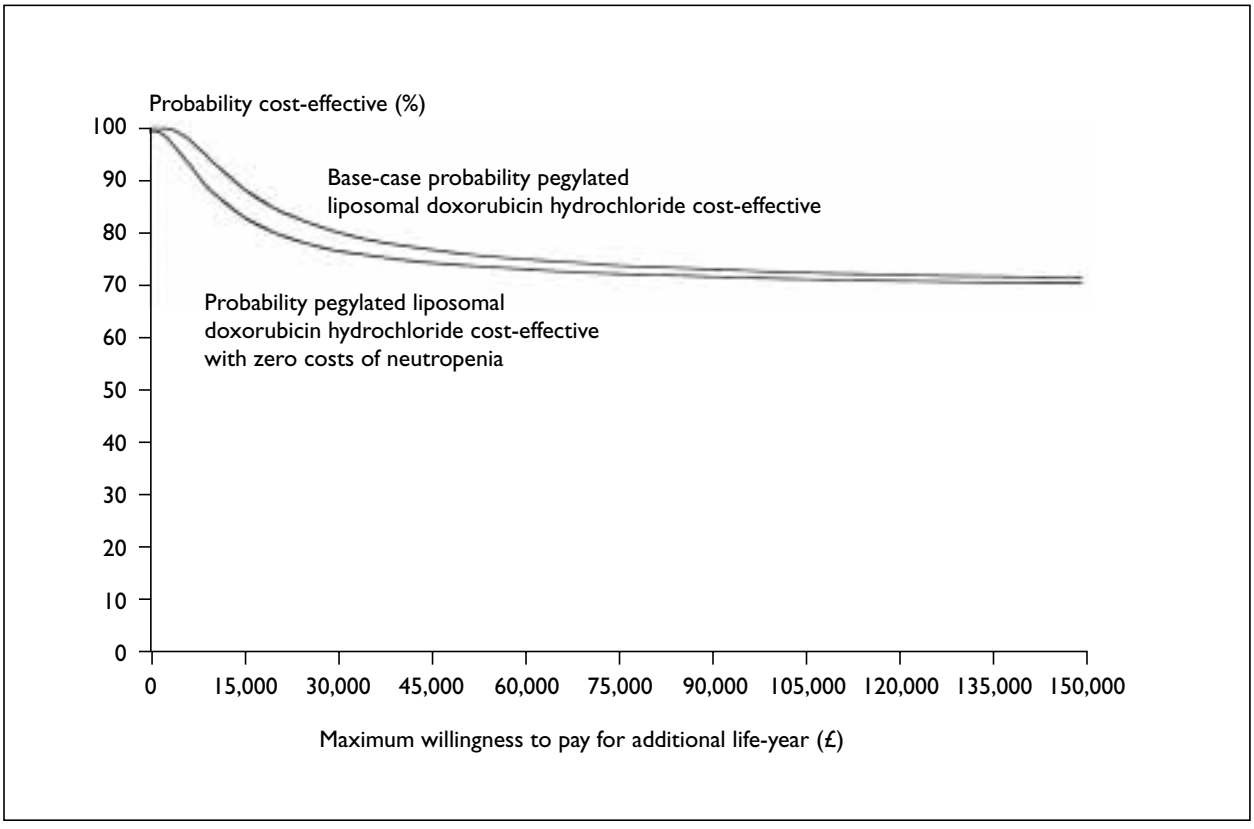


FIGURE 12 *CEAC*

achieve the same mean QALYs as pegylated liposomal doxorubicin hydrochloride. For this threshold, topotecan would need to have had a higher utility exactly equivalent to the proportionately higher overall survival shown by pegylated liposomal doxorubicin hydrochloride. In this instance, if HRQoL, in terms of utility, was 6.58% higher with topotecan than pegylated liposomal doxorubicin hydrochloride, the two treatments would be identical in terms of QALYs. This might be equivalent, for example, to an overall utility in the pegylated liposomal doxorubicin hydrochloride group of 0.6 compared to 0.64 in the topotecan group. Given the small differential in overall survival duration, this is a relatively modest difference in utility.

However, in the case of equal QALYs, pegylated liposomal doxorubicin hydrochloride would remain the dominant intervention because of its lower mean cost. If HRQoL were sufficiently higher in the topotecan group, overall mean QALYs could be higher in the topotecan group and the latter could generate an incremental cost-effectiveness ratio considered of reasonable value to the NHS. Using mean survival durations of 1.79 years for topotecan and 1.91 years for pegylated liposomal doxorubicin hydrochloride and using the mean difference in costs between the two groups in the base-case analysis (£2657), a mean overall utility of 0.5 for pegylated liposomal doxorubicin hydrochloride would require topotecan patients to experience a mean overall utility of 0.58 for topotecan to achieve a cost per life-year gained of £30,000. If pegylated liposomal doxorubicin hydrochloride were associated with a mean utility of 0.8, topotecan would require a mean utility of 0.9 to achieve an incremental cost per life-year gained of £30,000. The implication of this analysis is that cost-effectiveness is likely to be very sensitive to the overall HRQoL in the two groups. The HRQoL data reviewed in the QoL section on page 25 show similar QoL effects on all domains except pain, which is worse in pegylated liposomal doxorubicin hydrochloride patients. This apparent excess of pain could result in sufficiently different overall utility values in the two groups for topotecan to be more cost-effective in terms of QALYs. The lack of robustness in the results to alternative values for HRQoL makes conclusions about the relative cost-effectiveness of pegylated liposomal doxorubicin hydrochloride and topotecan highly uncertain.

EVPI

The EVPI curve in *Figure 13* presents the expected costs associated with the uncertainty (shown in the

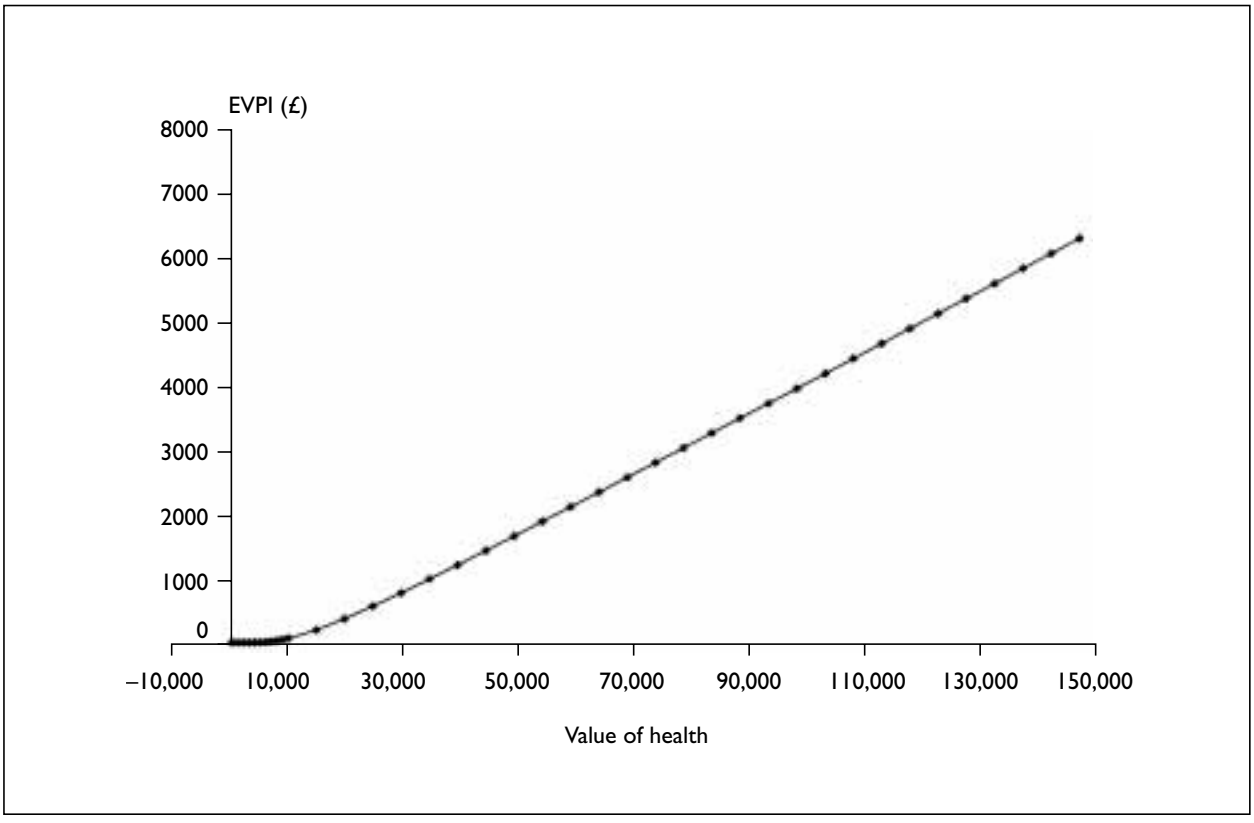


FIGURE 13 *EVPI*

CEAC in *Figure 12*) surrounding a decision based on mean costs and mean effects, again over a range of maximum values for an additional life-year. Effects are represented in terms of mean survival duration, thus uncertainty in HRQoL is not reflected in the estimates of EVPI. The figure shows that with a life-year valued at £30,000, EVPI would be approximately £800 per patient. If the useful lifetime of additional information was 5 years and the condition had an annual incidence of 3000 suitable for treatment with either pegylated liposomal doxorubicin hydrochloride or topotecan, then the EVPI for the population would be approximately £10.7 million (using a discount rate of 6% per annum). The key factor driving this figure is the level of uncertainty around the outcome measure. While there is little difference in the means, *Figure 13* illustrates that the distance from the axis is considerable and that combined with the value given to (in this case) life-years gained, the consequences of making a wrong decision are high. In addition, the existing analysis does not consider the quality of any survival improvements and any subsequent analysis should include an assessment on the impact of QoL. There is, therefore, a strong *prima facie* case for carrying out additional research and this would represent good value for money as long as an appropriately designed trial could be undertaken for less than this sum.

Budgetary implications

The company submission stated that there would be a net saving of £8 million from using pegylated liposomal doxorubicin hydrochloride as opposed to topotecan. This figure is derived from a suitable treatment cohort of 3000 per annum and a cost difference per patient treated of £2657. Using the upper and lower boundaries of the 95% CI gave a saving of £1.7–14 million, while excluding the costs of treating neutropenia from the analysis gave a saving of £5.4 million. Consultation with one expert suggested that this base-case estimate of annual potential saving is slightly high, and a more suitable size of treatment cohort would be approximately one-third rather than one-half of the annual incidence figure of 6000. This would reduce the potential savings to about £5.3 million per annum.

Chapter 4

Relevance to the NHS

At present, paclitaxel, hexamethylmelamine, treosulfan, carboplatin, topotecan and pegylated liposomal doxorubicin hydrochloride are licensed for the second-line treatment of ovarian cancer. However, recent guidance issued by NICE in May 2000 recommended the use of paclitaxel in combination with platinum therapy (cisplatin/carboplatin) for the first-line treatment of ovarian cancer, leaving hexamethylmelamine, topotecan, treosulfan and pegylated liposomal doxorubicin hydrochloride as the only current options for second-line therapy. Recent guidance from NICE has recommended that topotecan should be considered as one of the options for second-line treatment.[23] In addition, NICE has also recommended "the use of paclitaxel/platinum combination therapy in the treatment of recurrent (or resistant) ovarian cancer (i.e. second-line or salvage therapy), but only if the patient has not previously received this drug combination" due to problems of drug resistance.[22] A number of alternative chemotherapy agents at various stages of development are under investigation, but the options for the treatment of recurrent/resistant ovarian cancer are currently limited.

Chapter 5

Discussion and conclusions

In summary, the assessment of clinical effectiveness identified two international, multicentre RCTs (trials 30-49 and 30-57) comparing pegylated liposomal doxorubicin hydrochloride with topotecan (n = 474) and paclitaxel (n = 212 at date of stopping trial), respectively. However, due to the early termination of trial 30-57, no outcome data were available and, consequently, only the findings of trial 30-49 have been reported. In addition, six non-comparative Phase II studies of pegylated liposomal doxorubicin hydrochloride were identified and described briefly in this report. However, the findings of these studies were not considered in the assessment of clinical effectiveness due to the poorer quality of the evidence. Consequently, the assessment of clinical effectiveness centres on the findings of trial 30-49, which was of reasonably good quality overall.

The assessment of cost-effectiveness identified only two economic evaluations (CMAs) of reasonable quality, both of which were based on data from trial 30-49 and were very similar. Consequently, as with the assessment of clinical effectiveness and although the report is based on limited evidence, this is the best available evidence at the current time.

Issues about the quality of the clinical effectiveness evidence

In terms of the assessment of clinical effectiveness, trial 30-49 appeared to be of reasonably good quality. The only main area of concern centred on the analysis of ITT data. In total, 481 participants were randomised to take part in the trial, but the ITT analysis reported by the study authors only included 474 participants and, effectively, was not a true ITT analysis. ITT analyses represent a more conservative estimate of effects more closely resembling clinical practice.

As has already been stated, Phase II studies were also included in the review, but their non-comparative design was weak and suffered from a number of methodological issues, which could have biased their findings. In addition, the possibility of publication bias may have existed with such studies (i.e. studies showing less favourable results may remain unpublished). Study 30-47E reported the lowest treatment response rate (6.5% overall versus 13.1 and 25.7% in the other two studies) and the lowest median overall survival (25.1 weeks (5.8 months) versus 11 months in the other studies) of all the Phase II studies sponsored by the drug manufacturers of pegylated liposomal doxorubicin hydrochloride. The final unpublished trial report of study 30-47 reported three treatment-related deaths that were not reported in the earlier published interim reports of the study; and also the highest treatment withdrawal rate (10.5%) amongst those studies sponsored by the drug manufacturers of pegylated liposomal doxorubicin hydrochloride.

Consequently, although the data from non-comparative Phase II studies were reported, they were not considered in the overall assessment of clinical effectiveness for the various reasons previously explained in this report.

Summary and statistical significance of the clinical effectiveness data

The assessment of clinical effectiveness was based on the best evidence currently available, although this was limited to trial 30-49. One further RCT that compared pegylated liposomal doxorubicin hydrochloride with paclitaxel was identified, but, as has already been reported, the trial was terminated due to paclitaxel being adopted as a first-line treatment for ovarian cancer. Attempts were made to obtain data gathered before the termination of the trial, but the trial sponsors (Schering-Plough Ltd) were unable to supply any data.

Trial 30-49 reported the outcomes response rate, median survival time, median time to response, median time to progression, median duration of response, QoL and the incidence of adverse events. No major statistically significant differences were observed in the main effectiveness outcomes (*Table 19*). Those differences that were identified as statistically significant related to outcomes within specific subgroups of patients, where there

were serious concerns about the validity and appropriateness of the analyses. By continually subdividing the study population into subgroups containing very small numbers of patients, the likelihood of finding statistically significant differences in effect by pure chance increases as the power of the tests of significance is reduced. Tests of interaction can be performed in order to try and gain some insight into how likely it is that a significant difference in outcome is important for a particular subgroup. These tests were used in this report, and suggested that it was unlikely that the differences observed in the subgroup analyses were of any real relevance.

In some instances, the trial failed to describe how various outcomes were measured. This may have been due to incomplete reporting or could have been a true concern, which could have potentially biased the measurement of these outcomes. This potential for bias should be borne in mind when considering the data for these outcomes.

A considerable amount of data from the trial focused on the assessment of response rates. Response rates can be useful in determining whether a drug has any biological activity, but, ultimately, survival is the most important outcome. In addition, particularly in the case of ovarian cancer, response is a very subjective and difficult outcome to assess, hence the importance of using a blinded assessor. In the case of second-line therapy in ovarian cancer, which is currently aimed at palliation rather than cure, response rates may be useful, but ideally new chemotherapy agents would lead to a significant improvement in quality-adjusted survival and not just response.

Time to event data, such as survival and time to progression, should be analysed appropriately using Kaplan–Meier methods and HRs, as was the case in trial 30-49. Such analyses take into account the fact that the outcome of interest may never be observed over the period of follow-up (i.e. observation may be censored) and that, throughout the follow-up period, individuals will be lost to the analysis (e.g. due to death). However, the HRs presented in trial 30-49 were reported with 90% CIs. In the interim analysis of the trial, 91.6% CIs were used, but no reasons were given for changing these limits in the final analysis. Statistical data are usually presented with 95% CIs, the higher the interval the more confidence can be placed on the estimate. Using 90% CIs, results in HRs that are more often significant. For the purposes of this review, traditional 95% CIs were calculated.

There was no good evidence of statistically significant differences in effect. It could be that, in such a seriously ill population of patients with little hope of cure or long-term survival, small but statistically non-significant differences in effects could be significant to the patients concerned, that is, in alleviating symptoms. However, in view of the fact that the trial did not demonstrate many significant differences in QoL between the patient groups, it seems unlikely that the differences in effect would make any real impact on patients' lives. Two statistically significant differences in QoL were identified that were limited to the pain subscale score, however, these differences were based on data available from only 50% of the patients. In patients in general and in platinum-sensitive patients, significantly more patients had a maintained or improved QoL pain score at 12 weeks in the topotecan-treated group as opposed to the pegylated liposomal doxorubicin hydrochloride-treated group. Q-TWiST analysis suggested that pegylated liposomal doxorubicin hydrochloride has quality-adjusted survival advantages over topotecan. However, the Q-TWiST analysis included a major assumption that may not have been justified, namely that a day with toxicity was valued the same (in terms of utility) whatever the type of adverse event the patient was experiencing. The analyses were also based on data that were not patient-reported.

Despite the lack of significant differences in response between pegylated liposomal doxorubicin hydrochloride and topotecan, differences in the incidence of adverse events were found to be statistically significant. It should be noted, however, that only acute toxicity was addressed in the scope of this review. Topotecan was shown to be significantly associated with a higher incidence of neutropenia, leukopenia, thrombocytopenia, anaemia and nausea/vomiting. These haematological toxicities can be managed using blood transfusions and therapies, such as G-CSF, but these add to the cost of the therapy and the inconvenience to the patient. Compared with pegylated liposomal doxorubicin hydrochloride, topotecan was associated with a significantly higher incidence of alopecia. In addition, two patient deaths related to haematological complications associated with topotecan were reported. No deaths were reported in the pegylated liposomal doxorubicin hydrochloride treatment group. However, pegylated liposomal doxorubicin hydrochloride was associated with a significantly higher incidence of PPE and stomatitis compared with topotecan. Mucous membrane disorders and skin rashes were also significantly increased in the

pegylated liposomal doxorubicin hydrochloride-treated patients. PPE affects the palms of the hands and soles of the feet and causes a macular, often painful, reddening of the skin, which, in severe cases, can lead to epidermal necrosis. Various options are available for the management of PPE and it has been suggested that pretreatment with dexamethasone may prevent the development of PPE. In addition, instances of myalgia, arthralgia, neuropathy and paraesthesia were also increased, although RR estimates for these effects could not be calculated.

Quality and summary of the cost-effectiveness data

The economic analyses in the review were of reasonable quality. They both concluded that pegylated liposomal doxorubicin hydrochloride was more cost-effective than topotecan given equivalent overall survival and lower mean costs to the health service. Further analysis reported in this report showed that when the measure of effectiveness was taken as life-years, the results in the two papers were robust to plausible changes in assumptions. When uncertainty in mean costs and mean life-years was considered, pegylated liposomal doxorubicin hydrochloride had a probability of being more cost-effective than topotecan of 70–80% when an additional life-year was valued at £30,000. This represented a higher level of uncertainty than in the CMA, which assumed zero uncertainty in life-years, but suggested that the use of pegylated liposomal doxorubicin hydrochloride is consistent with maximising life-years given existing data.

The major limitation of the economic analyses included in the review was the fact that effectiveness had not been quantified in terms of QALYs. Although trial 30-49 demonstrated similar survival durations between the two arms, equivalence in HRQoL was not established. Indeed, the review of HRQoL data in the QoL section on page 25 indicated that most health domains were similar between the two groups with the exception of pain, which had a more marked impact on pegylated liposomal doxorubicin hydrochloride patients. Further sensitivity analysis in this review showed that plausible advantages in HRQoL for topotecan could generate incremental cost per QALY ratios that would be considered reasonable by the NHS. Until utility data are collected in these patients, the cost-effectiveness of the two therapies in terms of QALYs is highly uncertain.

Comparison with other systematic reviews

No previous systematic reviews of second-line therapy for advanced ovarian cancer were identified, which included data relating to the use of pegylated liposomal doxorubicin hydrochloride.

Implications for further research

In view of the evidence presented in this review, there is a need for basic research into new more effective agents for second-line chemotherapy and a need for more good quality RCTs comparing the effectiveness of pegylated liposomal doxorubicin hydrochloride to existing agents, including topotecan. Future trials should ensure that data are gathered with respect to a range of outcomes as discussed in this review. Data on the QoL of patients with advanced ovarian carcinoma undergoing second-line therapy are particularly important in view of the current poor prognosis and limited survival of these patients. These data should be collected in a way suitable for CEA, that is, in a form that can be appropriately valued in terms of utilities. Ovarian cancer is a very difficult disease to treat, and methods of prevention and detection are limited such that the disease often progresses to an advanced stage before it is detected. Although first-line therapy may be successful in the short term, the majority of patients will be refractory or resistant to treatment. At present, second-line chemotherapy is mainly palliative with little hope of being curative.

Future trials should be adequately randomised and the allocation of treatment concealed to avoid selection bias. In addition, steps should be taken to ensure that data are analysed on an ITT basis and that those assessing the outcome measures are blinded to the intervention assignment. This latter point is particularly important in order to avoid bias in the final effect sizes. With respect to time to event data, it is also important that data are presented in the form of Kaplan–Meier survival curves and compared using HRs (with CIs, preferably 95% CIs). The presentation of dichotomous data in terms of RRs (with 95% CIs) is also preferable, and, where these are not available, the absolute numbers of events and participants should be stated so as to allow others to calculate RR estimates.

Formal estimation of the EVPI was reported here, which assumed that the appropriate measure of effectiveness to use in evaluating

these interventions is life-years. Given the degree of uncertainty around these life-year estimates, the EVPI was relatively large (£10 million when an additional life-year was valued at £30,000). This provides a strong *prima facie* case that the collection of more trial evidence would be efficient. In addition, although it was not formally addressed in the EVPI analysis, the collection of utilities is likely to be important.

Updating the review

Unfortunately, no further ongoing RCTs or economic evaluations were identified. One ongoing Phase II study was identified, but, as already discussed, this should not be of major significance to this review, which aims to only consider the best-quality evidence available. In view of the length of time required to plan and conduct suitably designed good-quality RCTs and economic evaluations, it would seem reasonable not to update the current review until new evidence from such evaluations becomes available.

Conclusions

This review suggests that there is little evidence in the form of RCTs on which to base an assessment of the effectiveness of pegylated liposomal doxorubicin hydrochloride in comparison to existing and new chemotherapy agents for the second-line treatment of advanced ovarian cancer. Data from only one clinical effectiveness study comparing pegylated liposomal doxorubicin with topotecan were available for consideration in this review. In addition, only one relevant economic evaluation (with two variants) was identified. This was based on the aforementioned trial of clinical effectiveness.

From the limited evidence available, it would appear that there were no statistically significant differences in the effects of pegylated liposomal doxorubicin hydrochloride and topotecan. The few statistically significant differences that were observed were limited to questionable subgroup analyses. However, statistically significant differences between the drugs were identified in terms of treatment-related adverse events. The adverse events of concern for topotecan were related to the drug's haematological toxicity. In comparison, pegylated liposomal doxorubicin hydrochloride was associated with PPE and stomatitis. Overall, the efficacy of pegylated liposomal doxorubicin hydrochloride could, at best, be described as modest. However, the only other comparator considered in this review, topotecan, offered no real advantages in terms of effect either. If anything, pegylated liposomal doxorubicin hydrochloride offered possible advantages over topotecan in terms of adverse events and cost-effectiveness.

Given this essentially neutral finding on effects, the costs associated with the drugs become crucial. The economic evaluations included a robust analysis of costs and showed a significant reduction in the costs associated with pegylated liposomal doxorubicin hydrochloride when compared with topotecan. When effectiveness was expressed in terms of mean survival duration, there was a high probability that pegylated liposomal doxorubicin hydrochloride is the more cost-effective intervention (70–80%). However, the possible differences in HRQoL between the two therapies, reflecting differences in the incidence of adverse events, may produce quite different cost-effectiveness results when effectiveness is expressed in terms of QALYs – a preferable measure when both length of life and QoL are potentially influenced. Therefore, although pegylated liposomal doxorubicin hydrochloride is very likely to have lower costs than topotecan, its overall cost-effectiveness is unclear.

In conclusion, further good-quality RCTs are required comparing pegylated liposomal doxorubicin hydrochloride with other licensed and potentially useful (soon to be licensed) second-line chemotherapy agents for ovarian cancer. It is essential that these studies attempt to measure overall HRQoL in a way suitable for incorporation into CEAs. At present, it is difficult to make any choices about pegylated liposomal doxorubicin hydrochloride and other drugs for the second-line treatment of ovarian cancer without such good-quality direct comparisons.

Acknowledgements

The authors wish to thank the expert peer review panel for their comments on the draft protocol and report. The members included Dr Malcolm Adams (Velindre Hospital, Cardiff, UK), Professor Hilary Calvert (University of Newcastle-upon-Tyne Medical School, Newcastle-upon-Tyne, UK), Dr Trivadi S Ganesan (Imperial Cancer Research Fund Medical Oncology Unit, Oxford, UK), Dr Martin Gore (The Royal Marsden NHS Trust, London, UK), Dr Dirk Hasenclever (Institut für Medizinische Informatik, Statistik & Epidemiologie, Leipzig, Germany), Mr Niels Neymark (EORTC, Brussels, Belgium), Dr Tim Root (The Royal Marsden Hospital London and Surrey, London, UK), Dr Maurice L Slevin (St Bartholomew's Hospital, London, UK) and Dr Jayne Tierney (MRC Clinical Trials Unit, London, UK). The following members had declared competing interests: Professor Hilary Calvert (investigator in a clinical trial of an unlicensed potential competitor of topotecan (liposomal lurtotecan, Gilead) and a consultant for Bristol-Myers Squibb and Eli-Lilly), Dr Martin Gore (assisting the Joint Council of Clinical Oncology with their submission to NICE, and a recipient of funding from Schering-Plough Ltd, Bristol-Myers Squibb, SmithKline Beecham, Novartis, AstraZeneca, Debioclinic, Pierre Fabre Ltd, Novis-pharma, Genta, Nextstar, Roche, Chiron, Knoll, British Biotech, Cantab, CAT, Cobra and Novacs) and Dr Maurice Slevin (Chairman of the cancer support charity CancerBACUP).

The authors are grateful to Penny Whiting for assisting in the development of the Access database, and Professor Keith Abrams and Dr Alex Sutton from the University of Leicester for advice relating to the additional economic analysis. Mark Sculpher has a Career Scientist Award in Public Health from the NHS R&D HTA Programme.

Contributions of the authors

Dr Carol Forbes (Research Fellow) was the lead reviewer responsible for writing the scope, protocol and final review. She was also involved in the selection of studies and the extraction and synthesis of data. Jennifer Wilby (Research Fellow) was involved in producing the scope and protocol. She read and commented on the final draft report and assisted in the selection of studies and the extraction and checking of data. Gerry Richardson (Research Fellow) wrote and analysed data for the economic effectiveness sections of the protocol and final report. He also read and commented on the draft protocol and final report, and devised the economic quality assessment, data extraction and methods of further analysis. Lisa Mather (Information Officer) devised the search strategy and carried out the literature searches. She wrote the search methodology sections of the protocol and final report, and managed the interlibrary loans and the Endnote library. Professor Mark Sculpher (Economic Evaluation Manager) was responsible for the overall management of the economic evaluation sections of the review, and he read and commented on the draft, protocol and final report. He also devised the economic quality assessment, data extraction and methods of further analysis. Dr Rob Reimsma (Senior Research Fellow) was the review manager responsible for the overall management of the project. He assisted in the development of the adapted economic and quality checklists, and provided advice and comments on the scope, protocol and final report.

This report was commissioned by the NHS R&D HTA Programme on behalf of NICE. The views expressed in this report are those of the authors and not necessarily those of the NHS R&D HTA Programme. Any errors are the responsibility of the authors.

References

1. Beltz SE, Yee GC. Pharmacoeconomics of cancer therapy. *Cancer Control* 1998;**5**:415–24.
2. Lister-Sharp D, McDonagh MS, Khan KS, Kleijnen J. A rapid and systematic review of the effectiveness and cost-effectiveness of the taxanes used in the treatment of advanced breast and ovarian cancer. *Health Technol Assess* 2000;**4**(7).
3. Forbes C, Shirran L, Bagnall AM, Duffy S, ter Riet G. A rapid and systematic review of the clinical effectiveness and cost-effectiveness of topotecan for ovarian cancer. *Health Technol Assess* 2001;**5**(28).
4. Smith DH, Drummond MF, Johnston S, Gordon A. Economic evaluation of liposomal doxorubicin versus topotecan for recurrent ovarian cancer in the UK. *Value in Health* 2001;**4**:88.
5. Office for National Statistics. Cancer: rates per 100,000 population of newly diagnosed cases of cancer (provisional): major sites, sex and age, England and Wales, 1994–1996. London: Government Statistical Service; 1997.
6. Cancer Research Campaign. CRC CancerStats: survival. England and Wales 1971–1995 [monograph online]. London: Cancer Research Campaign; 1999. [cited 2001 Sep 30]. URL: http://www.crc.org.uk/cancer/pageimages/cssurvival.pdf
7. Gore M. The evidence base for medical intervention in ovarian cancer. In: Maclean A, Gore M, Miles A, editors. The effective management of ovarian cancer. London: Aesculapius Medical Press; 1999. p. 76–90.
8. Kitchener H. Gynaecological cancer. *Postgrad Med* 1999;**75**:332–8.
9. ACOG educational bulletin. Ovarian cancer. Number 250, August 1998 (replaces Number 141, May 1990). American College of Obstetricians and Gynecologists. *Int J Gynaecol Obstet* 1998;**63**:301–10.
10. Lynch HT, Lunch JF, Conway TA. Hereditary ovarian cancer. In: Rubin SG, Sutton GP, editors. Ovarian cancer. New York: McGraw-Hill; 1993. p. 189–217.
11. Markman M, Kennedy A, Webster K, Peterson G, Kulp B, Belinson J. Phase 2 trial of liposomal doxorubicin (40 mg/m^2) in platinum/paclitaxel-refractory ovarian and Fallopian tube cancers and primary carcinoma of the peritoneum. *Gynecol Oncol* 2000;**78**(3 Pt 1):369–72.
12. Parazzini F, Franceschi S, La Vecchia C, Fasoli M. The epidemiology of ovarian cancer. *Gynecol Oncol* 1991;**43**:9–23.
13. Whittemore AS, Wu ML, Paffenbarger Jr RS, Sarles DL, Kampert JB, Grosser S, *et al.* Epithelial ovarian cancer and the ability to conceive. *Cancer Res* 1989;**49**:4047–52.
14. Rossing MA, Daling JR, Weiss NS, Moore DE, Self SG. Ovarian tumors in a cohort of infertile women. *N Engl J Med* 1994;**331**:771–6.
15. Cramer DW, Welch WR, Scully RE, Wojciechowski CA. Ovarian cancer and talc: a case-control study. *Cancer* 1982;**50**:372–6.
16. Cramer DW, Harlow BL, Willett WC, Welch WR, Bell DA, Scully RE, *et al.* Galactose consumption and metabolism in relation to the risk of ovarian cancer. *Lancet* 1989;**2**(8654):66–71.
17. Greene MH, Clark JW, Blayney DW. The epidemiology of ovarian cancer. *Semin Oncol* 1984;**11**:209–26.
18. The reduction in risk of ovarian cancer associated with oral-contraceptive use. The Cancer and Steroid Hormone Study of the Centers for Disease Control and the National Institute of Child Health and Human Development. *N Engl J Med* 1987;**316**:650–5.
19. Epithelial ovarian cancer and combined oral contraceptives. The WHO Collaborative Study of Neoplasia and Steroid Contraceptives. *Int J Epidemiol* 1989;**18**:538–45.
20. Whittemore AS, Harris R, Itnyre J. Characteristics relating to ovarian cancer risk: collaborative analysis of 12 US case–control studies. II. Invasive epithelial ovarian cancers in white women. Collaborative Ovarian Cancer Group. *Am J Epidemiol* 1992;**136**:1184–203.
21. Berek JS, Bertelsen K, Du Bois A, Brady MF, Carmichael J, Eisenhauer EA, *et al.* Advanced epithelial ovarian cancer: 1998 consensus statements. *Ann Oncol* 1999;**10** (Suppl 1):S87–92.
22. National Institute for Clinical Excellence. Guidance on the use of taxanes for ovarian cancer [monograph online]. London: NICE; 2000. [cited 2002 Sep 30]. URL: http://www.nice.org.uk/nice-web/Embcat.asp?page=oldsite/appraisals/tax_guide.htm&ss=taxanes

23. National Institute for Clinical Excellence. Guidance on the use of topotecan for the treatment of advanced ovarian cancer. London: NICE; August 2001. Report No.: Technology Appraisal Guidance No. 28.

24. Electronic medicines compendium: Caelyx [monograph online]. London: Datapharm Communications Ltd; 2000. [cited 2001 Jun 11]. URL: http://srs.vhn.net/eMC/documents/01800/01853/SPC.1853.html

25. British Medical Association, Royal Pharmaceutical Society of Great Britain. British National Formulary. No. 41. London: BMA, RPSGB; 2000.

26. NHS Centre for Reviews and Dissemination. Undertaking systematic reviews of research on effectiveness: CRD's guidance for carrying out or commissioning reviews. 2nd ed. York: NHS Centre for Reviews and Dissemination; 2001. Report No.: CRD Report 4.

27. Drummond MF, O'Brien B, Stoddart GL, Torrance GW. Methods for the economic evaluation of health care programmes. 2nd ed. Oxford: Oxford Medical Publications; 1997.

28. National Institute for Clinical Excellence. Technical guidance for manufacturers and sponsors on making a submission to a technology appraisal. London: NICE; 2001.

29. Castaldo TW, Ballon SC, Lagasse LD, Petrilli ES. Reticuloendothelial neoplasia of the female genital tract. *Obstet Gynecol* 1979;**54**:167–70.

30. Caelyx in the treatment of ovarian carcinoma. *Deutsche Apotheker Zeitung* 2000;**140**(33):43.

31. Cook SE, Penson R, Nikrui N, Goodman A, Fuller Jr A, Seiden MV. Efficacy and hematologic toxicity of salvage chemotherapy following PBSCT in women with recurrent ovarian carcinoma. *Gynecol Oncol* 1999;**72**:500.

32. Frykman G, Williams G, Pazdur R. Conflicting Phase II efficacy data for Doxil. *J Clin Oncol* 2001;**19**:596–7.

33. Hornreich G, Schloss C, Hoskins WJ, Muggia FM. Doxil-induced radiation recall: a cause for false-positive PET scan findings. *Gynecol Oncol* 2001;**80**:422–3.

34. Ortner P. Eine neue Option fur die Therapie des Ovarialkarzinoms [Pegylated liposomal doxorubicin – a new option for the treatment of ovarian carcinoma]. *Onkol Serv Aktuell* 2000;**3**:9.

35. Skelton H, Linstrum J, Smith K. Host vs altered-host eruptions in patients on liposomal doxorubicin [poster presentation]. *J Cutan Pathol* 1999;**26**:471.

36. Approval of Caelyx registered for the treatment of ovarian carcinoma. *Deutsche Apotheker Zeitung* 2000;**140**(47):46.

37. Muggia FM, Safra T, Groshen S, Jeffers S, Roman L, Tan M, *et al.* Pegylated liposomal doxorubicin: antitumor activity in epithelial ovarian cancer or cancers of peritoneal origin. *Oncol USA* 1997; **11**(10 Suppl 11):38–44.

38. Seiden M. Highlights in ovarian cancer. *The Oncologist* 2000;**5**:267–73.

39. Delgado G, Potkul RK, Treat JA, Lewandowski GS, Barter JF, Forst D, *et al.* A Phase I/II study of intraperitoneally administered doxorubicin entrapped in cardiolipin liposomes in patients with ovarian cancer. *Am J Obstet Gynecol* 1989;**160**:812–19.

40. Vogl SE, Greenwald E, Kaplan BH, Moukhtar M, Wollner D. Ovarian cancer. Effective treatment after alkylating-agent failure. *JAMA* 1979;**241**:1908–11.

41. Herzog TJ, Gandhi S, Swisher EM, Rader JS, Mutch DG, Elbendary AA. Liposomal doxorubicin in advanced relapsed gynecologic malignancies. *Gynecol Oncol* 1999;**72**:470.

42. Jahanzeb M, Vogel M, Elkrish A, *et al.* Stealth liposomal doxorubicin (Doxil) causes a mild and delayed leukopenia compared to standard doxorubicin in patients with solid tumors [meeting abstract]. Proceedings of the 33rd Annual Meeting of the American Society of Clinical Oncology; 1997 May 17–20; Denver, CO, USA. Alexandria, VA: ASCO; 1997. 239a.

43. Safra T, Jeffers S, Groshen S, Uziely B, Roman L, Muderspach L, *et al.* Doxil® (D) in platinum-refractory epithelial ovarian cancer (EOC): results from three consecutive Phase I/II studies [meeting abstract]. Proceedings of the 33rd Annual Meeting of the American Society of Clinical Oncology; 1997 May 17–20; Denver, CO, USA. Alexandria, VA: ASCO; 1997. 349a.

44. Safra T, Groshen S, Jeffers S, Tsao Wei DD, Zhou L, Muderspach L, *et al.* Treatment of patients with ovarian carcinoma with pegylated liposomal doxorubicin: analysis of toxicities and predictors of outcome. *Cancer* 2001;**91**:90–100.

45. Martin FJ. Doxil (pegylated liposomal doxorubicin): clinical update. *Abstracts Papers Am Chem Soc* 1996;**211**(1–2):CARB 034.

46. Gordon AN, Fleagle JT, Guthrie D, Parkin DE, Gore M, Lacave AJ, *et al.* Interim analysis of a Phase III randomized trial of Doxil/Caelyx (D) versus topotecan (T) in the treatment of patients with relapsed ovarian cancer [meeting abstract]. Proceedings of the 36th Annual Meeting of the American Society of Clinical Oncology; 2000 May 20–23; New Orleans, LA, USA. Alexandria, VA: ASCO; 2000. Abstract 1504.

47. Overview of the study 30-49 final results [unpublished]. Welwyn Garden City: Schering-Plough Ltd; 2000.

48. Gordon AN, Fleagle JT, Guthrie D, Parkin DE, Gore ME, Lacave AJ. Recurrent epithelial ovarian carcinoma: a randomized Phase III study of pegylated liposomal doxorubicin versus topotecan. *J Clin Oncol* 2001;**19**:3312–22.

49. Whittaker J. Phase III randomised open-label comparative study of Caelyx versus paclitaxel in patients with epithelial ovarian carcinoma following failure of first time platinum based chemotherapy (Caelyx) [NRR ongoing project]. In: The National Research Register CD-ROM 2001 Issue 1. Oxford: Update Software; 2001.

50. Muggia F, Hainsworth J, Jeffers S, Groshen S, Tan M, Greco FA. Liposomal doxorubicin (Doxil) is active against refractory ovarian cancer [meeting abstract]. Proceedings of the 32nd Annual Meeting of the American Society of Clinical Oncology; 1996 May 18–21; Philadelphia, PA, USA. Alexandria, VA: ASCO; 1996. 287.

51. Muggia FM, Hainsworth JD, Jeffers S, Miller P, Groshen S, Tan M, *et al.* Phase II study of liposomal doxorubicin in refractory ovarian cancer: antitumor activity and toxicity modification by liposomal encapsulation. *J Clin Oncol* 1997;**15**:987–93.

52. Gordon AN. Doxil® (doxorubicin HCl liposome injection) in the treatment of patients with refractory advanced epithelial ovarian carcinoma – results of an interim analysis [meeting abstract]. Proceedings of the 34th Annual Meeting of the American Society of Clinical Oncology; 1998 May 15–18; Los Angeles, CA, USA. Alexandria, VA: ASCO; 1998. 349a.

53. Rose P, Gordon A, Granai CO, Hainsworth J, Weissman C, Lopez Ana M, *et al.* Interim analysis of a non-comparative, multicenter study of Doxil/Caelyx in the treatment of patients with refractory ovarian cancer [meeting abstract]. Proceedings of the 35th Annual Meeting of the American Society of Clinical Oncology; 1999 May 15–18; Atlanta, GA, USA. Alexandria, VA: ASCO; 1999. 360a.

54. Gordon AN, Granai CO, Rose PG, Hainsworth J, Lopez A, Weissman C, *et al.* Phase II study of liposomal doxorubicin in platinum- and paclitaxel-refractory epithelial ovarian cancer. *J Clin Oncol* 2000;**18**:3093–100.

55. Amended end of planned treatment report for protocol 30-47. A noncomparative, multicenter study of Caelyx/Doxil in the treatment of patients with advanced epithelial ovarian carcinoma. [Unpublished trial report]. Mountain View, CA: Alza Corporation; September 1999.

56. End of planned treatment report for protocol 30-47E. A noncomparative, multicenter study of Caelyx/Doxil in the treatment of patients with advanced epithelial ovarian carcinoma. [Unpublished trial report]. Mountain View, CA: Alza Corporation; August 1999.

57. Israel VP, Garcia AA, Roman L, Muderspach L, Burnett A, Jeffers S, *et al.* Phase II study of liposomal doxorubicin in advanced gynecologic cancers. *Gynecol Oncol* 2000;**78**:143–7.

58. Linardou H, Aravantinos G, Bafaloukos D, Skarlos D, Kalofonos H, Papadimitriou C, *et al.* Salvage therapy in heavily pretreated ovarian cancer with single agent pegylated liposomal doxorubicin (PLD): preliminary results of a multicenter Phase II study of the Hellenic Co-operative Oncology Group. *Ann Oncol* 2000;**11**(Suppl 4):376P.

59. Cervantes A, Garcia T, Martinez de Duenas E, Insa A, de Paz L, Lluch A, *et al.* Phase II trial of liposomal doxorubicin (Caelyx) in relapses of cisplatin refractory ovarian carcinoma. *Eur J Cancer* 1999;**35**:S86.

60. European Agency for the Evaluation of Medicinal Products. European Public Assessment Report (EPAR) – Caelyx: revision 5 [monograph online]. [cited 2001 Jan 9]. URL: http://web.is.eudra.org/humandocs/humans/EPAR/Caelyx/CaelyxM.htm

61. Cole BF, Gelber RD, Kirkwood JM, Goldhirsch A, Barylak E, Borden E. Quality-of-life-adjusted survival analysis of interferon alfa-2b adjuvant treatment of high-risk resected cutaneous melanoma: an Eastern Cooperative Oncology Group study. *J Clin Oncol* 1996;**14**:2666–73.

62. Cole BF, Solal-Celigny P, Gelber RD, Lepage E, Gisselbrecht C, Reyes F, *et al.* Quality-of-life-adjusted survival analysis of interferon alfa-2b treatment for advanced follicular lymphoma: an aid to clinical decision making. *J Clin Oncol* 1998;**16**:2339–44.

63. Gelber RD, Cole BF, Gelber S, Goldhirsch A. The Q-TWiST method. In: Spilker B, editor. Quality of life and pharmacoeconomics in clinical trials. Philadelphia: Lippincott-Raven; 1995. p. 437–44.

64. Glasziou PP, Simes RJ, Gelber RD. Quality adjusted survival analysis. *Stat Med* 1990;**9**:1259–76.

65. Parsons SK, Gelber S, Cole BF, Ravindranath Y, Ogden A, Yeager AM, *et al.* Quality-adjusted survival after treatment for acute myeloid leukemia in childhood: a Q-TWiST analysis of the Pediatric Oncology Group study 8821. *J Clin Oncol* 1999;**17**:2144.

66. Zee B, Cole BF, Li T, Browman G, James K, Johnston D, *et al.* Quality-adjusted time without symptoms or toxicity analysis of interferon maintenance in multiple myeloma. *J Clin Oncol* 1998;**16**:2834–9.

67. Schering-Plough Ltd. Caelyx (pegylated liposomal doxorubicin hydrochloride). Caelyx in the treatment of recurrent ovarian cancer in the United Kingdom: a submission to the National Institute for Clinical Excellence, 2001. Welwyn Garden City: Schering-Plough Ltd; August 2001.

68. Black WC. A graphic representation of cost-effectiveness. *Med Decis Making* 1990;**10**:212–14.

69. Van Hout BA, Al MJ, Gordon GS, Rutten FFH. Costs, effects and c/e-ratios alongside a clinical trial. *Health Econ* 1994;**3**:309–19.

70. Claxton K, Posnett J. An economic approach to clinical trial design and research priority-setting. *Health Econ* 1996;**5**:513–24.

71. Williams C. Cancer biology and management: an introduction. Chichester: Wiley; 1990.

72. Crombie IK. The standard appraisal questions. In: The pocket guide to critical appraisal: a handbook for health care professionals. London: BMJ Publishing Group; 1996. p. 23–9.

73. Crombie IK. Appraising clinical trials. In: The pocket guide to critical appraisal: a handbook for health care professionals. London: BMJ Publishing Group; 1996. p. 43–9.

74. British Medical Association, Royal Pharmaceutical Society of Great Britain. British National Formulary. No. 37. London: BMA, RPSGB; 1999.

Appendix 1

Search strategies

The core search strategy used for this review was as follows:

#1 doxil
#2 doxorubicin hydrochloride
#3 doxorubicin hcl
#4 liposomal doxorubicin
#5 pegylated liposomal doxorubicin
#6 caelyx
#7 liposome-encapsulated doxorubicin
#8 liposome encapsulated doxorubicin
#9 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8
#10 "Ovarian-Neoplasms"/all subheadings
#11 (ovar* near4 (cancer* or tumo?r* or malignan*)) in ti,ab
#12 (ovar* near4 (oncolog* or carcinoma* or neoplas*)) in ti,ab
#13 #10 or #11 or #12
#14 #9 and #13

This strategy was designed for searching the MEDLINE electronic database (on SilverPlatter), and was adapted, as appropriate, for all other databases searched, taking into account differences in indexing terms and search syntax for each database. Search strategies were not designed to restrict the retrieved results by study type. In total, 142 references were retrieved. Full details of all databases searched and search strategies used are provided below.

Clinical effectiveness

Initial searches were undertaken to identify any existing systematic reviews in the area, using databases of systematic reviews. The search was then broadened to retrieve all study designs. The administrative database for the Database of Abstracts of Reviews of Effectiveness was searched rather than the public (Internet-based) version in order to retrieve details of systematic reviews that did not meet the quality inclusion criteria for the database.

Searches for systematic reviews

Database of Abstracts of Reviews of Effectiveness: administrative database

The Database of Abstracts of Reviews of Effectiveness was searched on 19 May 2001 and the following strategy was used.

s1 caelyx or doxil
s2 doxorubicin(w)hydrochloride
s3 doxorubicin(w)hcl
s4 liposomal(w)doxorubicin
s5 liposome(w)encapsulated(w)doxorubicin
s6 s1 or s2 or s3 or s4 or s5
s7 ovarian-neoplasms/kwo
s8 ovar$
s9 s7 or s8
s10 s6 and s9

Cochrane Database of Systematic Reviews: CD-ROM (Cochrane Library 2001, Issue 2)

The Cochrane Database of Systematic Reviews was searched on 29 May 2001 and the following strategy was used.

#1 caelyx or doxil
#2 doxorubicin next hydrochloride
#3 doxorubicin next hcl
#4 liposomal next doxorubicin
#5 liposomal next (encapsulated next doxorubicin)
#6 #1 or #2 or #3 or #4 or #5
#7 ovarian-neoplasms:me
#8 ovar*
#9 #7 or #8
#10 #6 and #9

Searches for other study designs

BIOSIS: Edina

The BIOSIS database was searched from 1985–May 2001 on 29 May 2001, and the following strategy was used.

(caelyx or doxil or doxorubicin w hydrochloride or doxorubicin w hcl or liposomal w doxorubicin or liposome w encapsulated w doxorubicin) and ovar*

CANCERLIT: Internet (<http://cancernet.nci.nih.gov/cancerlit.shtml>)

The CANCERLIT database was searched from 1966–May 2001 on 29 May 2001 and the following strategy was used.

(caelyx or doxil or "doxorubicin hydrochloride" or "doxorubicin hcl" or "liposomal doxorubicin" or "liposome encapsulated doxorubicin") and ovar*

CINAHL: SilverPlatter

The CINAHL database was searched from 1982–February 2001 on 29 May 2001, and the following strategy was used.

#1 doxil
#2 doxorubicin hydrochloride
#3 doxorubicin hcl
#4 liposomal doxorubicin
#5 pegylated liposomal doxorubicin
#6 caelyx
#7 liposome-encapsulated doxorubicin
#8 liposome encapsulated doxorubicin
#9 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8
#10 "Ovarian-Neoplasms"/all subheadings
#11 (ovar* near4 (cancer* or tumo?r* or malignan*)) in ti,ab
#12 (ovar* near4 (oncolog* or carcinoma* or neoplas*)) in ti,ab
#13 #10 or #11 or #12
#14 #9 and #13

HealthStar: SilverPlatter

The HealthStar database was searched from 1981–December 2000 on 18 June 2001, and the following strategy was used.

#1 doxil
#2 doxorubicin hydrochloride
#3 doxorubicin hcl
#4 liposomal doxorubicin
#5 pegylated liposomal doxorubicin
#6 caelyx
#7 liposome-encapsulated doxorubicin
#8 liposome encapsulated doxorubicin
#9 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8
#10 "Ovarian-Neoplasms"/all subheadings
#11 (ovar* near4 (cancer* or tumo?r* or malignan*)) in ti,ab
#12 (ovar* near4 (oncolog* or carcinoma* or neoplas*)) in ti,ab
#13 #10 or #11 or #12
#14 #9 and #13

MEDLINE: SilverPlatter

The MEDLINE database was searched from 1966–December 2000 on 29 May 2001, and the following strategy was used.

#1 doxil
#2 doxorubicin hydrochloride
#3 doxorubicin hcl
#4 liposomal doxorubicin
#5 pegylated liposomal doxorubicin
#6 caelyx
#7 liposome-encapsulated doxorubicin
#8 liposome encapsulated doxorubicin
#9 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8
#10 "Ovarian-Neoplasms"/all subheadings
#11 (ovar* near4 (cancer* or tumo?r* or malignan*)) in ti,ab
#12 (ovar* near4 (oncolog* or carcinoma* or neoplas*)) in ti,ab
#13 #10 or #11 or #12
#14 #9 and #13

PubMed: Internet (<http://www.ncbi.nlm.nih.gov/PubMed/>)

The PubMed database was searched from January–May 2001 on 29 May 2001, and the following strategy was used.

#1 doxil
#2 doxorubicin hydrochloride
#3 doxorubicin hcl
#4 liposomal doxorubicin
#5 pegylated liposomal doxorubicin
#6 caelyx
#7 liposome-encapsulated doxorubicin
#8 liposome encapsulated doxorubicin
#9 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8
#10 "Ovarian-Neoplasms"/all subheadings
#11 (ovar* near4 (cancer* or tumo?r* or malignan*)) in ti,ab
#12 (ovar* near4 (oncolog* or carcinoma* or neoplas*)) in ti,ab
#13 #10 or #11 or #12
#14 #9 and #13

Cochrane Controlled Trials Register: CD-ROM (Cochrane Library 2001, Issue 2)

The Cochrane Controlled Trials Register database was searched on 29 May 2001, and the following strategy was used.

#1 caelyx or doxil
#2 doxorubicin next hydrochloride
#3 doxorubicin next hcl
#4 liposomal next doxorubicin
#5 liposomal next (encapsulated next doxorubicin)
#6 #1 or #2 or #3 or #4 or #5
#7 ovarian-neoplasms:me
#8 ovar*
#9 #7 or #8
#10 #6 and #9

EMBASE: SilverPlatter

The EMBASE database was searched from 1980–February 2001 on 29 May 2001, and the following strategy was used.

#1 doxil
#2 doxorubicin hydrochloride
#3 doxorubicin hcl

#4 liposomal doxorubicin
#5 pegylated liposomal doxorubicin
#6 caelyx
#7 liposome-encapsulated doxorubicin
#8 liposome encapsulated doxorubicin
#9 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8
#10 (ovar* near4 (cancer* or tumo?r* or malignan*)) in ti,ab
#11 (ovar* near4 (oncolog* or carcinoma* or neoplas*)) in ti,ab
#12 explode "ovary-tumor"/all subheadings
#13 #10 or #11 or #12
#14 #9 and #13

HTA database: Internet (Public version <http://nhscrd.york.ac.uk/welcome.htm>)
The HTA database was searched on 29 May 2001, and the following strategy was used.

s1 caelyx or doxil
s2 doxorubicin(w)hydrochloride
s3 doxorubicin(w)hcl
s4 liposomal(w)doxorubicin
s5 liposome(w)encapsulated(w)doxorubicin
s6 s1 or s2 or s3 or s4 or s5
s7 ovarian-neoplasms/kwo
s8 ovar$
s9 s7 or s8
s10 s6 and s9

Index to Scientific and Technical Proceedings: Web of Science
The Index to Scientific and Technical Proceedings database was searched from 1990–May 2001 on 29 May 2001, and the following strategy was used.

(caelyx or doxil or doxorubicin hydrochloride or doxorubicin hcl or liposomal doxorubicin or liposome encapsulated doxorubicin) and ovar*

Science Citation Index: Web of Science
The Science Citation Index database was searched from 1981–May 2001 on 29 May 2001, and the following strategy was used.

(caelyx or doxil or doxorubicin hydrochloride or doxorubicin hcl or liposomal doxorubicin or liposome encapsulated doxorubicin) and ovar*

Searches for ongoing trials

American Society of Clinical Oncology: Internet (<http://www.asco.org/>)
The American Society of Clinical Oncology website was searched on 31 May 2001, and the following search terms were used.

caelyx or doxil or doxorubicin

CenterWatch Clinical Trials Listing Service: Internet (<http://www.centerwatch.com/>)
The CenterWatch Clinical Trials Listing Service was searched on 31 May 2001, and the following search terms were used.

caelyx or doxil or doxorubicin

National Institute of Health Clinical Trials database: Internet (<http://clinicaltrials.govct/gui/c/r/>)
The National Institute of Health website was searched on 31 May 2001, and the following search terms were used.

caelyx or doxil or doxorubicin

Current Controlled Trials (including the mRCT database): Internet (<http://www.controlled-trials.com/>)
The Current Controlled Trials website was searched on 31 May 2001, and the following search terms were used.

caelyx or doxil or doxorubicin

National Cancer Institute of Canada: Internet (<http://www.ncic.cancer.ca/>)
The National Cancer Institute of Canada website was searched on 31 May 2001, and the following search terms were used.

caelyx or doxil or doxorubicin

National Cancer Institute PDQ clinical trials database: Internet (<http://cancernet.nci.nih.gov/trialsrch.shtml>)
The National Cancer Institute website was searched on 29 May 2001, and the following search terms were used.

caelyx or doxil or doxorubicin

United Kingdom Coordinating Committee on Cancer Research Register of Cancer Trials: Internet (<http://www.cto.mrc.ac.uk/ukcccr/>)
The United Kingdom Coordinating Committee on Cancer Research Register website was searched on 29 May 2001, and the following search terms were used.

caelyx or doxil or doxorubicin

National Research Register: CD-ROM (2001, Issue 1)
The National Research Register database was searched on 29 May 2001, and the following search strategy was used.

#1 caelyx or doxil
#2 doxorubicin next hydrochloride
#3 doxorubicin next hcl
#4 liposomal next doxorubicin
#5 liposomal next (encapsulated next doxorubicin)
#6 #1 or #2 or #3 or #4 or #5
#7 ovarian-neoplasms:me
#8 ovar*
#9 #7 or #8
#10 #6 and #9

Searches for background and additional information

The following Internet searches were carried out. In all cases, due to the basic search facilities of each website, it was not possible to conduct a full search, and, therefore, search terms were kept to a minimum and only the key terms listed below were used.

Schering-Plough Ltd: Internet (<http://www.schering-plough.com/>)
caelyx
doxil
doxorubicin

RxList: Internet (<http://www.rxlist.com>)
caelyx
doxil
doxorubicin

BNF 41: Internet (<http://www.bnf.vhn.net/>)
caelyx
doxil
doxorubicin

In addition to the databases listed above, general searches of the Internet were undertaken using the search engines Google (<http://www.google.com>), Metaeureka (<http://www.metaeureka.com/>) and Altavista (<http://uk.altavista.com/>).

Cost-effectiveness

The following specialist economic evaluation databases were searched in order to retrieve details of any research on the cost-effectiveness of pegylated liposomal doxorubicin hydrochloride, which had not been retrieved by searches of previous databases. The administrative database for the NHS EED was searched rather than the public (Internet-based) version in order to retrieve details of systematic reviews that did not meet the quality inclusion criteria for the database.

NHS EED: administrative database

The NHS EED was searched on 29 May 2001, and the following strategy was used.

s1 caelyx or doxil
s2 doxorubicin(w)hydrochloride
s3 doxorubicin(w)hcl
s4 liposomal(w)doxorubicin
s5 liposome(w)encapsulated(w)doxorubicin
s6 s1 or s2 or s3 or s4 or s5
s7 ovarian-neoplasms/kwo
s8 ovar$
s9 s7 or s8
s10 s6 and s9

Health Economic Evaluations Database: CD-ROM (produced by the Office of Health Economics)

The Health Economics Evaluations Database was searched on 29 May 2001, and the following search terms were used.

caelyx or doxil or doxorubicin

Appendix 2

Trialists and organisations contacted for information on studies

K Blake
Research and Development
Riddell House
St. Thomas' Hospital
Lambeth Palace Road
London
SE1 7EH

P Bliss
Department of Oncology
Royal Devon and Exeter Hospital
Barrack Road
Exeter
EX2 5DW

R Coleman*
Cancer Research Centre
YCR Department of Clinical Oncology
Weston Park Hospital
Sheffield
S10 2SJ

M Crawford*
Airedale NHS Trust
Airedale General Hospital
Steeton
Keighley
BD20 6TD

H Earl*
Box 193
Clinical Oncology Centre
Addenbrooke's NHS Trust
Cambridge
CB2 2QQ

C Gallagher
Medical Oncology Department
St Bartholomew's Hospital
West Smithfield
London
EC1A 7BE

M Gore
Medicine Section
The Royal Marsden NHS Trust
Fulham Road
Chelsea
London
SW3 6JJ

A Hong
Department of Oncology
Royal Devon and Exeter Hospital
Barrack Road
Exeter
EX2 5DW

K O'Byrne*
c/o Research and Development Office
Clinical Research Unit
Leicester Royal Infirmary NHS Trust
Infirmary Square
Leicester
LE1 5WW

ML Slevin
St Bartholomew's Hospital
King George V Building (1st Floor)
West Smithfield
London
EC1A 7BE

NSA Stuart
Oncology Department
Gwynedd Hospitals NHS Trust
Ysbyty Gwynedd
Bangor
Gwynedd
LL57 2PW

H Thomas*
Department of Clinical Oncology
Imperial College School of Medicine
Hammersmith Hospital
Du Cane Road
London
W12 0HS

J Whittaker*
Sequus Pharmaceuticals Inc.
Profile West
950 Great West Road
Brentford
Middlesex
TW8 9ES

* Response received

Appendix 3

Details about FIGO cancer staging[71]

Stage I: growth limited to the ovaries

Ia one ovary involved
Ib both ovaries involved
Ic ascites (an accumulation of fluid in the abdominal (peritoneal) cavity) present or positive peritoneal washings.

Stage II: growth limited to the pelvis

IIa extension to gynaecological adnexae (on or in a structure associated with the uterus, such as an ovary, Fallopian tube or uterine ligament)
IIb extension to other pelvic tissues
IIc ascites or positive washings.

Stage III: extra-pelvic tumour present – limited to the true pelvis but with superficial liver metastases, peritoneal surface seedlings or histologically proven malignant extension to the omentum

IIIa limited to the true pelvis with negative nodes, but seeding of abdominal peritoneal surfaces or histologically proven extension to the small bowel or mesentery
IIIb peritoneal metastasis of abdominal peritoneal surfaces, none exceeding 2 cm in diameter; nodes negative
IIIc peritoneal metastasis beyond the pelvis > 2 cm in diameter and/or positive retroperitoneal or inguinal nodes.

Stage IV: metastases to distant sites (including hepatic parenchymal disease)

Appendix 4

Details of data extraction

Note that [ ] indicates a list of options included in a pull down box, ( ) indicates a click on/off button, where 'on' represents 'yes' and 'off' represents 'no' and { } indicates free text entered in a box.

A. Clinical effectiveness data

Clinical effectiveness data were extracted and entered into an Access form under the following headings.

Study details

- Name of trial {trial name, identification or not stated}
- Endnote reference {endnote reference number}
- Primary source [database, handsearching, company submission]
- Author {i.e. Jones *et al.*}
- Date {i.e. year of publication or date of interim data collection}
- Type of report [abstract, full manuscript, interim report]
- Type of study phase [Phase II, Phase III, ..., not stated]
- Comparison group included [placebo, alternative drug, unclear, not stated]
- Intervention 1 {i.e. drug(s) name(s)}
- Dose of intervention 1 {dose}
- Number of cycles of intervention 1 {number}
- Length per cycle of intervention 1 {length}
- Route of administration of intervention 1 [intravenous, oral, intraperitoneal]
- Intervention 2 {i.e. drug(s) name(s)}
- Dose of intervention 2 {dose}
- Number of cycles of intervention 2 {number}
- Length per cycle of intervention 2 {length}
- Route of administration of intervention 2 [intravenous, oral, intraperitoneal]
- Comments about interventions {summary of comments or none}

Participants

- Disease focus [epithelial, stromal, germline]
- Stage of disease using FIGO staging [stage I, stage II, stage III, stage IV, mixed, ..., not stated]
- Early stage [yes, no, unclear, not stated]
- Advanced stage [yes, no, unclear, not stated]
- Evidence of secondary spread [yes, no, unclear, not stated]
- Type of therapy [first line, second line, salvage, mixed, ..., not stated]
- Previous treatment {summary of drugs or other treatments, such as debulking or radiotherapy, or NA}
- Residual disease present after first treatment [yes, no, unclear, not stated, NA]
- Refractory disease present after first treatment [yes, no, unclear, not stated, NA]
- Age or age range of participants {age(s)}
- Other participant characteristics {summary of characteristics}
- Comments about participants {summary of comments or none}

Numbers in conditions

- Number recruited or accrued {summary or not stated}
- Length of follow-up after treatment finishes {summary or not stated}
- Number and times of follow-up measurements {summary or not stated}
- Attrition intervention 1 {summary of number involved and reasons for loss}
- Attrition intervention 2 {summary of number involved and reasons for loss}
- Per protocol analysis performed [yes, no, not stated, unclear]
- Comments {summary of comments or not stated}

Results (data for all outcomes specified in the protocol were each entered in the following format)

- Outcome 1 {description of outcome measure}
- Intervention 1 baseline data {data for outcome 1}
- Intervention 2 baseline data {data for outcome 1}
- Intervention 1 follow-up data {data for outcome 1}
- Intervention 2 follow-up data {data for outcome 1}
- Comments on outcome 1 {summary of comments}
- Overall comments {summary of comments}

B. Cost data

Cost data were extracted and entered into an Access form under the following headings.

- Endnote reference {endnote reference number}
- Primary source [database, handsearching, company submission]

- Author {i.e. Jones *et al.*}
- Date {i.e. year of publication or date of interim data collection}
- Type of economic evaluation [CEA, CUA, CBA]
- Currency used [US$, £ sterling, ..., not stated]
- Year to which costs applied {enter year or not stated}
- Perspective used [health service, societal, hospital, third-party payer, patient, unclear]
- Study population {describe the population characteristics}
- Intervention 1 {description of intervention 1}
- Intervention 2 {description of intervention 2}
- Source of effectiveness data [single study, review/synthesis of previous studies, expert opinion, not stated]
- Source of cost data [literature, data from actual source, not stated]
- Link between cost and effectiveness data [prospective/concurrent, retrospective/disconnected]
- Clinical outcomes measured and methods of valuation used {summary of outcomes and valuation methods used}
- Clinical benefits measured and methods of valuation used {summary of outcomes and valuation methods used}
- Source of cost data used {summary of sources used}
- Modelling {summary of models used, type of model, purpose of model, components of model}
- Summary estimates of clinical outcomes used {summary of outcome data}
- Valuation for clinical outcomes or benefits {summary of outcomes/benefits and methods of valuation, such as direct measurements based on primary study or estimates based on certain clinical assumptions; list instruments used, such as QALYs, monetary value}
- Estimation of clinical costs used {summary of cost data}
- Estimation of clinical benefits used {summary of benefit data}
- Outcome measures used in economic evaluations {summary of outcome measures used in economic evaluations, such as incremental cost-effectiveness, cost per QALY, net benefit or cost}
- Statistical analysis {summary of analyses used}
- Appropriateness of statistical analysis {comment on appropriateness}
- Sensitivity analysis {summary of analysis used}
- Appropriateness of sensitivity analysis {comment on appropriateness}
- Author's conclusions {list as in publication}
- Magnitude and direction of result [A, B, C, D, E, F, G, H, I (classification from matrix), unclear]
- Implications for practice {summary of implications}
- Comments {summary of comments}

Appendix 5

Details of quality assessment

A. Studies of clinical effectiveness (RCTs)

Studies of clinical effectiveness (RCTs) were assessed using the following criteria based on the NHS Centre for Reviews and Dissemination Report No. 4:[26]

1. Was the method used to assign participants to the treatment groups really random? (Computer generated random numbers and random number tables were accepted as adequate, whilst inadequate approaches included the use of alternation, case record numbers, birth dates or days of the week.)
2. Was the allocation of treatment concealed? (Concealment was deemed adequate where randomisation was centralised or pharmacy-controlled, or where the following were used: serially numbered containers, on-site computer-based systems where assignment was unreadable until after allocation, other methods with robust means to prevent foreknowledge of the allocation sequence to clinicians and patients. Inadequate approaches included the use of alternation, case record numbers, days of the week, open random number lists and serially numbered envelopes even if opaque.)
3. Was the number of participants who were randomised stated?
4. Were details of baseline comparability presented in terms of treatment-free interval, disease bulk, number of previous regimens, age, histology and performance status?
5. Was baseline comparability achieved for treatment-free interval, disease bulk, number of previous regimens, age, histology and performance status?
6. Were the eligibility criteria for study entry specified?
7. Were any co-interventions identified that may have influenced the outcomes for each group?
8. Were the outcome assessors blinded to the treatment allocation?
9. Were the individuals who administered the intervention blinded to the treatment allocation?
10. Were the participants who received the intervention blinded to the treatment allocation?
11. Was the success of the blinding procedure assessed?
12. Were ≥ 80% of the participants originally included in the randomisation process followed up in the final analysis?
13. Were the reasons for any withdrawals stated?
14. Was an ITT analysis included?

Items were graded as Yes, item adequately addressed; No, item not adequately addressed; Partially, item partially addressed; Unclear, not enough information or unclear; NA, not applicable; or Not stated.

B. Studies of clinical effectiveness (Phase II studies)

Studies of clinical effectiveness (Phase II studies) were assessed using the following criteria:[72,73]

1. Were the study participants adequately described (age, treatment-free interval, histology, performance status, number of previous regimens, disease bulk, all described)?
2. Did the researchers clearly state their aims?
3. Was a control group used?
4. Should a control group have been used?
5. Was the study design the best design to address the researchers' aims?
6. Were the participants followed up over a sufficiently long period of time?
7. Was an adequate sample size used (i.e. did the authors justify the size statistically)?
8. Were the outcome measures likely to be valid (e.g. were the assessors blinded or was independent verification used)?
9. Was compliance with the study treatment monitored and discussed?
10. Were any relevant outcomes not assessed?
11. Were the statistical methods used described adequately?
12. Did any untoward events happen during the trial that could affect the findings?
13. Did the researchers use a survival analysis where appropriate?
14. Were all participants accounted for in the analysis (i.e. was an ITT analysis used)?
15. Were the basic data described adequately (e.g. absolute numbers quoted)?

16. Was the statistical significance of the findings reported (e.g. *p*-values, 95% CIs)?
17. Could any other factors affect the outcomes (e.g. patient characteristics)?
18. Were null findings interpreted appropriately?
19. Were important effects overlooked?

Items were graded as Yes, item adequately addressed; No, item not adequately addressed; Partially, item partially addressed; Unclear, not enough information or unclear; NA, not applicable; or Not stated.

C. Studies of cost-effectiveness

Studies of cost-effectiveness were assessed using the following criteria based on the checklist developed by Drummond and colleagues:[27]

1. Was a well-defined question posed in answerable form?
   - 1.1 Did the study examine both costs and effects of the service(s) or programme(s)?
   - 1.2 Did the study involve a comparison of alternatives?
   - 1.3 Was a viewpoint for the analysis stated and was the study placed in any particular decision-making context?

2. Was a comprehensive description of the competing alternatives given? (i.e. could you tell who did what to whom, where and how often?)
   - 2.1 Were any important alternatives omitted?
   - 2.2 Was (should) a **do-nothing** alternative (have been) considered?

3. Was the effectiveness of the programmes or services established?
   - 3.1 Was this done through an RCT? If so, did the trial protocol reflect what would happen in regular practice?
   - 3.2 Was effectiveness established through an overview of clinical studies?
   - 3.3 Were observational data or assumptions used to establish effectiveness? If so, what were the potential biases in the results?

4. Were all the important and relevant costs and consequences for each alternative identified?
   - 4.1 Was the range wide enough for the research question at hand?
   - 4.2 Did it cover all relevant viewpoints? (Possible viewpoints included the community or social viewpoint and those of patients and third-party payers. Other viewpoints may have also been relevant depending upon the particular analysis.)
   - 4.3 Were capital costs, as well as operating costs, included?

5. Were costs and consequences measured accurately in appropriate physical units? (e.g. hours of nursing time, number of physician visits, lost work days, gained life-years)
   - 5.1 Were any of the identified items omitted from measurement? If so, did this mean that they carried no weight in the subsequent analysis?
   - 5.2 Were there any special circumstances (e.g. joint use of resources) that made measurement difficult? Were these circumstances handled appropriately?

6. Were costs and consequences valued credibly?
   - 6.1 Were the sources of all values clearly identified? (Possible sources included market values, patient or client preferences and views, policy-makers' views and health professionals' judgements.)
   - 6.2 Were market values employed for changes involving resources gained or depleted?
   - 6.3 Where market values were absent (e.g. volunteer labour) or market values did not reflect actual values (such as clinic space donated at a reduced rate), were adjustments made to approximate market values?
   - 6.4 Was the valuation of consequences appropriate for the question posed? (i.e. was (were) the appropriate type(s) of analysis – CEA, CBA, CUA – selected?)

7. Were costs and consequences adjusted for differential timing?
   - 7.1 Were costs and consequences that occur in the future 'discounted' to their present values?
   - 7.2 Was any justification given for the discount rate used?

8. Was an incremental analysis of costs and consequences of alternatives performed?
   - 8.1 Were the additional (incremental) costs generated by one alternative over another compared to the additional effects, benefits or utilities generated?

9. Was allowance made for uncertainty in the estimates of costs and consequences?
   - 9.1 If data on costs or consequences were stochastic, were appropriate statistical analyses performed?

9.2 If a sensitivity analysis was employed, was justification provided for the ranges of values (for key study parameters)?
9.3 Were study results sensitive to changes in the values (within the assumed range for the sensitivity analysis, or within the CIs around the ratio of costs to consequences)?

10. Did the presentation and discussion of study results include all issues of concern to users?
10.1 Were the conclusions of the analysis based on some overall index or ratio of costs to consequences (e.g. cost-effectiveness ratio)? If so, was the index interpreted intelligently or in a mechanistic fashion?
10.2 Were the results compared with those of others who had investigated the same question? If so, were allowances made for potential differences in study methodology?
10.3 Did the study discuss the generalisability of the results to other settings and patient/client groups?
10.4 Did the study allude to, or take into account, other important factors in the choice or decision under consideration (e.g. distribution of costs and consequences or relevant ethical issues)?
10.5 Did the study discuss issues of implementation, such as the feasibility of adopting the 'preferred' programme given existing financial or other constraints, and whether any freed resources could be redeployed to other worthwhile programmes?

Appendix 6

Checklist for assessing economic evaluations

Pegylated liposomal doxorubicin hydrochloride in the treatment of recurrent ovarian cancer in the UK (Schering-Plough Ltd)

Checklist question	Yes	No	Reviewers' comments
1. Was a well-defined question posed in answerable form?	✔		
1.1. Did the study examine both costs and effects of the service(s) or programme(s)?	✔		Effects were not included in the economic analysis as equivalence in health outcomes was assumed and a CMA was performed. Equivalence in overall HRQoL was not established
1.2. Did the study involve a comparison of alternatives?	✔		Topotecan was an appropriate (although not the only possible) choice of comparator
1.3. Was a viewpoint for the analysis stated and was the study placed in any particular decision-making context?	✔		Perspective was the NHS
2. Was a comprehensive description of the competing alternatives given? (i.e. could you tell who did what to whom, where and how often?)	✔		Dosing schedule and duration were identified and assumptions about administration detailed
2.1. Were any important alternatives omitted?	✔		Additional comparators that were not included were platinum-based compounds, such as carboplatin, or taxanes, such as paclitaxel
2.2. Was (should) a **do-nothing** alternative (have been) considered?		✔	Not included and probably unethical to do nothing
3. Was the effectiveness of the programmes or services established?	✔		RCT was used to justify equivalence in overall survival, but not in HRQoL
3.1. Was this done through an RCT? If so, did the trial protocol reflect what would happen in regular practice?	✔		Dosages were consistent with UK practice
3.2. Was effectiveness established through an overview of clinical studies?		✔	Only one RCT available
3.3. Were observational data or assumptions used to establish effectiveness? If so, what were the potential biases in the results?		✔	
4. Were all the important and relevant costs and consequences for each alternative identified?	✔		Extensive list of adverse events, all relevant costs identified
4.1. Was the range wide enough for the research question at hand?	✔		No other large impact on costs or consequences likely
4.2. Did it cover all relevant viewpoints? (Possible viewpoints included the community or social viewpoint and those of patients and third-party payers. Other viewpoints may have also been relevant depending upon the particular analysis)	✔		Likely that the NHS perspective approximated that of society, as there would have been very few primary/social care costs and any omitted costs would have further favoured pegylated liposomal doxorubicin hydrochloride (e.g. cost of patients' travel)
4.3. Were capital costs, as well as operating costs, included?	✔		Capital costs seemed to be included in the cost of outpatient visits and inpatient stays

continued

Pegylated liposomal doxorubicin hydrochloride in the treatment of recurrent ovarian cancer in the UK (Schering-Plough Ltd) *contd*

Checklist question	Yes	No	Reviewers' comments
5. Were costs and consequences measured accurately in appropriate physical units? (e.g. hours of nursing time, number of physician visits, lost work days, gained life-years)	✔		Resource use included number of outpatient visits, adverse events, inpatient stays as well as use of study drugs
5.1. Were any of the identified items omitted from measurement? If so, did this mean that they carried no weight in the subsequent analysis?		✔	
5.2. Were there any special circumstances (e.g. joint use of resources) that made measurement difficult? Were these circumstances handled appropriately?		✔	Average costs rather than marginal costs were employed. It is possible that clinics for administration of these drugs would reduce the marginal cost. However, it is possible that these administrations should have been costed as a day case
6. Were costs and consequences valued credibly?	✔		Only problem could be with the treatment of neutropenia. In the UK, clinical advisors suggest that this is unlikely to be treated and, therefore, even grades 3–4 would have zero resource use attached to this adverse event
6.1. Were the sources of all values clearly identified? (Possible sources included market values, patient or client preferences and views, policy-makers' views and health professionals' judgements)	✔		References for unit costs were clearly stated, consequences were from the clinical trial although some resource use data were from an expert panel
6.2. Were market values employed for changes involving resources gained or depleted?	✔		
6.3. Where market values were absent (e.g. volunteer labour) or market values did not reflect actual values (such as clinic space donated at a reduced rate), were adjustments made to approximate market values?		✔	NA, although hospital discounts were included in the discussion of the budgetary implication of pegylated liposomal doxorubicin hydrochloride
6.4. Was the valuation of consequences appropriate for the question posed? (i.e. was (were) the appropriate type(s) of analysis – CEA, CBA, CUA – selected?)		✔	Given the possible differences in HRQoL, a CUA would have been preferable
7. Were costs and consequences adjusted for differential timing?		✔	All events occurred within a 12-week period and adjustments for differential timing were not appropriate
7.1. Were costs and consequences that occur in the future 'discounted' to their present values?		✔	NA
7.2. Was any justification given for the discount rate used?		✔	NA
8. Was an incremental analysis of costs and consequences of alternatives performed?	✔		Incremental analysis of costs was performed, no incremental analysis of effects given the use of a CMA
8.1. Were the additional (incremental) costs generated by one alternative over another compared to the additional effects, benefits or utilities generated?	✔		See above

continued

Pegylated liposomal doxorubicin hydrochloride in the treatment of recurrent ovarian cancer in the UK (Schering-Plough Ltd) *contd*

Checklist question	Yes	No	Reviewers' comments
9. Was allowance made for uncertainty in the estimates of costs and consequences?	✔		Costs were subjected to sensitivity analysis on most of the major costs although the cost of the drug (which made up 80% of the costs in the pegylated liposomal doxorubicin hydrochloride arm) was not included in the sensitivity analysis. No allowance was made for uncertainty in consequences; equivalence was assumed
9.1. If data on costs or consequences were stochastic, were appropriate statistical analyses performed?	✔		CIs were calculated and bootstrapping was performed to check these
9.2. If a sensitivity analysis was employed, was justification provided for the ranges of values (for key study parameters)?	✔		Extreme scenarios for resource use were based on expert panel data
9.3. Were study results sensitive to changes in the values (within the assumed range for the sensitivity analysis, or within the CI around the ratio of costs to consequences)?		✔	Results were robust to changes in values of variables included in the sensitivity analysis
10. Did the presentation and discussion of study results include all issues of concern to users?	✔		
10.1. Were the conclusions of the analysis based on some overall index or ratio of costs to consequences (e.g. cost-effectiveness ratio)? If so, was the index interpreted intelligently or in a mechanistic fashion?		✔	Study was a CMA and thus index NA
10.2. Were the results compared with those of others who had investigated the same question? If so, were allowances made for potential differences in study methodology?		✔	The two drugs have not previously been compared directly
10.3. Did the study discuss the generalisability of the results to other settings and patient/client groups?		✔	
10.4. Did the study allude to, or take into account, other important factors in the choice or decision under consideration (e.g. distribution of costs and consequences or relevant ethical issues)?	✔		Authors mentioned equity and discussed budgetary implications
10.5. Did the study discuss issues of implementation, such as the feasibility of adopting the 'preferred' programme given existing financial or other constraints and whether any freed resources could be redeployed to other worthwhile programmes?	✔		Authors discussed freed resources (e.g. clinic time and hospitalisations) as well as budget implications

A comparative economic analysis of pegylated liposomal doxorubicin versus topotecan in ovarian cancer in the USA and UK (Smith DH, Adams JR, Johnston SRD, Gordon A, Drummond MF, Bennett CL)

Checklist question	Yes	No	Reviewers' comments
1. Was a well-defined question posed in answerable form?	✔		
1.1. Did the study examine both costs and effects of the service(s) or programme(s)?	✔		Effects were not included in the economic analysis because equivalence in health outcomes was assumed and a CMA was performed. Equivalence in overall HRQoL was not established
1.2. Did the study involve a comparison of alternatives?	✔		Topotecan was an appropriate (although not the only possible) choice of comparator
1.3. Was a viewpoint for the analysis stated and was the study placed in any particular decision-making context?	✔		Perspective was the NHS
2. Was a comprehensive description of the competing alternatives given? (i.e. could you tell who did what to whom, where and how often?)	✔		Dosing schedule and duration were identified and assumptions about administration detailed
2.1. Were any important alternatives omitted?	✔		Additional comparators that were not included were platinum-based compounds, such as carboplatin, or taxanes, such as paclitaxel
2.2. Was (should) a **do-nothing** alternative (have been) considered?		✔	Not included and probably unethical to do nothing
3. Was the effectiveness of the programmes or services established?	✔		RCT was used to demonstrate equivalence in overall survival, but not in HRQoL
3.1. Was this done through an RCT? If so, did the trial protocol reflect what would happen in regular practice?	✔		Dosages were consistent with UK practice
3.2. Was effectiveness established through an overview of clinical studies?		✔	Only one RCT available
3.3. Were observational data or assumptions used to establish effectiveness? If so, what were the potential biases in the results?		✔	
4. Were all the important and relevant costs and consequences for each alternative identified?	✔		Extensive list of adverse events, all relevant costs identified
4.1. Was the range wide enough for the research question at hand?	✔		No other large impact on costs or consequences was likely; key resource use differences between options was likely to occur in hospital setting
4.2. Did it cover all relevant viewpoints? (Possible viewpoints included the community or social viewpoint and those of patients and third-party payers. Other viewpoints may have also been relevant depending upon the particular analysis)	✔		Likely that NHS perspective approximated that of society, as there would have been very few primary/social care costs and any omitted costs would have further favoured pegylated liposomal doxorubicin hydrochloride (e.g. cost of patients' travel)
4.3. Were capital costs, as well as operating costs, included?	✔		Capital costs seemed to be included in the cost of outpatient visits and inpatient stays
5. Were costs and consequences measured accurately in appropriate physical units? (e.g. hours of nursing time, number of physician visits, lost work days, gained life-years)	✔		Resource use included number of outpatient visits, adverse events, inpatient stays as well as the use of study drugs
5.1. Were any of the identified items omitted from measurement? If so, did this mean that they carried no weight in the subsequent analysis?		✔	

continued

A comparative economic analysis of pegylated liposomal doxorubicin versus topotecan in ovarian cancer in the USA and UK (Smith DH, Adams JR, Johnston SRD, Gordon A, Drummond MF, Bennett CL) *contd*

Checklist question	Yes	No	Reviewers' comments
5.2. Were there any special circumstances (e.g. joint use of resources) that made measurement difficult? Were these circumstances handled appropriately?		✔	Average costs rather than marginal costs were employed. It is possible that clinics for administration of these drugs would reduce the marginal cost. However, it is possible that these administrations should have been costed as a day case
6. Were costs and consequences valued credibly?	✔		Only problem could be with the treatment of neutropenia. In the UK, this is unlikely to be treated and, therefore, even grades 3–4 would have zero resource use attached to this adverse event
6.1. Were the sources of all values clearly identified? (Possible sources included market values, patient or client preferences and views, policy-makers' views and health professionals' judgements)	✔		References for unit costs were clearly stated, consequences were from the clinical trial although some resource use data were from an expert panel
6.2. Were market values employed for changes involving resources gained or depleted?	✔		
6.3. Where market values were absent (e.g. volunteer labour) or market values did not reflect actual values (such as clinic space donated at a reduced rate), were adjustments made to approximate market values?		✔	NA, although hospital discounts were included in the discussion of the budgetary implication of pegylated liposomal doxorubicin hydrochloride
6.4. Was the valuation of consequences appropriate for the question posed? (i.e. was (were) the appropriate type(s) of analysis – CEA, CBA, CUA – selected?)		✔	Given the possible differences in HRQoL, a CUA would have been preferable
7. Were costs and consequences adjusted for differential timing?		✔	All events occurred within a 12-week period and adjustments for differential timing were not appropriate
7.1. Were costs and consequences that occur in the future 'discounted' to their present values?		✔	NA
7.2. Was any justification given for the discount rate used?		✔	NA
8. Was an incremental analysis of costs and consequences of alternatives performed?	✔		Incremental analysis of costs was performed, no incremental analysis of effects given the use of CMA
8.1. Were the additional (incremental) costs generated by one alternative over another compared to the additional effects, benefits or utilities generated?	✔		See above
9. Was allowance made for uncertainty in the estimates of costs and consequences?	✔		Costs were subjected to sensitivity analysis on most of the major costs although the cost of the drug (which made up 80% of the costs in the pegylated liposomal doxorubicin hydrochloride arm) was not included in the sensitivity analysis. No allowance was made for uncertainty in consequences; equivalence was assumed

continued

A comparative economic analysis of pegylated liposomal doxorubicin versus topotecan in ovarian cancer in the USA and UK (Smith DH, Adams JR, Johnston SRD, Gordon A, Drummond MF, Bennett CL) *contd*

Checklist question	Yes	No	Reviewers' comments
9.1. If data on costs or consequences were stochastic, were appropriate statistical analyses performed?	✔		CIs were calculated and bootstrapping was performed to check these
9.2. If a sensitivity analysis was employed, was justification provided for the ranges of values (for key study parameters)?	✔		Extreme scenarios for resource use were based on expert panel data
9.3. Were study results sensitive to changes in the values (within the assumed range for the sensitivity analysis, or within the CI around the ratio of costs to consequences)?		✔	Results were robust to changes in values of variables included in the sensitivity analysis
10. Did the presentation and discussion of study results include all issues of concern to users?	✔		
10.1. Were the conclusions of the analysis based on some overall index or ratio of costs to consequences (e.g. cost-effectiveness ratio)? If so, was the index interpreted intelligently or in a mechanistic fashion?		✔	Study was a CMA and thus index NA
10.2. Were the results compared with those of others who had investigated the same question? If so, were allowances made for potential differences in study methodology?		✔	The two drugs have not previously been compared directly
10.3. Did the study discuss the generalisability of the results to other settings and patient/client groups?		✔	
10.4. Did the study allude to, or take into account, other important factors in the choice or decision under consideration (e.g. distribution of costs and consequences or relevant ethical issues)?	✔		Authors mentioned equity and discussed budgetary implications
10.5. Did the study discuss issues of implementation, such as the feasibility of adopting the 'preferred' programme given existing financial or other constraints and whether any freed resources could be redeployed to other worthwhile programmes?	✔		Authors discussed freed resources (e.g. clinic time and hospitalisations) as well as budget implications

Appendix 7

List of excluded studies and reasons for exclusion

Study	Reason for exclusion
Anonymous, 2000[30]	Not an RCT or Phase II study, but reported on the approval of pegylated liposomal doxorubicin hydrochloride
Anonymous, 2000[36]	Not an original report of an RCT, but discussed trial 30-49 and other Phase II studies of pegylated liposomal doxorubicin hydrochloride
Castaldo *et al*., 1979[29]	Not an RCT or Phase II study, but reported on the problems of making specific diagnoses in women with cancers of the genital tract
Cook *et al*., 1999[31]	Not an RCT or Phase II study, but an abstract of a retrospective case study of ovarian cancer patients, some of whom were treated with pegylated liposomal doxorubicin hydrochloride
Delgado *et al*., 1989[39]	Not a report of pegylated liposomal doxorubicin hydrochloride, but a Phase I/II study of intraperitoneally administered doxorubicin trapped in cardiolipin liposomes (not Caelyx)
Frykman *et al*., 2001[32]	Not an RCT or Phase II study, but a letter to the editor about a recently published report of a Phase II study of pegylated liposomal doxorubicin hydrochloride in ovarian cancer
Herzog *et al*., 1999[41]	No relevant outcome data. A Phase II study of pegylated liposomal doxorubicin hydrochloride, but also included other cancer patients besides those with ovarian cancer, and the outcome data was not reported separately for ovarian patients
Hornreich *et al*., 2001[33]	Not an RCT or Phase II study, but a case report of a woman suffering from endometrial cancer treated with pegylated liposomal doxorubicin hydrochloride
Jahanzeb *et al*., 1997[42]	No relevant outcome data. Seemed to be a Phase II study of pegylated liposomal doxorubicin hydrochloride, but examined a variety of solid tumours, only two of which were ovarian cancers, and the outcome data was not presented separately for these
Markman *et al*., 2000[11]	No relevant outcome data. Phase II study examining the use of pegylated liposomal doxorubicin hydrochloride to treat ovarian and Fallopian tube cancers and primary cancer of the peritoneum, but did not report the data separately for ovarian cancer patients
Martin, 1996[45]	Did not focus on trials of ovarian patients. The main focus of the report was the use of pegylated liposomal doxorubicin hydrochloride in the treatment of Kaposi's sarcoma
Muggia *et al*., 1997[37]	Not an original report of an RCT or Phase II study, but a non-systematic review of pegylated liposomal doxorubicin hydrochloride trials (RCT and Phase II)
Ortner, 2000[34]	Not an RCT or Phase II study, but a non-systematic review of pegylated liposomal doxorubicin hydrochloride trials (RCT and Phase II studies)
Safra *et al*., 1997[43]	No relevant outcome data. Reported on a meta-analysis of Phase I and II studies of pegylated liposomal doxorubicin hydrochloride, but the data for the Phase II study was not presented separately
Safra *et al*., 2001[44]	No relevant outcome data. Reported on a meta-analysis of Phase I and II studies of pegylated liposomal doxorubicin hydrochloride, but the data for the Phase II study was not presented separately
Seiden, 2000[38]	Not an original report of an RCT or Phase II study, but a summary of findings from an American Society of Clinical Oncology meeting, which included a brief mention of the interim findings of trial 30-49
Skelton *et al*., 1999[35]	Not an RCT or Phase II study, but reported on adverse events data from two case reports
Vogl *et al*., 1979[40]	Not a report of pegylated liposomal doxorubicin hydrochloride, but examined the non-liposomal form of the drug (doxorubicin hydrochloride)

Appendix 8

Data extraction tables for clinical effectiveness studies (RCTs)

Study details and design	Participant details	Intervention details	Withdrawals and adverse events	Conclusions and comments
Gordon *et al.*, 2000[46] ***Source*** Database ***Aim*** To determine the effectiveness of pegylated liposomal doxorubicin hydrochloride versus topotecan in the treatment of patients with relapsed ovarian cancer ***Type of publication*** Abstract of interim report ***Trial identification*** 30-49 ***Phase*** Phase III ***Method of randomisation*** Not stated ***Concealed allocation*** Not stated ***Blinding*** Assessor: not stated Carer: no Patient: no Success of blinding checked: not stated ***Length of follow-up*** Not stated (interim analysis) ***ITT analysis performed*** Yes	***Number randomised*** Not stated; 237 ITT ***Disease type*** Not stated; relapsed disease, occurrence of secondary spread not stated ***Therapy stage*** Second-line ***Previous treatments*** First-line platinum-based chemotherapy ***Disease present after first-line treatment*** Residual: yes Refractory: yes ***Age of participants*** Not stated ***Characteristics*** Not stated ***Inclusion criterion*** Failure of first-line platinum-based chemotherapy 237 patients from 71 sites (n = 119 in the control arm, n = 118 in the intervention arm) were included in the interim analysis. 117 patients (n = 59 in the control arm, n = 58 in the intervention arm) had platinum-refractory disease	***Intervention*** Pegylated liposomal doxorubicin hydrochloride **Number randomised** 118 (ITT) **Route of administration** i.v. **Dose** 50 mg/m^2 as a 1-hour infusion **Number of cycles** Not stated **Length per cycle** 28 days ***Control*** Topotecan **Number randomised** 119 (ITT) **Route of administration** i.v. **Dose** 1.5 mg/m^2/day as a 30-minute infusion for 5 days **Number of cycles** Not stated **Length per cycle** 21 days	***Withdrawals*** Withdrawals due to adverse events: 14 (including four PPE) with intervention, 16 (including five sepsis) with control Treatment-related deaths: none with intervention, two with control ***Adverse events*** Neutropenia: 71% with control, 12% with intervention Anaemia: 33% with control, 5% with intervention Thrombocytopenia: 35% with control, 1% with intervention PPE: 0% with control, 25% with intervention Alopecia: 8% with control, 0% with intervention	***Authors' conclusions*** The differentiated safety profile combined with clinically equivalent efficacy supported the role of pegylated liposomal doxorubicin hydrochloride in patients failing first-line platinum-based chemotherapy. This is an ongoing study and updated results will be presented at a later date ***Comments*** The number of patients suffering from sepsis was not presented in the table of common adverse events. It was unclear if discontinuations were included in the table of common adverse events The total number of patients randomised was not stated, so it was not possible to confirm that a true ITT analysis was performed Interim results published in this abstract and final results submitted in confidence by Schering-Plough Ltd[47]

continued

Results		
Outcome 1 Median time to progression (not defined)	**Outcome 2 Overall survival (not defined)**	**Outcome 3 Response rate (not defined)**
Follow-up data 22.4 weeks with intervention, 20.4 weeks with control	***Follow-up data*** 66.0 weeks with intervention, 56.3 weeks with control	***Follow-up data*** **Confirmed objective** 20.3% (24/118) with intervention, 16.8% (20/119) with control **Objective** 12.1% (7/58) in the platinum-refractory subpopulation of the intervention group, 6.8% (4/59) in the platinum-refractory subpopulation of the control group

Study details and design	Participant details	Intervention details	Withdrawals and adverse events	Conclusions and comments
Gordon *et al.*, 2001[48] ***Source*** Database ***Aim*** To compare the efficacy and safety of pegylated liposomal doxorubicin hydrochloride with topotecan in patients with epithelial ovarian carcinoma that recurred after or did not respond to first-line platinum-based chemotherapy ***Type of publication*** Final report ***Trial identification*** 30-49 ***Phase*** Phase III ***Method of randomisation*** Centrally randomised and stratified for platinum sensitivity and bulky disease* ***Concealed allocation*** No* ***Blinding*** Assessor: no* Carer: no Patient: no Success of blinding checked: not stated ***Length of follow-up*** Up to 1 year or less if disease progression occurred ***ITT analysis performed*** No	***Number randomised*** 481; 474 ITT ***Disease type*** Epithelial; advanced, occurrence of secondary spread in the majority of cases, but not all ***Therapy stage*** Second-line ***Previous treatments*** Chemotherapy (platinum-based first-line regimen); radiotherapy (but only if involved < one-third of haemopoietic sites) ***Disease present after first-line treatment*** Residual: yes Refractory: yes ***Age of participants*** Median = 60.0 years (range 27–87) in the intervention group; median = 60.0 years (range 25–85) in the control group ***Characteristics*** **Initial FIGO stage** I: 11/239 (4.6%) in the intervention group, 15/235 (6.4%) in the control group II: 13/239 (5.4%) in the intervention group, 8/235 (3.4%) in the control group III: 175/239 (73.2%) in the intervention group, 164/235 (69.8%) in the control group IV: 40/239 (16.7%) in the intervention group, 48/235 (20.4%) in the control group **Drug-free interval** Median = 7.0 months (range 0.9–82.1) in the intervention group; median = 6.7 months (range 0.5–109.6) in the control group **CA-125** Median = 199 U/ml (range 3–18801) in the intervention group; median = 178 U/ml (range 3–29330) in the control group	***Intervention*** Pegylated liposomal doxorubicin hydrochloride **Number randomised** 239 (ITT) **Route of administration** i.v. **Dose** 50 mg/m^2 as a 1-hour infusion **Number of cycles** Not stated **Length per cycle** 28 days ***Control*** Topotecan **Number randomised** 235 (ITT) **Route of administration** i.v. **Dose** 1.5 mg/m^2/day as a 30-minute infusion for 5 days **Number of cycles** Not stated **Length per cycle** 21 days	***Withdrawals*** Overall, seven participants were lost to follow-up prior to the first dose. The study group assignment and reason for these withdrawals were not stated. No other reasons for losses to follow-up were reported ***Adverse events*** 43 participants withdrew from the intervention group and 37 withdrew from the control group due to treatment-related adverse events. No participants died in the intervention group and three died (all from complications of neutropenia and sepsis) in the control group due to treatment-related adverse events **All grades of adverse events** Neutropenia: 84/239 (35.1%) with intervention, 191/235 (81.3%) with control Anaemia: 85/239 (35.6%) with intervention, 169/235 (71.9%) with control Thrombocytopenia: 31/239 (13.0%) with intervention, 152/235 (64.7%) with control Leukopenia: 87/239 (36.4%) with intervention, 148/235 (63.0%) with control Alopecia: 38/239 (15.9%) with intervention, 114/235 (48.5%) with control PPE: 117/239 (49.0%) with intervention, 2/235 (0.9%) with control Stomatitis: 95/239 (39.7%) with intervention, 35/235 (14.9%) with control	***Authors' conclusions*** The comparable efficacy, favourable safety profile and convenient dosing supported the role of pegylated liposomal doxorubicin hydrochloride as a valuable treatment option in this patient population ***Comments*** This was designed as an equivalence study with 80% power to detect statistical equivalence of the two drugs. A sample size calculation was performed prior to recruitment, which suggested a total of 350 participants, 175 in each treatment group, were required to ensure with a probability of 80% that the lower 95% one-sided CI of the HR of topotecan to pegylated liposomal doxorubicin hydrochloride would not fall below 0.757. However, the sample size was increased to 460 to cover anticipated losses to follow-up Karnofsky performance status data were not provided in terms of the individual study groups 481 participants were originally randomised, but the analysis performed by the trialists, which was reported to be an ITT analysis, was only based on 474 patients and was, therefore, not a true ITT analysis. All the data quoted in this summary as ITT were based on the trialists figures and, therefore, are not true ITT analyses HRs were not reported for time to event data and a number of secondary outcomes mentioned in the trial report supplied by the company (Schering-Plough Ltd)[47] were not quoted in this published version of the report Individual assessing response to therapy was not independent or blinded. However, the responses have now been reassessed independently and this additional data was provided by the company and included in this summary Interim results published.[46] Final results also submitted in confidence by Schering-Plough Ltd[47]

continued

Study details and design	Participant details	Intervention details	Withdrawals and adverse events	Conclusions and comments
contd **Gordon *et al.*, 2001**[48]	**Sum of lesions** Median = 20 cm^2 (range 1–441) in the intervention group; median = 20 cm^2 (range 1–296) in the control group **Platinum sensitivity** Sensitive: 109/239 (45.6%) in the intervention group, 111/235 (47.2%) in the control group Refractory: 130/239 (54.4%) in the intervention group, 124/235 (52.8%) in the control group **Presence of bulky disease** Present: 111/239 (46.4%) in the intervention group, 111/235 (47.2%) in the control group Absent: 128/239 (53.6%) in the intervention group, 124/235 (52.8%) in the control group ***Inclusion criteria*** Women ≥ 18 years of age; measurable and assessable disease that recurred or failed first-line platinum-based therapy; adequate bone marrow, renal, liver and cardiac function; Karnofsky performance status of ≥ 60%; disease-free period of > 5 years from prior malignancies (except skin and cervical carcinoma) ***Exclusion criteria*** Pregnancy and breastfeeding; life expectancy of ≤ 3 months; prior radiation therapy to > one-third of haemopoietic sites; history of cardiac disease; received investigational drug within 30 days of first dose of study drug; received prior pegylated liposomal doxorubicin hydrochloride or topotecan; received chemotherapy within 29 days of first dose of study drug; no concurrent investigational or antineoplastic agents	***Grade 3/4 adverse events*** Neutropenia: 29/239 (12.1%) with intervention, 180/235 (76.6%) with control Anaemia: 13/239 (5.4%) with intervention, 66/235 (28.1%) with control Thrombocytopenia: 3/239 (1.3%) with intervention, 80/235 (34.0%) with control Leukopenia: 24/239 (10.0%) with intervention, 117/235 (49.8%) with control Alopecia: 3/239 (1.3%) with intervention, 14/235 (6.0%) with control PPE: 55/239 (23.0%) with intervention, 0/235 (0.0%) with control Stomatitis: 20/239 (8.4%) with intervention, 1/235 (0.4%) with control		

continued

Results		
Outcome 1 QoL (not defined)	**Outcome 2 Survival (not defined)**	**Outcome 3 Response rate**
Baseline data Not stated, but function and symptom scale scores were similar with both intervention and control ***Follow-up data*** No statistical differences between intervention and control	***Follow-up data*** **All participants (*n* = 239 in the intervention group, *n* = 235 in the control group)** Median progression-free survival: 16.1 weeks with intervention, 17.0 weeks with control, *p* = 0.095 Median overall survival: 60 weeks with intervention, 56.7 weeks with control, *p* = 0.341 **Platinum-sensitive participants (*n* = 109 in the intervention group, *n* = 111 in the control group)** Median progression-free survival: 28.9 weeks with intervention, 23.3 weeks with control, *p* = 0.037 Median overall survival: 108.0 weeks with intervention, 71.1 weeks with control, *p* = 0.008 **Platinum-resistant participants (*n* = 130 in the intervention group, *n* = 124 in the control group)** Median progression-free survival: 9.1 weeks with intervention, 13.6 weeks with control, *p* = 0.733 Median overall survival: 35.6 weeks with intervention, 41.3 weeks with control, *p* = 0.455	Complete response was defined as the complete disappearance of all known measurable/assessable disease, no new lesions of disease-related symptoms; partial response was defined as ≥ 50% decrease in the sum of products of bidimensionable perpendicular diameters of all measurable lesions ***Follow-up data*** **All participants (*n* = 239 in the intervention group, *n* = 235 in the control group; *p* = 0.390)** Complete response: 9/239 (3.8%) with intervention, 11/235 (4.7%) with control Partial response: 38/239 (15.9%) with intervention, 29/235 (12.3%) with control Overall response: 47/239 (19.7%) with intervention, 40/235 (17.0%) with control **Platinum-sensitive participants (*n* = 109 in the intervention group, *n* = 111 in the control group; *p* = 0.964)** Complete response: 8/109 (7.3%) with intervention, 10/111 (9.0%) with control Partial response: 23/109 (21.1%) with intervention, 22/111 (19.8%) with control Overall response: 31/109 (28.4%) with intervention, 32/111 (28.8%) with control **Platinum-resistant participants (*n* = 130 in the intervention group, *n* = 124 in the control group; *p* = 0.118)** Complete response: 1/130 (0.8%) with intervention, 1/124 (0.8%) with control Partial response: 15/130 (11.5%) with intervention, 7/124 (5.6%) with control Overall response: 16/130 (12.3%) with intervention, 8/124 (6.5%) with control

* *Additional data obtained from study authors*

Study details and design	Participant details	Intervention details	Withdrawals and adverse events	Conclusions and comments
Schering-Plough Ltd, 2000[47] ***Source*** Company submission ***Aim*** To compare the efficacy and safety of pegylated liposomal doxorubicin hydrochloride versus topotecan in patients with epithelial ovarian carcinoma following failure of first-line platinum-based chemotherapy ***Type of publication*** Final report ***Trial identification*** 30-49 ***Phase*** Phase III ***Method of randomisation*** Not stated ***Concealed allocation*** Not stated ***Blinding*** Assessor: not stated Carer: not stated Patient: not stated Success of blinding checked: not stated ***Length of follow-up*** Not stated; 24 weeks for QoL ***ITT analysis performed*** Yes	***Number randomised*** Not stated; 474 (ITT) ***Disease type*** Epithelial; advanced, occurrence of secondary spread not stated ***Therapy stage*** Second-line ***Previous treatments*** Platinum-based chemotherapy ***Disease present after first-line treatment*** Residual: yes Refractory: yes ***Age of participants*** Mean = 59 years, median = 60 years (range 27–87) in the intervention group; mean = 60 years, median = 60 years (range 25–85) in the control group ***Characteristics*** **Drug-free interval** Mean = 10 months (SD = 12 months), median = 7.0 months (range < 1–82) in the intervention group; mean = 10 months (SD = 14 months), median = 6.7 months (range < 1–110) in the control group **CA-125 level (*n* = 224/239 in the intervention group, *n* = 224/239 in the control group)** Mean = 900 U/ml (SD = 1933), median = 199 U/ml (range 3–18801) in the intervention group; mean = 932 U/ml (SD = 2455), median = 178 U/ml (range 3–29330) in the control group **FIGO stage at diagnosis** I: 11/239 (4.6%) in the intervention group, 15/235 (6.4%) in the control group II: 13/239 (5.4%) in the intervention group, 8/235 (3.4%) in the control group III: 175/239 (73.3%) in the intervention group, 164/235 (69.8%) in the control group IV: 40/239 (16.7%) in the intervention group, 48/235 (20.4%) in the control group	***Intervention*** Pegylated liposomal doxorubicin hydrochloride **Number randomised** Not stated; 239 ITT; 207 (evaluable) **Route of administration** i.v. **Dose** 50 mg/m^2 as a 1-hour infusion. Median dose received was 50 mg/m^2 (range 34–58) **Number of cycles** Most patients received four to five cycles (estimated by dividing cumulative dose by cycle dose) **Length per cycle** 28 days; median = 30 days (range 27–56) ***Control*** Topotecan **Number randomised** Not stated; 235 (ITT); 209 (evaluable) **Route of administration** i.v. **Dose** 1.5 mg/m^2 as a 30-minute infusion for 5 days starting on day 1. Median dose received was 7 mg/m^2 (range 3–10)	***Withdrawals (ITT population)*** Disease progression: 110 (46.0%) with intervention, 114 (48.5%) with control Adverse event: 29 (12.1%) with intervention, 39 (16.6%) with control Death: 18 (7.5%) with intervention, 15 (6.4%) with control Non-compliance: 1 (< 1.0%) with intervention, 1 (< 1.0%) with control Inappropriate enrollment: 1 (< 1.0%) with intervention, 0 (0.0%) with control Other/unknown: 35 (14.6%) with intervention, 31 (13.2%) with control Protocol-completed (6 months of treatment): 39 (16.3%) with intervention, 34 (14.5%) with control Ongoing: 2 (< 1.0%) with intervention, 5 (2.1%) with control ***Adverse events*** 222/239 (92.9%) patients in the intervention group and 232/235 (98.7%) in the control group reported adverse events (any grade). 132/239 (55.2%) patients in the intervention group versus 176/235 (74.9%) in the control group reported grade 3 adverse events. 20/239 (8.4%) patients treated with intervention and 158/235 (67.2%) treated with control reported grade 4 adverse events The most common adverse events related to topotecan were haematological (neutropenia, anaemia, thrombocytopenia and leukopenia), nausea and alopecia. Haematological events, nausea and alopecia were less frequent in the intervention group. Most adverse events in the intervention group were mild to moderate in severity with the exception of PPE that was severe in 23% and stomatitis that was severe in 8% of the intervention group ***Adverse events (ITT population n = 239 in the intervention group, n = 235 in the control group)*** **All grades** Stomatitis: 95/239 (39.7%) with intervention, 35/235 (14.9%) with control	***Authors' conclusions*** This final analysis confirmed that pegylated liposomal doxorubicin hydrochloride is superior to topotecan for the protocol-specified primary endpoint (time to progression for the evaluable population). In addition, the more favourable safety profile of pegylated liposomal doxorubicin hydrochloride as compared with topotecan, together with its ease of administration, support its role as a valuable therapeutic option for patients failing first-line platinum-containing treatment regimens ***Comments*** ITT results were mainly presented, and where these were not available evaluable patient results were presented instead. However, as the total number of patients randomised was not stated, it was not possible to confirm that a true ITT analysis was performed

continued

Study details and design	Participant details	Intervention details	Withdrawals and adverse events	Conclusions and comments
contd **Schering-Plough Ltd, 2000**[47]	**Karnofsky performance status** < 80: 39/239 (16.3%) in the intervention group,* 37/235 (15.7%) in the control group ≥ 80: 199/239 (83.3%) in the intervention group,* 195/235 (83.0%) in the control group **Mean sum of lesions at baseline** 39 (SD = 54) in the intervention group, 34 (SD = 39) in the control group **Bulky disease (tumour mass > 5 cm)** Present: 111/239 (46.4%) in the intervention group, 111/235 (47.2%) in the control group Absent: 128/239 (53.6%) in the intervention group, 124/235 (52.8%) in the control group **Platinum sensitivity/bulky disease** Refractory/present: 64/239 (26.8%) in the intervention group, 64/235 (27.2%) in the control group Refractory/absent: 66/239 (27.6%) in the intervention group, 60/235 (25.5%) in the control group Sensitive/present: 47/239 (19.7%) in the intervention group, 47/235 (20.0%) in the control group Sensitive/absent: 62/239 (25.9%) in the intervention group, 64/235 (27.2%) in the control group **Histology** Differentiated: 4/239 (1.7%) in the intervention group, 3/235 (1.3%) in the control group Moderately differentiated: 16/239 (6.7%) in the intervention group, 13/235 (5.5%) in the control group Poorly differentiated: 53/239 (22.2%) in the intervention group, 72/235 (30.6%) in the control group Unspecified differentiation: 125/239 (52.3%) in the intervention group, 110/235 (46.8%) in the control group Not specified: 41/239 (17.2%) in the intervention group, 37/235 (15.7%) in the control group ***Inclusion criterion*** Documented clinically-measurable recurrent or persistent epithelial ovarian cancer that was resistant to first-line chemotherapy with a platinum-based regimen	**Number of cycles** Most patients received four to five cycles (estimated by dividing cumulative dose by cycle dose) **Length per cycle** 21 days; median = 24 days (range 20–38) Participants were stratified according to platinum sensitivity and bulky disease. The authors stated that the demographic characteristics of the participants were representative of patients with advanced epithelial ovarian carcinoma and were similar between treatment groups	Neutropenia: 84/239 (35.1%) with intervention, 191/235 (81.3%) with control Leukopenia: 87/239 (36.4%) with intervention, 149/235 (63.4%) with control Anaemia: 85/239 (35.6%) with intervention, 169/235 (71.9%) with control Thrombocytopenia: 31/239 (13.0%) with intervention, 152/235 (64.7%) with control PPE: 117/239 (49.0%) with intervention, 2/235 (< 1.0%) with control Alopecia: 38/239 (15.9%) with intervention, 115/235 (48.9%) with control **Grades 3/4** Stomatitis: 20/239 (8.4%) with intervention, 1/235 (< 1.0%) with control Neutropenia: 29/239 (12.1%) with intervention, 180/235 (76.6%) with control (includes two deaths) Leukopenia: 24/239 (10.0%) with intervention, 117/235 (49.8%) with control Anaemia: 13/239 (5.4%) with intervention, 66/235 (28.1%) with control Thrombocytopenia: 3/239 (1.3%) with intervention, 80/235 (34.0%) with control PPE: 55/239 (23.0%) with intervention, 0/235 (0.0%) with control Alopecia: 3/239 (1.3%) with intervention, 14/235 (6.0%) with control	

continued

Results

Outcome 1 Time to progression (not defined)	Outcome 2 Overall survival (not defined)	Outcome 3 Response rates
Follow-up data **ITT population (*n* = 239 in the intervention group, *n* = 235 in the control group)** Number progressed: 217/239 with intervention, 222/235 with control Number censored: 22/239 with intervention, 13/235 with control Median time to progression (Kaplan–Meier estimate): 113 days with intervention, 119 days with control; *p* (stratified log-rank test) = 0.095, HR = 1.176 (90% CI, 1.002 to 1.381; 91.6% CI, 0.994 to 1.392) **Evaluable patients only (*n* = 207 in the intervention group, *n* = 209 in the control group)** Number progressed: 185/207 with intervention, 197/209 with control Number censored: 22/207 with intervention, 12/209 with control Median time to progression (Kaplan–Meier estimate): 148 days with intervention, 134 days with control; *p* (stratified log-rank test) = 0.0261, HR = 1.262 (90% CI, 1.062 to 1.500; 91.6% CI, 1.053 to 1.513) **Subgroup analysis for the ITT population using Cox regression analysis (*n* = 239 in the intervention group, *n* = 235 in the control group)** *Age* < 65 years: median time to progression = 121 days (156/239) with intervention, median time to progression = 119 days (138/235) with control; HR = 1.176 (90% CI, 1.002 to 1.381) ≥ 65 years: median time to progression = 103 days (83/239) with intervention, median time to progression = 128 days (97/235) with control; HR = 1.147 (90% CI, 0.879 to 1.498) *Karnofsky performance status* < 80: median time to progression = 53 days (39/239) with intervention, median time to progression = 71 days (37/235) with control; HR = 0.867 (90% CI, 0.567 to 1.327) ≥ 80: median time to progression = 131 days (200/239) with intervention, median time to progression = 134 days (194/235) with control group; HR = 1.157 (90% CI, 0.971 to 1.379)	***Follow-up data*** **ITT population (*n* = 239 in the intervention group, *n* = 235 in the control group)** Number dead: 136/239 with intervention, 149/235 with control Number alive: 103/239 with intervention, 86/235 with control Median survival (based on Kaplan–Meier estimates): 420 days with intervention, 397 days with control; *p* (stratified log-rank test) = 0.34, HR = 1.121 (90% CI, 0.920 to 1.367; 91.6% CI, 0.911 to 1.381) **Evaluable patients only (*n* = 207 in the intervention group, *n* = 209 in the control group)** Number dead: 108/207 with intervention, 123/209 with control Number alive: 99/207 with intervention, 86/209 with control Median survival (based on Kaplan–Meier estimates): 483 days with intervention, 454 days with control; *p* (stratified log-rank test) = 0.41, HR = 1.116 (90% CI, 0.895 to 1.392; 91.6% CI, 0.885 to 1.408) **Subgroup analysis for the ITT population using Cox regression analysis (*n* = 239 in the intervention group, *n* = 235 in the control group)** *Age* < 65 years: median survival = 439 days (156/239) with intervention, median survival = 394 days (138/235) with control; HR = 1.143 (90% CI, 0.886 to 1.474) ≥ 65 years: median survival = 407 days (83/239) with intervention, median survival = 435 days (97/235) with control; HR = 1.008 (90% CI, 0.728 to 1.396) *Karnofsky performance status* < 80: median survival = 137 days (39/239) with intervention, median survival = 144 days (37/235) with control;* HR = 0.847 (90% CI, 0.544 to 1.319) ≥ 80: median survival = 462 days (200/239) with intervention, median survival = 460 days (194/235) with control;* HR = 1.147 (90% CI, 0.915 to 1.437) *Drug-free interval after first-line therapy* ≤ 6 months: median survival = 249 days (102/239) with intervention, median survival = 276 days (109/235) with control; HR = 1.017 (90% CI, 0.777 to 1.332)	A responder was defined as a patient with at least a durable (complete or partial) response. Durable response was the patient's maximum confirmed response ***Baseline data*** Not stated ***Follow-up data*** **ITT population (*n* = 239 in the intervention group, *n* = 235 in the control group)** *All patients* Complete response: 9/239 (3.8%) with intervention, 11/235 (4.7%) with control Partial response: 38/239 (15.9%) with intervention, 29/235 (12.3%) with control Total response: 47/239 (19.7%) with intervention, 40/235 (17.0%) with control *Platinum-sensitive patients* Complete response: 8/109 (7.3%) with intervention, 10/111 (9.0%) with control Partial response: 23/109 (21.1%) with intervention, 22/111 (19.8%) with control Total response: 31/109 (28.4%) with intervention, 32/111 (28.8%) with control *Platinum-refractory patients* Complete response: 1/130 (0.8%) with intervention, 1/124 (0.8%) with control Partial response: 15/130 (11.5%) with intervention, 7/124 (5.6%) with control Total response: 16/130 (12.3%) with intervention, 8/124 (6.5%) with control **Evaluable patients only (*n* = 207 in the intervention group, *n* = 209 in the control group)** *Responders (47/207 (22.7%) with intervention, 40/209 (19.1%) with control; p (Cochran–Mantel–Haenzel) = 0.332)* Complete response: 9/207 (4.3%) with intervention, 11/209 (5.3%) with control Partial response: 38/207 (18.4%) with intervention, 29/209 (13.9%) with control

continued

Results *contd*

Outcome 1 Time to progression (not defined)	Outcome 2 Overall survival (not defined)	Outcome 3 Response rates
Drug-free interval after first-line therapy ≤ 6 months: median time to progression = 57 days (102/239) with intervention, median time to progression = 94 days (109/235) with control; HR = 1.095 (90% CI, 0.855 to 1.401) > 6 to ≤ 18 months: median time to progression = 148 days (107/239) with intervention, median time to progression = 131 days (94/235) with control; HR = 1.170 (90% CI, 0.916 to 1.496) > 18 months: median time to progression = 290 days (30/239) with intervention, median time to progression = 228 days (32/235) with control; HR = 1.530 (90% CI, 0.918 to 2.549) *Bulky disease* Present: median time to progression = 92 days (111/239) with intervention, median time to progression = 110 days (111/235) with control; HR = 1.143 (90% CI, 0.903 to 1.447) Absent: median time to progression = 131 days (128/239) with intervention, median time to progression = 128 days (124/235) with control; HR = 1.206 (90% CI, 0.969 to 1.500) *Platinum sensitivity* Sensitive: median time to progression = 202 days (109/239) with intervention, median time to progression = 163 days (111/235) with control; HR = 1.349 (90% CI, 1.065 to 1.709) Refractory: median time to progression = 66 days (130/239) with intervention, median time to progression = 95 days (124/235) with control; HR = 1.046 (90% CI, 0.841 to 1.301) *Ascites* Present: median time to progression = 63 days (77/239) with intervention, median time to progression = 102 days (65/235) with control;* HR = 0.930 (90% CI, 0.691 to 1.254) Absent: median time to progression = 157 days (162/239) with intervention, median time to progression = 134 days (168/235) with control;* HR = 1.295 (90% CI, 1.065 to 1.575)	> 6 to ≤ 18 months: median survival = 523 days (107/239) with intervention, median survival = 491 days (94/235) with control; HR = 1.126 (90% CI, 0.815 to 1.557) > 18 months: median survival = 785 days (30/239) with intervention, median survival = 661 days (32/235) with control; HR = 1.782 (90% CI, 0.795 to 3.992) *Bulky disease* Present: median survival = 376 days (111/239) with intervention, median survival = 343 days (111/235) with control; HR = 1.093 (90% CI, 0.833 to 1.436) Absent: median survival = 523 days (128/239) with intervention, median survival = 463 days (124/235) with control; HR = 1.154 (90% CI, 0.865 to 1.539) *Platinum sensitivity* Sensitive: median survival = 756 days (109/239) with intervention, median survival = 498 days (111/235) with control; HR = 1.720 (90% CI, 1.222 to 2.422) Refractory: median survival = 249 days (130/239) with intervention, median survival = 289 days (124/235) with control; HR = 0.895 (90% CI, 0.700 to 1.143) *Ascites* Present: median survival = 197 days (77/239) with intervention, median survival = 276 days (65/235) with control; HR = 0.982 (90% CI, 0.708 to 1.361) Absent: median survival = 539 days (162/239) with intervention, median survival = 447 days (168/235) with control; HR = 1.330 (90% CI, 1.025 to 1.726)	95% CI for response rate: 17.0 to 28.4 with intervention, 13.8 to 24.5 with control 95% CI for treatment difference: –4.2 to 11.4 *Non-responders (160/207 (77.3%) in the intervention group, 169/209 (80.9%) in the control group)* Unconfirmed complete response: 1/207 (0.5%) with intervention, 3/209 (1.4%) with control Unconfirmed partial response: 11/207 (5.3%) with intervention, 18/209 (8.6%) with control Stable disease: 73/207 (35.3%) with intervention, 91/209 (43.5%) with control Progressive disease: 70/207 (33.8%) with intervention, 50/209 (23.9%) with control No data available: 5/207 (2.4%) with intervention, 7/209 (3.3%) with control

continued

Results *contd*

Outcome 4 Time to response (not defined)	Outcome 5 Duration of response (not defined)	Outcome 6 QoL (assessed using the self-administered EORTC QLQ-C30 at 12 weeks)
Follow-up data **ITT population (*n* = 239 in the intervention group, *n* = 235 in the control group)** Data not provided **Evaluable patients only (*n* = 47 in the intervention group, *n* = 40 in the control group)** Median (Kaplan–Meier estimate): 8.1 months (range 4.0–28.4) with intervention, 8.1 months (range 5.6–44.1) with control; *p* (log-rank test) = 0.448	***Follow-up data*** **ITT population (*n* = 239 in the intervention group, *n* = 235 in the control group)** Data not provided **Evaluable patients only (*n* = 47 in the intervention group, *n* = 40 in the control group)** % censored: 57.4 with intervention, 62.5 with control Median (Kaplan–Meier estimate): 30.1 months (range 5.0–90.4) with intervention, 25.7 months (range 7.0–55.1) with control; both censored observations; *p* (log-rank test) = 0.891	Q-TWiST was also used to compare the two agents. Time (in months) spent in the Q-TWiST health state was 4.65 months with intervention and 5.53 months with control (difference = 1.14 months, 95% CI, 0.46 to 1.82) ***Baseline data*** Not stated, but function and symptom scale scores were similar for both groups ***Follow-up data*** **Patients with maintenance of or improvement in QoL scores at 12 weeks (based on number of patients remaining)** *All patients* Physical functioning: 66/118 (55.9%) with intervention, 61/107 (57.0%) with control Role functioning: 77/118 (65.3%) with intervention, 63/109 (57.8%) with control Emotional functioning: 80/119 (67.2%) with intervention, 80/108 (74.1%) with control Cognitive functioning: 87/119 (73.1%) with intervention, 79/108 (73.1%) with control Social functioning: 82/119 (68.9%) with intervention, 69/108 (63.9%) with control Global QoL: 68/117 (58.1%) with intervention, 54/104 (51.9%) with control Fatigue: 67/118 (56.8%) with intervention, 61/109 (56.0%) with control Nausea/vomiting: 86/119 (72.3%) with intervention, 77/109 (70.6%) with control Pain: 76/119 (63.9%) with intervention, 88/109 (80.7%) with control *Platinum-sensitive patients* Physical functioning: 38/65 (58.5%) with intervention, 30/57 (52.6%) with control Role functioning: 36/65 (55.4%) with intervention, 30/59 (50.8%) with control Emotional functioning: 38/65 (58.5%) with intervention, 40/58 (69.0%) with control Cognitive functioning: 48/65 (73.8%) with intervention, 42/58 (72.4%) with control Social functioning: 39/65 (60.0%) with intervention, 34/58 (58.6%) with control Global QoL: 36/64 (56.3%) with intervention, 25/56 (44.6%) with control Fatigue: 29/65 (44.6%) with intervention, 30/59 (50.8%) with control Nausea/vomiting: 44/65 (67.7%) with intervention, 42/59 (71.2%) with control Pain: 35/65 (53.8%) with intervention, 49/59 (83.1%) with control *Platinum-refractory patients* Physical functioning: 28/53 (52.8%) with intervention, 30/50 (60.0%) with control Role functioning: 41/53 (77.4%) with intervention, 33/50 (66.0%) with control Emotional functioning: 42/54 (77.8%) with intervention, 40/50 (80.0%) with control Cognitive functioning: 39/54 (72.2%) with intervention, 37/50 (74.0%) with control Social functioning: 43/54 (79.6%) with intervention, 35/50 (70.0%) with control Global QoL: 32/53 (60.4%) with intervention, 29/48 (60.4%) with control Fatigue: 38/53 (71.7%) with intervention, 31/50 (62.0%) with control

continued

Results *contd*		
Outcome 4 Time to response (not defined)	**Outcome 5 Duration of response (not defined)**	**Outcome 6 QoL (assessed using the self-administered EORTC QLQ-C30 at 12 weeks)**
		Nausea/vomiting: 42/54 (77.8%) with intervention, 35/50 (70.0%) with control Pain: 41/54 (75.9%) with intervention, 39/50 (78.0%) with control **Global QoL (no other scales) in ITT patients** *Intervention group* (n = *239)* Week 4: improved/stable score = 40.2%, worsened score = 32.6% Week 8: improved/stable score = 33.5%, worsened score = 28.9% Week 12: improved/stable score = 28.5%, worsened score = 20.5% Week 16: improved/stable score = 21.8%, worsened score = 19.2% Week 20: improved/stable score = 18.0%, worsened score = 16.7% Week 24: improved/stable score = 12.1%, worsened score = 14.6% *Control group* (n = *235)* Week 3: improved/stable score = 39.6%, worsened score = 31.9% Week 6: improved/stable score = 33.6%, worsened score = 29.4% Week 9: improved/stable score = 27.2%, worsened score = 23.0% Week 12: improved/stable score = 23.4%, worsened score = 20.4% Week 15: improved/stable score = 20.0%, worsened score = 17.4% Week 18: improved/stable score = 20.0%, worsened score 13.2% Week 21: improved/stable score = 11.9%, worsened score = 10.6% Week 24: improved/stable score = 10.2%, worsened score = 9.4%

SD, standard deviation

* *Data taken from the study report. Discrepancies in the total number of participants in each group may be due to missing patient data*

Appendix 9

Data extraction tables for clinical effectiveness studies (Phase II non-comparative studies)

Study details and design	Participant details	Intervention details	Withdrawals and adverse events	Conclusions and comments
Anonymous 1999[55] ***Source*** Company submission ***Aim*** To determine response rate, time to response, duration of response, time to progression, survival and safety of pegylated liposomal doxorubicin hydrochloride in patients with locally advanced or metastatic epithelial ovarian carcinoma refractory to platinum- and taxane-based chemotherapy and who have failed topotecan chemotherapy. In addition, pilot data and information about the use of HRQoL questionnaires for patients with ovarian cancer were to be obtained, and patients were to be monitored for changes during treatment when compared to baseline in measuring the effects of pegylated liposomal doxorubicin hydrochloride on HRQoL in this clinical trial ***Type of publication*** Final report ***Trial identification*** 30-47 ***Length of follow-up*** Until death or six cycles of drug ***ITT analysis performed*** Authors stated an ITT analysis was performed, but this was not a true ITT analysis because it did not include all participants recruited	***Number of participants*** 123 recruited; 122 ITT ***Description of participants (based on only 122 treated participants)*** Participants had locally advanced or metastatic epithelial ovarian cancer following the failure of at least two but no more than three prior cytotoxic chemotherapeutic regimens. Recruited from 24 USA sites from July 1996 to May 1999 **Karnofsky performance status** Median = 90% **CA-125 level** Median = 290.25 U/ml (range 7–46594), mean = 1569.35 U/ml **FIGO staging** I: 7/122 (5.7%) II: 8/122 (6.6%) III: 82/122 (67.2%) IV: 25/122 (20.5%) **Tumour grade** Unspecified differentiation: 82/122 (67.2%) Poorly differentiated: 30/122 (24.6%) Moderately differentiated: 7/122 (5.7%) Well differentiated: 2/122 (1.6%) Unspecified tumour grade: 1/122 (0.8%) **Histology** Serous papillary: 78/122 (63.9%) Unspecified adenocarcinoma: 20/122 (16.4%) Endometrioid: 11/122 (9.0%) Mucinous: 5/122 (4.1%) Clear cell: 3/122 (2.5%) Serous and endometrioid: 3/122 (2.5%) Transitional cell type: 1/122 (0.8%) Unspecified: 1/122 (0.8%) ***Therapy stage*** Second-line	***Intervention*** Pegylated liposomal doxorubicin hydrochloride **Route of administration** i.v. infusion over 1 hour **Dose** 50 mg/m^2. Median cumulative dose = 150 mg/m^2 **Number of cycles** Six cycles or until disease progression or dose-limiting toxicity. Patients who still received clinical benefit after six cycles were allowed to continue therapy upon approval of the sponsoring company. Median length of treatment = 57 days **Length per cycle** 28 days	***Withdrawals*** 11/122 (9.0%) due to death (three caused by adverse events, including one from neutropenic sepsis considered related to the study drug), 19/122 (15.6%) due to adverse events (13 were considered study drug-related): five grade 3 PPE, two grade 3 asthenia, one severe oedema of the feet and hands, one grade 4 neutropenia, one grade 1 decline in cardiac function, one grade 4 stomatitis, one grade 2 cardiotoxicity and one grade 3 dehydration/grade 2 hydronephrosis and abnormal kidney function/grade 1 vaginal haemorrhage ***Adverse events*** Overall, the common adverse events (myelosuppression, PPE, nausea, asthenia, stomatitis and rash) associated with the drug were predictable and managed by dose adjustment or delays. There were no unexpected toxicities experienced by participants and no evidence of drug-related liver or renal toxicity 116/122 (95.1%) participants had adverse events deemed to be possibly or probably related to the study drug. The most commonly reported (≥ 10%) were as follows. **All grades** Anaemia: 53/122 (43.4%) Leukopenia: 52/122 (42.6%) PPE: 48/122 (39.3%) Neutropenia: 48/122 (39.3%) Nausea: 47/122 (38.5%)	***Authors' conclusions*** Pegylated liposomal doxorubicin hydrochloride showed activity in the treatment of patients with advanced epithelial ovarian carcinoma refractory to both platinum and paclitaxel. Adverse events associated with pegylated liposomal doxorubicin hydrochloride were predictable and manageable by dose adjustments ***Comments*** This is the same study as that reported in the interim reports by Gordon *et al.*, 1998,[52] Gordon *et al.*, 2000[54] and Rose *et al.*, 1999.[53] This is the final confidential study report obtained from Schering-Plough Ltd Sample size was predetermined. If three or fewer patients responded from the first 33 participants recruited then the study was to be terminated. The chance of rejecting the drug having an activity rate of ≥ 22% would have been < 5%. For every four participants who responded from this initial population, 20 additional participants were required to be recruited. For more than 8/53 evaluable patients determined to have a response, accepting pegylated liposomal doxorubicin hydrochloride with ≥ 22% rate of activity was > 85% (power 85%) with an alpha value of 0.0457 123 participants were recruited, but only 122 were treated. The authors state that an ITT analysis was performed, but this was not a true ITT analysis because only the 122 treated participants were included It was unclear if an independent assessor carried out response assessments QoL was not assessed, although it was mentioned in the aims of the study ***Definitions*** Refractory disease: progression while being treated with a platinum- or taxane-based regimen

continued

Study details and design	Participant details	Intervention details	Withdrawals and adverse events	Conclusions and comments
contd **Anonymous 1999**[55]	***Previous treatments*** **Number of prior chemotherapy regimens** One: 13/122 (10.7%) Two: 63/122 (51.6%) Three: 46/122 (37.7%) **Prior drug-free interval** Median = 1.5 months (range not stated) ***Disease present after first-line treatment*** Refractory to platinum and paclitaxel (double refractory): 50/122 (41.0%) Refractory to platinum, paclitaxel and topotecan (triple refractory): 67/122 (54.9%) Combined refractory population (double and triple): 117/122 (95.9%) ***Disease type*** Measurable or measurable and evaluable: 121/122 (99.2%) Evaluable disease only: 1/122 (0.8%) ***Age*** Median = 61 years (range 34–85) ***Inclusion criteria*** Histologically proven advanced epithelial ovarian cancer; measurable disease or measurable and evaluable disease; at least two but no more than three failed previous chemotherapy regimens that must have included taxane, topotecan and platinum-based therapy; Karnofsky performance status of ≥ 60%; aged ≥ 18 years; adequate renal, bone marrow, liver and cardiac function; provided informed consent; disease-free from prior malignancies for at least 5 years with the exception of curatively treated basal cell carcinoma of the skin or carcinoma *in situ* of the cervix ***Exclusion criteria*** Pregnancy or breastfeeding; life expectancy of ≤ 3 months; prior radiation therapy to more than one-third of haematopoietic sites; resolution of		Asthenia: 47/122 (38.5%) Stomatitis: 40/122 (32.8%) Rash: 37/122 (30.3%) Mucous membrane disorder: 26/122 (21.3%) Vomiting: 24/122 (19.7%) Anorexia: 19/122 (15.6%) Diarrhoea: 15/122 (12.3%) Thrombocytopenia: 15/122 (12.3%) Alopecia: 14/122 (11.5%) **Severe (grades 3/4)** Anaemia: 13/122 (10.7%) Leukopenia: 9/122 (7.4%) PPE: 25/122 (20.5%) Neutropenia: 18/122 (14.8%) Nausea: 7/122 (5.7%) Asthenia: 8/122 (6.6%) Stomatitis: 10/122 (8.2%) Rash: 4/122 (3.3%) Mucous membrane disorder: 6/122 (4.9%) Vomiting: 4/122 (3.3%) Anorexia: 2/122 (1.6%) Diarrhoea: 3/122 (2.5%) Thrombocytopenia: 3/122 (2.5%) Alopecia: 0/122 (0.0%) **Moderate (grade 2)** Anaemia: 26/122 (21.3%) Leukopenia: 22/122 (18.0%) PPE: 14/122 (11.5%) Neutropenia: 14/122 (11.5%) Nausea: 8/122 (6.6%) Asthenia: 14/122 (11.5%) Stomatitis: 16/122 (13.1%) Rash: 15/122 (12.3%) Mucous membrane disorder: 8/122 (6.6%) Vomiting: 4/122 (3.3%) Anorexia: 8/122 (6.6%) Diarrhoea: 1/122 (0.8%)	Measurable disease: bidimensionally measurable lesion(s) with clearly defined margins by X-ray, computed tomography, magnetic resonance imaging or other scan with both diameters greater than the distance between cuts of the imaging study; or palpation with both diameters ≥ 2 cm Evaluable disease: unidimensionable measurable lesions with margins not clearly defined, lesions with both diameters ≤ 0.5 cm, lesions on scan with either diameter less than the distance between cuts or palpation with both diameters ≤ 2 cm and bone disease Complete response: the complete disappearance of all lesions Partial response: a decrease in lesion size of ≥ 50% Progressive disease: an increase in lesion size of ≥ 50% from the smallest previous lesion size; or any reappearance of disease from a complete response Stable disease: no previous confirmed complete or partial response or progression

continued

Study details and design	Participant details	Intervention details	Withdrawals and adverse events	Conclusions and comments
contd **Anonymous 1999**[55]	haematopoietic toxicities prior to treatment; history of cardiac disease, with New York Heart Association class II or greater with congestive heart failure; uncontrolled systemic infection; use of any investigational drug within 30 days of first dose of study drug; prior therapy with pegylated liposomal doxorubicin hydrochloride; prior chemotherapy within 28 days of first dose of study drug (or within 42 days if patient had received nitrosourea or mitomycin)		Thrombocytopenia: 0/122 (0.0%) Alopecia: 1/122 (0.8%) **Mild (grade 1)** Anaemia: 14/122 (11.5%) Leukopenia: 21/122 (17.2%) PPE: 9/122 (7.4%) Neutropenia: 16/122 (13.1%) Nausea: 32/122 (26.2%) Asthenia: 25/122 (20.5%) Stomatitis: 14/122 (11.5%) Rash: 18/122 (14.8%) Mucous membrane disorder: 12/122 (9.8%) Vomiting: 16/122 (13.1%) Anorexia: 9/122 (7.4%) Diarrhoea: 11/122 (9.0%) Thrombocytopenia: 12/122 (9.8%) Alopecia: 13/122 (10.7%)	
Results				
Outcome 1 Survival (measured from time of first dose of study drug to death)		**Outcome 2 Response (see definitions above)**		**Outcome 3 QoL**
Median = 314 days (range 8–824; 44.9 weeks)		***ITT population (n = 122)*** Complete response: 1/122 (0.8%) Partial response: 15/122 (12.3%) Total response: 16/122 (13.1%, 95% CI, 7.1 to 19.1) Median time to response = 106 days (range 23–230; 15.1 weeks) Median duration of response = 285 days (range 45–338; 40.7 weeks) Median time to progression = 142 days (range 5–528; 20.3 weeks) ***Combined refractory population (n = 118)*** Complete response: 1/118 (0.9%) Partial response: 15/118 (12.7%) Total response: 16/118 (13.6%, 95% CI, 7.4 to 19.9) Median time to response = 106 days (range 23–230; 15.1 weeks) Median duration of response = 285 days (range 45–338; 40.7 weeks) Median time to progression = 135 days (range 5–528; 20.3 weeks)	Not reported

Study details and design	Participant details	Intervention details	Withdrawals and adverse events	Conclusions and comments
Anonymous 1999[56] ***Source*** Company submission ***Aim*** To determine response rate, time to response, duration of response, time to progression, survival and safety of pegylated liposomal doxorubicin hydrochloride in patients with locally advanced or metastatic epithelial ovarian carcinoma refractory to platinum- and taxane-based chemotherapy ***Type of publication*** Final report ***Trial identification*** 30-47E ***Length of follow-up*** Until death or six cycles of drug ***ITT analysis performed*** Yes	***Number of participants*** 62 recruited; 62 ITT ***Description of participants*** Advanced or metastatic ovarian cancer refractory to platinum- and taxane-based chemotherapy **Karnofsky performance status** Median = 90% (range not stated) **FIGO staging*** I: 6/62 (9.7%) II: 2/62 (3.2%) III: 44/62 (71.0%) IV: 9/62 (14.5%) **Histology** Serous: 35/62 (56.5%) Unspecified adenocarcinoma: 22/62 (35.5%) Endometrioid: 2/62 (3.2%) Clear cell subtype: 2/62 (3.2%) Mucinous: 1/62 (1.6%) **Differentiation** Unspecified: 28/62 (45.2%) Poorly differentiated: 21/62 (33.9%) Moderately differentiated: 11/62 (17.7%) Well differentiated: 2/62 (3.2%) **CA-125 level** Median = 680 U/ml (range 7–31990) **Baseline lesion ≥ 5 cm in one dimension** 30/62 (48.4%) ***Therapy stage*** Second-line ***Previous treatments*** At least two but no more than three previous chemotherapy drugs including platinum, taxanes and topotecan **Prior drug-free interval** Median = 2.6 months (range not stated)	***Intervention*** Pegylated liposomal doxorubicin hydrochloride **Route of administration** i.v. infusion over 1 hour **Dose** 50 mg/m^2. Median cumulative dose = 100.4 mg/m^2. A total of 191 doses were administered to the 62 participants **Number of cycles** Six cycles or until disease progression or dose-limiting toxicity (mean = 3.1 cycles per participant). Patients who still received clinical benefit after six cycles were allowed to continue therapy upon approval of sponsoring company. Median length of treatment = 29.5 days **Length per cycle** 28 days	***Withdrawals*** 39/62 (62.9%) participants withdrew due to disease progression, 8/62 (12.9%) withdrew due to adverse events, 3/62 (4.8%) died, 2/62 (3.2%) withdrew for other reasons, 1/62 (1.6%) was lost to follow-up and 1/62 (1.6%) was withdrawn due to non-compliance ***Adverse events*** No deaths were considered to be related to the study drug. 8/62 (12.9%) withdrew from the study due to adverse events. For four of these participants, the events were considered to be related to the study drug (one grade 3 infusion reaction, two grade 3 PPE, one grade 3 exfoliative dermatitis) Overall, the common adverse events associated with the drug were managed by dose adjustment or delays. There were no unexpected toxicities experienced by participants and no evidence of drug-related liver or renal toxicity 59/62 (95.2%) participants had adverse events deemed to be possibly or probably related to the study drug. The most commonly reported (≥ 10%) were as follows. **All grades** Nausea: 25/62 (40.3%) Vomiting: 21/62 (33.9%) PPE: 19/62 (30.6%) Stomatitis: 18/62 (29.0%) Asthenia: 13/62 (21.0%) Anaemia: 12/62 (19.4%)	***Authors' conclusions*** Pegylated liposomal doxorubicin hydrochloride showed activity in the treatment of patients with advanced epithelial ovarian carcinoma refractory to both platinum and paclitaxel. The response rate was 6.5%. Most participants withdrew from the trial before the third cycle due to progressive disease. Adverse events associated with pegylated liposomal doxorubicin hydrochloride were predictable and manageable by dose adjustments and delays ***Comments*** No details about the study have been published Outcome data were analysed in terms of ITT and evaluable patients only. In this summary of the study only the ITT analysis is presented Time to event data were analysed using Kaplan–Meier survival analysis. Despite this, the report only gave survival curves and did not present the data in terms of HRs Although the authors stated that the original trial protocol said that approximately 66 patients should be recruited, no details of any statistical analysis were reported to support this number Patient QoL was not assessed The response assessments did not appear to have been confirmed by an independent assessor ***Definitions*** Refractory disease: progression while being treated with a platinum- or taxane-based regimen Measurable disease: bidimensionally measurable lesion(s) with clearly defined margins by X-ray, computed tomography, magnetic resonance imaging or other scan with both diameters greater than the distance between cuts of the imaging study or palpation with both diameters ≥ 2 cm

continued

Study details and design	Participant details	Intervention details	Withdrawals and adverse events	Conclusions and comments
contd **Anonymous 1999**[56]	***Disease present after first-line treatment*** Refractory to platinum and paclitaxel (double refractory): 32/62 (51.6%) Refractory to platinum, paclitaxel and topotecan (triple refractory): 11/62 (17.7%) ***Disease type*** Measurable or measurable and evaluable disease: 60/62 (96.8%) Evaluable disease only: 2/62 (3.2%) ***Age*** Median = 53 years (range 22–80) ***Inclusion criteria*** Histologically proven advanced epithelial ovarian cancer; measurable disease or measurable and evaluable disease; treated with at least two but no more than three prior chemotherapy regimens; Karnofsky performance status of ≥ 60%; aged ≥ 18 years; adequate bone marrow, renal, liver and heart function; provided informed consent; disease-free from prior malignancies for ≥ 5 years with the exception of curatively treated basal cell or squamous carcinoma of the skin or carcinoma *in situ* of the cervix ***Exclusion criteria*** Pregnant or breastfeeding; life expectancy of ≤ 3 months; prior radiation therapy to more than one-third of haematopoietic sites; history of cardiac disease with New York Heart Association class II or greater with congestive heart failure; uncontrolled systemic infection; use of any investigational drug within 30 days of first dose of study drug; prior therapy with pegylated liposomal doxorubicin hydrochloride; prior chemotherapy within 30 days of first dose of study drug (or within 42 days if patient had received a nitrosourea or mitomycin)		Rash: 12/62 (19.4%) Leukopenia: 11/62 (17.7%) Constipation: 9/62 (14.5%) Anorexia: 7/62 (11.3%) **Severe (grades 3/4)** Nausea: 2/62 (3.2%) Vomiting: 2/62 (3.2%) PPE: 5/62 (8.1%) Stomatitis: 4/62 (6.5%) Asthenia: 3/62 (4.8%) Anaemia: 1/62 (1.6%) Rash: 1/62 (1.6%) Leukopenia: 4/62 (6.5%) Constipation: 1/62 (1.6%) Anorexia: 0/62 (0.0%) **Moderate (grade 2)** Nausea: 7/62 (11.3%) Vomiting: 9/62 (14.5%) PPE: 10/62 (16.1%) Stomatitis: 5/62 (8.1%) Asthenia: 3/62 (4.8%) Anaemia: 6/62 (9.7%) Rash: 6/62 (9.7%) Leukopenia: 3/62 (4.8%) Constipation: 2/62 (3.2%) Anorexia: 3/62 (4.8%) **Mild (grade 1)** Nausea: 16/62 (25.8%) Vomiting: 10/62 (16.1%) PPE: 4/62 (6.5%) Stomatitis: 9/62 (14.5%) Asthenia: 7/62 (11.3%) Anaemia: 5/62 (8.1%) Rash: 5/62 (8.1%) Leukopenia: 4/62 (6.5%) Constipation: 6/62 (9.7%) Anorexia: 4/62 (6.5%)	Evaluable disease: unidimensionable measurable lesions with margins not clearly defined, lesions with both diameters ≤ 0.5 cm, lesions on scan with either diameter less than the distance between cuts or palpation with both diameters ≤ 2 cm and bone disease Complete response: the complete disappearance of all lesions Partial response: a decrease in lesion size of ≥ 50% Progressive disease: an increase in lesion size of ≥ 50% from the smallest previous lesion size or any reappearance of disease from a complete response Stable disease: no previous confirmed complete or partial response or progression

continued

Results		
Outcome 1 Survival (measured from time of first dose of study drug to death)	**Outcome 2 Response (see definitions above)**	**Outcome 3 QoL**
Median survival = 176 days (range 1–531; 25.1 weeks)	Complete response: 0/62 (0.0%) Partial response: 4/62 (6.5%, 95% CI, 0.3 to 12.6) Total response: 4/62 (6.5%, 95% CI, 0.3 to 12.6) Stable disease: 15/62 (24.2%) Progressive disease: 22/62 (35.5%) One responder was double-refractory Median time to progression = 81 days (range 1–399; 11.6 weeks) Median time to response = 57 days (range 53–120; 8.1 weeks) Median duration of response = 124 days (range 114–280; 17.7 weeks)	Not reported
* *Data taken from the study report. Discrepancies in the total number of participants in each group may be due to missing patient data*		

Study details and design	Participant details	Intervention details	Withdrawals and adverse events	Conclusions and comments
Cervantes *et al.*, 1999[59] ***Source*** Database ***Aim*** To determine the activity of pegylated liposomal doxorubicin hydrochloride in patients with recurrences of ovarian carcinoma after treatment with cisplatin using a Phase II trial ***Type of publication*** Abstract of final report ***Trial identification*** Not stated ***Length of follow-up*** Not stated ***ITT analysis performed*** Yes	***Number of participants*** 18 recruited ***Description of participants*** **Histology** Serous: 14/18 (77.8%) Other: 4/18 (22.2%) **Number of lesions** < three: 5/18 (27.8%) ≥ three: 13/18 (72.2%) **Size of largest lesion** < 5 cm: 10/18 (55.6%) > 5 cm: 8/18 (44.4%) **Ascites** Present: 6/18 (33.3%); Absent: 12/18 (66.7%) **WHO performance status** Median = 2 (range 0–2) ***Therapy stage*** Second-line ***Previous treatments*** Median number of previous treatments = 2 (range 2–5) Median time from last treatment = 2 months (range not stated) ***Disease present after first-line treatment*** Resistant or progressive disease ***Age*** Median = 60 years (range 32–78) ***Inclusion criteria*** Normal hepatic, renal, cardiac and marrow function; WHO performance status of < 3; histologically confirmed ovarian carcinoma; resistance or progression after cisplatin treatment and measurable disease ***Exclusion criteria*** Not stated	***Intervention*** Pegylated liposomal doxorubicin hydrochloride **Route of administration** i.v. infusion over 1 hour **Dose** 50 mg/m^2. This dose was reduced to 40 mg/m^2 from the second dose onwards **Number of cycles** Median number of cycles = 3 (range 2–10) per person **Length per cycle** 21 days	***Withdrawals*** Not stated ***Adverse events*** Most commonly reported toxicities were skin toxicity and mucositis (grade 3, *n* = 3/18 (16.7%)). The numbers involved were unclear from the abstract. However, no other grade 3/4 toxicities were observed	***Authors' conclusions*** Treatment with pegylated liposomal doxorubicin hydrochloride had good tolerance but low activity in this selected population of cisplatin-refractory patients ***Comments*** Available in abstract form only so minimal details provided. Attempts were made to contact the authors for additional information, but these were unsuccessful Unclear whether assessment of response was independent Survival and QoL outcomes were not assessed Not stated how long participants were followed up for

Results		
Outcome 1 Survival (not defined)	**Outcome 2 Response (not defined)**	**Outcome 3 QoL**
Not reported	Complete response: 0/18 (0.0%) Partial response: 1/18 (5.6%) Overall response: 1/18 (5.6%)	Not reported

Study details and design	Participant details	Intervention details	Withdrawals and adverse events	Conclusions and comments
Gordon 1998[52] ***Source*** Database ***Aim*** To conduct a Phase II, open-label, two-stage study to evaluate the safety and efficacy of pegylated liposomal doxorubicin hydrochloride in the treatment of locally advanced or metastatic refractory epithelial ovarian carcinoma ***Type of publication*** Abstract of interim data ***Trial identification*** 30-47 ***Length of follow-up*** Participants were followed up until progression of disease or unacceptable toxicity. Median time in the study was 56 days ***ITT analysis performed*** No	***Number of participants*** 50 recruited; 34 evaluable for response ***Description of participants*** **Karnofsky performance status** Median = 90% (range 70–100) ***Therapy stage*** Second-line ***Previous treatments*** **Prior drug-free interval** Median = 1.8 months (range 0–9) ***Disease present after first-line treatment*** Locally advanced or metastatic refractory ***Age*** Median = 57.5 years (range 34–83) ***Inclusion criteria*** Failure of up to three prior chemotherapy regimens (including platinum-/taxane-based regimens or topotecan); histologically proven and measurable disease ***Exclusion criteria*** None stated	***Intervention*** Pegylated liposomal doxorubicin hydrochloride **Route of administration** i.v. infusion over 1 hour **Dose** 50 mg/m^2. Median cumulative dose = 150 mg/m^2 **Number of cycles** Six cycles or until disease progression or dose-limiting toxicity **Length per cycle** 28 days	***Withdrawals*** No details reported ***Adverse events*** Only interim data was presented and absolute values and percentages relate to 45 patients evaluable for adverse events. It was unclear how many participants should be included in an ITT analysis and thus the data below only relates to the evaluable participants (i.e. *n* = 45; the abstract uses the demoninator *n* = 41, which is only the number of evaluable participants experiencing adverse events and not the whole evaluable population). In total, 41/45 (91.1%) participants had drug-related adverse events (4/41 (9.8%) were classed as grade 4) Grade 4 stomatitis: 1/45 (2.2%) Grade 4 leukopenia: 2/45 (4.4%) Grade 4 thrombocytopenia: 1/45 (2.2%) Grade 3: PPE 10/45 (22.2%) Note, only percentage values and not absolute values were quoted for the following adverse events. Nausea (all grades): 44.4% Stomatitis (all grades): 37.8% Asthenia (all grades): 37.8% Skin rash (all grades): 28.9% Mild/severe leukopenia (all grades): 24.4%	***Authors' conclusions*** Preliminary results in 34 patients evaluable for response showed that pegylated liposomal doxorubicin hydrochloride was generally well tolerated and efficacious in the treatment of refractory advanced epithelial ovarian carcinoma. Based on this positive experience, this study is being continued ***Comments*** Same trial as reported in interim reports by Rose *et al*., 1999[53] and Gordon *et al*., 2000.[54] Also reported as final confidential company report[55] Only interim data presented and absolute values and percentages relate to the 34 patients evaluable for response. It was unclear how many participants should be included in an ITT analysis and thus the data included in this summary only relate to the evaluable patients The response assessments were reported as an objective, but no further details were provided and thus it was not possible to tell if the responses were truly independent. In addition, definitions of complete and partial responses were not reported Age, Karnofsky performance status and drug-free interval were reported for the study population at baseline, but disease bulk, number of previous regimens and histology were not

continued

Results		
Outcome 1 Survival (not defined)	**Outcome 2 Response (not defined)**	**Outcome 3 QoL**
Not reported	In addition to the responses listed below, one unconfirmed partial response was also reported (along with 19 with stable disease, ten with disease progression and no data for 13 participants) Complete response: 0/34 (0.0%) Partial response: 7/34 (20.6%) Overall response: 7/34 (20.6%) Median time to response = 16.1 weeks (range 12.4–20.9) Median duration of response = 17.1 weeks (range 5.3–39.7)	Not reported

Study details and design	Participant details	Intervention details	Withdrawals and adverse events	Conclusions and comments
Gordon *et al.*, 2000[54] ***Source*** Database ***Aim*** To examine the activity of pegylated liposomal doxorubicin hydrochloride in platinum- and paclitaxel-refractory ovarian cancer ***Type of publication*** Abstract of interim data ***Trial identification*** 30-47 ***Length of follow-up*** Every 4 weeks until progression or unacceptable toxicity ***ITT analysis performed*** Yes	***Number of participants*** 90 recruited; 89 ITT ***Description of participants (ITT (n = 89))*** **Karnofsky performance status** Median = 90% (range 60–100) **Tumour grade** 1: 1/89 (1.1%) 2: 5/89 (5.6%) 3: 22/89 (24.7%) Unspecified: 61/89 (68.5%) ***Therapy stage*** Second-line ***Previous treatments*** **Prior regimens** One: 13/89 (14.6%) Two: 47/89 (52.8%) Three: 29/89 (32.6%) **Drug-free interval** Median = 1.6 months (range 0.6–9.2) ***Disease present after first-line treatment*** Platinum- and paclitaxel-refractory disease ***Age*** Median = 61 years (range 34–85) ***Inclusion criteria*** Histologically proven epithelial ovarian cancer with measurable disease; at least two but no more than three prior regimens including topotecan; taxane and platinum refractory; Karnofsky performance status of ≥ 60%; ≥ 18 years of age; adequate bone marrow function, blood counts, renal, liver and cardiac function; disease-free from prior malignancies for ≥ 5 years, with the exception of basal cell carcinoma of the skin or carcinoma *in situ* of the cervix; provided informed consent	***Intervention*** Pegylated liposomal doxorubicin hydrochloride **Route of administration** i.v. infusion over 1 hour **Dose** 50 mg/m^2. Mean cumulative dose = 211.2 mg/m^2 (median = 150 mg/m^2; range 50–808.4) **Number of cycles** Average = 4.4 per patient **Length per cycle** 28 days	***Withdrawals*** One participant withdrew before receiving any medication. Fifteen participants terminated the study due to adverse events, 42 due to disease progression and 18 for other reasons, which were not specified ***Adverse events*** All patients had at least one adverse event, but there were no treatment-related deaths. Of all the adverse events, eight were grade 4 (0.9%) and 80 were grade 3 (9.0%). Haematological toxicity was generally of short duration and easily managed. Stomatitis, PPE and skin lesions were managed by dose reductions and delays as required. Fifteen participants (16.9%) terminated the study due to adverse events Patients experiencing drug-related adverse events (out of 89) were as follows. **All grades** Asthenia: 37/89 (41.6%) PPE: 37/89 (41.6%) Anaemia: 35/89 (39.3%) Nausea: 34/89 (38.2%) Neutropenia: 33/89 (37.1%) Stomatitis: 31/89 (34.8%) Rash: 25/89 (28.1%) Mucositis: 19/89 (21.3%) Vomiting: 17/89 (19.1%) Anorexia: 12/89 (13.5%) Diarrhoea: 11/89 (12.4%) Thrombocytopenia: 8/89 (9.0%) Cardiovascular: 6/89 (6.7%)	***Authors' conclusions*** Stealth pegylated liposomal doxorubicin hydrochloride had activity in refractory epithelial ovarian cancer. PPE and stomatitis could usually be managed by dose adjustment. The ease of administration makes this an attractive agent ***Comments*** Only interim data was presented in abstract form, so few details available. Same trial as reported in interim abstracts by Rose *et al.*, 1999[53] and Gordon *et al.*, 1998.[52] Also reported as final confidential company report[55] The trialists reported that they performed an ITT analysis. However, this only included 89 of the 90 participants originally included in the study. Therefore, a true ITT analysis was not performed The authors report that if more than 8/53 assessable patients had a response, the probability of a response rate of ≥ 22% had an alpha of 0.0457 with a power of 85% Dose reductions (25%) or delays in administration of pegylated liposomal doxorubicin hydrochloride were allowed for adverse events Age, number of prior regimens, drug-free interval, performance status and tumour grade were reported at baseline. However, disease bulk and histology were not It was unclear whether responses were assessed independently. The trialists stated that the responses were objective but gave no further details No survival or QoL data were reported and it was unclear whether time to event data were analysed using survival analysis methods ***Definitions*** Measurable disease: bidimensionally measurable lesion(s) with clearly defined margins on X-ray with at least one diameter of 0.5 cm or on computed

continued

Study details and design	Participant details	Intervention details	Withdrawals and adverse events	Conclusions and comments
contd **Gordon et *al.*, 2000**[54]	***Exclusion criteria*** Pregnancy and breastfeeding; life expectancy ≤ 3 months; prior radiation therapy to more than one-third of haematopoietic sites; history of cardiac disease (New York Heart Association class II or greater with congestive heart failure); use of any investigational drug within 30 days of the first doxorubicin dose and any prior therapy with pegylated liposomal doxorubicin hydrochloride; prior chemotherapy within 28 days of the first dose of pegylated liposomal doxorubicin hydrochloride or within 42 days if received nitrosourea or mitomycin			tomography scan or magnetic resonance imaging with both diameters of ≥ 2 cm Taxane- and platinum refractory: progression on chemotherapy or within 6 months of completion of chemotherapy Complete response: complete disappearance of all measurable and assessable disease. No new disease or disease-related symptoms were allowed Partial response: a ≥ 50% decrease in the sum of the products of all bidimensionally measurable lesions. There was to be no progression of any assessable disease and no new lesions. All responses had to be confirmed by a second measurement 4 weeks later Progressive disease: a ≥ 50% increase in the sum of the products of bidimensionally measurable lesions. The reappearance of any lesion or clear worsening of assessable disease or the appearance of any new lesion was also considered progressive disease All other patients were classified as having stable disease
Results				
Outcome 1 Survival (not defined)		**Outcome 2 Response (not defined)**		**Outcome 3 QoL**
Not reported		***ITT (n = 89)*** Complete response: 1/89 (1.1%) Partial response: 14/89 (15.7%) Overall response: 15/89 (16.8%, 95% CI, 9.1 to 24.6) Stable disease: 36/89 (40.4%) Progressive disease: 19/89 (21.3%) Median time to progression = 19.3 weeks (range 0.7–86) Median time to response = 15.1 weeks (range 3.3–32.9) Median duration of response = 24.1 weeks (range 4.6–48.3) ***Platinum-/paclitaxel-refractory patients*** Complete response: 1/82 (1.2%) Partial response: 14/82 (17.1%) Overall response: 15/82 (18.3%, 95% CI, 9.9 to 26.7) Stable disease: 31/82 (37.8%) Progressive disease: 18/82 (22.0%) Median time to progression = 17 weeks (range 0.7–71.6)		Not reported

Study details and design	Participant details	Intervention details	Withdrawals and adverse events	Conclusions and comments
Israel *et al.*, 2000[57] ***Source*** Database ***Aim*** To evaluate the activity of pegylated liposomal doxorubicin hydrochloride in patients with ovarian cancer and explore activity in other gynaecological cancers ***Type of publication*** Final report ***Trial identification*** Not stated ***Length of follow-up*** Varied according to the individual. Followed up until progression or unacceptable toxicity occurred. Radiological assessments for response were carried out every four cycles ***ITT analysis performed*** Unclear	***Number of participants*** 63 recruited ***Description of participants*** 48/63 (76.2%) had confirmed recurrent or metastatic epithelial ovarian cancer, which was measurable or assessable. The remaining 15 participants had other gynaecological cancers (cervical, endometrial or vaginal) and are not discussed in this summary **Baseline characteristics (ovarian cancer patients only)** Tumour size (only patients with measurable disease, *n* = 21) Bulky (≥ 5 cm): 12/21 (57.1%) Non-bulky: 9/21 (42.9%) **Histology** Serous: 32/48 (66.7%) Adenocarcinoma: 10/48 (20.8%) Endometrioid: 3/48 (6.3%) Clear cell: 2/48 (4.2%) Transitional cell: 1/48 (2.1%) Age and Karnofsky performance status data given for the population as a whole and not just the ovarian cancer patients, therefore, not reported in this summary ***Therapy stage*** Second-line ***Previous treatments*** **Number of prior chemotherapy regimens** None: 0/48 (0.0%) One: 21/48 (43.8%) Two: 10/48 (20.8%) Three: 10/48 (20.8%) Four: 2/48 (4.2%) Five: 2/48 (4.2%) Six: 3/48 (6.3%)	***Intervention*** Pegylated liposomal doxorubicin hydrochloride **Route of administration** i.v. infusion over 1 hour **Dose** 50 mg/m^2 **Number of cycles** Until progression or unacceptable toxicity occurred **Length per cycle** 28 days. The second cycle was given after 21 days, but all subsequent cycles were given at 28-day intervals	***Withdrawals*** One patient experienced a grade 2 hypersensitivity reaction and withdrew from the study (unclear if this patient had ovarian cancer) ***Adverse events*** There were no severe hypersensitivity reactions. However, one patient experienced a grade 2 reaction (see above) Data were reported in terms of number of cycles and not number of participants, so unclear if based on an ITT analysis **Number of cycles with toxicity in ovarian cancer patients only** Leukopenia (grade 3): 17/204 Leukopenia (grade 4): 0/204 Neutropenia (grade 3): 18/204 Neutropenia (grade 4): 1/204 Anaemia (grade 3): 7/204 Anaemia (grade 4): 0/204 Thrombocytopenia (grade 3): 7/204 Thrombocytopenia (grade 4): 1/204 Stomatitis (grade 3): 5/204 Stomatitis (grade 4): 0/204 Skin irritation (grade 3): 3/204 Skin irritation (grade 4): 0/204 Fatigue (grade 3): 11/204 Fatigue (grade 4): 0/204 Nausea (grade 3): 2/204 Nausea (grade 4): 0/204 Vomiting (grade 3): 1/204 Vomiting (grade 4): 0/204 Infection (grade 3): 3/204 Infection (grade 4): 0/204 Gastritis (grade 3): 1/204 Gastritis (grade 4): 0/204 Neutropenic fever (grade 3): 0/204 Neutropenic fever (grade 4): 0/204	***Authors' conclusions*** This study demonstrated the activity of pegylated liposomal doxorubicin hydrochloride in heavily pretreated patients with ovarian cancer and poor prognostic features and confirmed the prolonged responses and favourable toxicity profile. Encouraging findings were also observed in the patients with non-ovarian gynaecological cancers ***Comments*** Pegylated liposomal doxorubicin hydrochloride doses were reduced 20% on subsequent cycles for any grade 3 or 4 toxicity, or any grade 2 toxicity persisting for 21 days or grade 1 toxicity persisting for 35 days. Subsequent treatments were delayed until resolution of all toxicity All participants received premedication with hydrocortisone 100 mg, diphenyldramine 50 mg and cimetidine 300 mg in order to avoid infusion reactions (back pain, flushing, wheezing, hypotension, etc.) Age, performance status and treatment-free interval were not reported for ovarian cancer patients QoL was not assessed as an outcome It was not reported whether those assessing the responses of participants to treatment were independently verified Data were not always reported in terms of ITT analyses, and adverse events data were presented in terms of the number of cycles and not the number of patients, which prevented the reassessment of the data in terms of an ITT analysis ***Definitions*** Assessable disease: non-measurable abnormalities on a computed tomography scan or by physical examination and an elevated serum CA-125 level Complete response: disappearance of all known

continued

Study details and design	Participant details	Intervention details	Withdrawals and adverse events	Conclusions and comments
contd **Israel *et al.*, 2000[57]**	***Disease present after first-line treatment*** **Response to platinum therapy** Resistant: 44/48 (91.7%) Sensitive: 4/48 (8.3%) ***Age*** Age only given for the population as a whole and not just the ovarian cancer patients, therefore, not reported in this summary ***Inclusion criteria*** Measurable/assessable recurrent or metastatic disease; adequate bone marrow, liver and cardiac function; Karnofsky performance status of ≥ 60%; failed at least one prior cisplatin-based therapy; provided informed consent ***Exclusion criteria*** Not stated			disease for a minimum of 4 weeks Partial response: ≥ 50% decrease and no appearance of new lesions for a minimum of 4 weeks

Results

Outcome 1 Survival (not defined)	Outcome 2 Response (not defined)	Outcome 3 QoL
Unclear if the survival data was based on an ITT analysis, but was based on Kaplan–Meier survival analysis Overall survival = 10 months (range 0.25–33) Progression-free survival = 3 months (range 0.25–18)	Response data did not appear to be based on an ITT analysis, but, instead, was based on only those patients with measurable disease (n = 21) Complete response: 1/21 (4.8%) Partial response: 3/21 (14.3%) Total response: 4/21 (19.1%) RR = 19% (no CIs reported) Median duration of response = 4.5 months (range 3–12)	Not reported

Study details and design	Participant details	Intervention details	Withdrawals and adverse events	Conclusions and comments
Linardou *et al.*, 2000[58] ***Source*** Database ***Aim*** To evaluate the safety and efficacy of pegylated liposomal doxorubicin hydrochloride in the treatment of patients with recurrent ovarian cancer ***Type of publication*** Abstract of interim data ***Trial identification*** Not stated ***Length of follow-up*** Median follow-up = 10 months (interim results only; not stated how long follow-up will continue for) ***ITT analysis performed*** No	***Number of participants*** 35 recruited; 27 evaluable ***Description of participants*** **Eastern Cooperative Oncology Group performance status** Median = 1 ***Therapy stage*** Second-line ***Previous treatments*** **Number of prior chemotherapy regimens per patient** Median = 3.0 (range 1–7) **Treatment-free interval** Median = 2 months ***Disease present after first-line treatment*** All participants had platinum-resistant (i.e. relapse within 6 months) recurrent disease and had previously received paclitaxel ***Age*** Median = 66 years (range 28–77) ***Inclusion criteria*** Not stated ***Exclusion criteria*** Not stated	***Intervention*** Pegylated liposomal doxorubicin hydrochloride **Route of administration** i.v. infusion over 1 hour **Dose** 45 mg/m^2 ***Number of cycles*** Six cycles unless disease progression or unacceptable toxicity occurred (median = 3 cycles per patient) **Length per cycle** 28 days	***Withdrawals*** Not stated ***Adverse events*** Dose reduction (by 25%) due to toxicity was only necessary in one case Neutropenia (grade 3): 1/35 (2.9%) Anaemia (grade 3): 2/35 (5.7%) Thrombocytopenia (grade 3): 1/35 (2.9%) Thrombocytopenia (grade 4): 1/35 (2.9%) PPE (grade 3): 1/35 (2.9%)	***Authors' conclusions*** Preliminary results indicated that pegylated liposomal doxorubicin hydrochloride was very well tolerated and demonstrated modest but promising efficacy in heavily pretreated platinum-resistant ovarian cancer patients ***Comments*** Multicentre Phase II trial by the Hellenic Cooperative Oncology Group based in Athens, Greece. Only available in abstract form with very few details. Authors were contacted for further information, but no response was received The researchers presented their findings in terms of absolute numbers and also as % values in certain circumstances. These % values were not based on an ITT analysis, but on the 27 participants (27/35, 77.1%) who were evaluable at follow-up. However, the data used in this review were converted to give % values based on an ITT analysis (i.e. denominator = 35, the number of participants originally randomised to take part in the trial) QoL was not assessed as an outcome

Results

Outcome 1 Survival (not defined)	Outcome 2 Response (not defined)	Outcome 3 QoL
Median = 5 months (range 1–18+) over the median follow-up time of 10 months (range 1–23)	ITT analysis (27 participants were evaluable) over the median follow-up time of 10 months (range 1–23) Complete response: 0/35 (0.0%) Partial response: 2/35 (5.7%) Total response: 2/35 (5.7%) Progressive disease: 14/35 (40.0%) Stable disease: 11/35 (31.4%) Response duration for the two responders was 7 and 8+ months and median time to progression = 4 months (range 2–8)	Not reported

Study details and design	Participant details	Intervention details	Withdrawals and adverse events	Conclusions and comments
Muggia *et al.*, 1996[50] ***Source*** Database ***Aim*** Not stated ***Type of publication*** Abstract of interim data ***Trial identification*** 30-22 ***Length of follow-up*** Not stated (interim results) ***ITT analysis performed*** No	***Number of participants*** 37 recruited ***Description of participants*** All were platinum- and paclitaxel-refractory and had clinically measurable disease. No further details reported ***Therapy stage*** Second-line ***Previous treatments*** Platinum and paclitaxel ***Disease present after first-line treatment*** All had platinum- and paclitaxel-refractory disease ***Age*** Not stated ***Inclusion criteria*** Not stated ***Exclusion criteria*** Not stated	***Intervention*** Pegylated liposomal doxorubicin hydrochloride **Route of administration** i.v. infusion over 1 hour **Dose** 50 mg/m^2 **Number of cycles** Not stated **Length per cycle** 21 days	***Withdrawals*** Two patients were excluded post-randomisation (refusal of treatment and too early for response evaluation) and were not included in the response rate analyses ***Adverse events*** Most patients required dose delays of up to 4 weeks (and often a dose reduction to 40 mg/m^2) due to PPE or stomatitis. Only three participants experienced dose delays due to myelosuppression. No cardiac events were recorded so far and hair loss was exceptional	***Authors' conclusions*** Pegylated liposomal doxorubicin hydrochloride is a useful drug as salvage therapy for ovarian cancer, because it achieves durable responses at a rate and tolerance exceeding most other salvage regimens ***Comments*** Study published in abstract form so only very few details on which to base a quality assessment. Results were only interim. Same study as reported by Muggia *et al.*, 1997[51] QoL was not assessed as an outcome Unclear if responses were independently verified and if survival data were based on Kaplan–Meier survival analysis. Data were not based on an ITT analysis

Results

Outcome 1 Survival (not defined)	Outcome 2 Response (not defined)	Outcome 3 QoL
Median survival had not yet been reached (13 participants had died and eight were experiencing progression)	Interim results only so length of follow-up not stated. Results were based on a per protocol analysis discounting 2/37 participants who were withdrawn after randomisation Complete response: 0/35 (0.0%) Partial response: 7/35 (20.0%) Total response: 7/35 (20.0%, 95% CI, 10.4 to 36.9)	Not reported

Study details and design	Participant details	Intervention details	Withdrawals and adverse events	Conclusions and comments
Muggia *et al.*, 1997[51] ***Source*** Database ***Aim*** To conduct a Phase II study of pegylated liposomal doxorubicin hydrochloride in patients with ovarian cancer who failed to respond to platinum- and paclitaxel-based regimens ***Type of publication*** Final report ***Trial identification*** 30-22 ***Length of follow-up*** Every 12 weeks until disease progression or development of adverse events warranting cessation of treatment ***ITT analysis performed*** Yes	***Number of participants*** 35 recruited; 29 evaluable; 35 ITT ***Description of participants*** **Karnofsky performance status** Median = 80% (range 60–100) **Diameter of largest lesion** ≥ 5 cm: 13/35 (37.1%) < 5 cm: 22/35 (62.9%) **FIGO stage** IC: 1/35 (2.9%) IIA: 1/35 (2.9%) IIC: 2/35 (5.7%) IIIB: 4/35 (11.4%) IIIC: 17/35 (48.6%) IV: 10/35 (28.6%) **Histology** Serous papillary: 23/35 (65.7%) Serous and endometrioid: 2/35 (5.7%) Endometrioid: 2/35 (5.7%) Poorly differentiated: 7/35 (20.0%) Mucinous: 1/35 (2.9%) **Differentiation** Well differentiated: 1/35 (2.9%) Moderately differentiated: 3/35 (8.6%) Poorly differentiated: 12/35 (34.2%) Not specified: 19/35 (54.3%) ***Therapy stage*** Second-line ***Previous treatments*** **Number of systemic regimens*** One (platinum + paclitaxel): 8/35 (22.9%) Two (platinum + cyclophosphamide, then paclitaxel): 9/35 (25.7%) Three: 7/35 (20.0%) Four: 5/35 (14.3%)	***Intervention*** Pegylated liposomal doxorubicin hydrochloride **Route of administration** i.v. infusion over 1 hour **Dose** 50 mg/m^2 **Number of cycles** Not stated **Length per cycle** 21 days	***Withdrawals*** One participant (out of 35) who received a laparotomy 1 week after her first dose of pegylated liposomal doxorubicin hydrochloride refused further treatment, but was included in the final ITT analysis ***Adverse events*** Four patients required hospitalisation for adverse events Grade 3 stomatitis: 5/35 (14.3%) Grade 3 neutropenia: 7/35 (20.0%) Grade 3 PPE: 10/35 (28.6%) Grade 2 neutropenia: 1/35 (2.9%) Grade 2 stomatitis: 2/35 (5.7%) Grade 2 PPE: 4/35 (11.4%) In addition, febrile neutropenia infections included *Candida albicans* (*n* = ?), *Escherichia coli* (*n* = ?), *Herpes zoster* (*n* = 1), *Herpes simplex* virus reactivation (*n* = 3). Nausea and vomiting were never severe but occurred in participants with intra-abdominal disease. In four participants, intermittent swallowing complaints were reported. In addition, symptoms of gastro-oesophageal reflux prompted the use of antacids in two non-obstructed patients. There were no reports of alopecia, phlebitis/local reactions or drug-related liver dysfunction	***Authors' conclusions*** Pegylated liposomal doxorubicin hydrochloride had substantial activity against ovarian cancer refractory to platinum and paclitaxel. The responses achieved with pegylated liposomal doxorubicin hydrochloride were durable and maintained with minimal toxicity. This liposomal formulation should be evaluated further in combination with other drugs in less refractory patients ***Comments*** Same study as reported in interim report Muggia *et al.*, 1996.[50] Additional confidential information obtained from Schering-Plough Ltd showed that the sample size was predetermined. If at least one response was seen in the first 14 patients, then accrual of an additional 16 evaluable patients (total 30 evaluable patients) was deemed necessary to estimate the actual response rate with adequate precision Participants routinely received premedication with 100 mg i.v. hydrocortisone, 25 mg diphenyldramine and 300 mg cimetidine in case or acute infusion reactions during the first and second drug administrations Pegylated liposomal doxorubicin hydrochloride doses were reduced for grade 3 and 4 toxicities to 40 mg/m^2 (with additional 20% reductions if needed) and the interval was lengthened to 4 (and at times 5) weeks in the event of persistent toxicities (even if grade 1 or 2) that were not resolved by week 3 or 4 Response outcomes were reported as objective, but there were no further details to confirm how the assessments were carried out and if they were truly independent QoL was not assessed as an outcome

continued

Study details and design	Participant details	Intervention details	Withdrawals and adverse events	Conclusions and comments
contd **Muggia et *al.*, 1997**[51]	**Interval from last treatment** ≥ 6 months: 6/35 (17.1%) < 6 months: 29/35 (82.9%) ***Disease present after first-line treatment*** Failed to respond to first-line therapy ***Age*** Median = 65 years (range 46–78) ***Inclusion criteria*** Measurable/assessable ovarian cancer; progressive ovarian cancer after treatment with either cisplatin or carboplatin and paclitaxel, or at least one platinum- and paclitaxel-based regimen; adequate bone marrow function, blood cell counts, liver, renal and cardiac function; Karnofsky performance status of ≥ 50% (European Cooperative Oncology Group performance status ≤ 2); provided informed consent ***Exclusion criteria*** Failure of more than two prior treatment regimens, but consolidation with other regimens without an intervening clinical relapse was allowed			Confidential additional information obtained from Schering-Plough Ltd reported that the time to event data was based on appropriate Kaplan–Meier survival analyses ***Definitions*** Complete response: the disapppearance of all known disease Partial response: a ≥ 50% decrease in the sum of the product of cross-sectional diameters of the tumour(s) and no appearance of new lesions. Both definitions included the need for confirmation at least 4 weeks from the initial assessment Assessable disease: the presence of a non-measurable abnormality on computed tomography or by physical examination coupled with a CA-125 level of > 100

* *Data taken from the published report. Discrepancies in the total number of participants in each group may be due to missing patient data*

Results

Outcome 1 Survival (measured from time of first dose of study drug)	Outcome 2 Response (see definitions above)	Outcome 3 QoL
Median progression-free survival = 5.7 months Median overall survival = 11 months (range 1.5–21)	Complete response: 1/35 (2.9%) Partial response: 8/35 (22.9%) Overall response: 9/35 (25.8%) Median time to response = 5.5 months (range 2–8) Median duration of response = 6 months (range 3.6–16)	Not reported

Study details and design	Participant details	Intervention details	Withdrawals and adverse events	Conclusions and comments
Rose *et al.*, 1999[53] ***Source*** Database ***Aim*** To determine the efficacy and safety of pegylated liposomal doxorubicin hydrochloride in refractory ovarian cancer ***Type of publication*** Abstract of interim data ***Trial identification*** 30-47 ***Length of follow-up*** Not stated (interim analysis). Efficacy was followed up every 8 weeks by radiological assessment and confirmed after 4 weeks ***ITT analysis performed*** Yes	***Number of participants*** 89 recruited; 63 evaluable ***Description of participants*** Participants had measurable and histologically proven epithelial ovarian cancer **Karnofsky performance status** Median = 90% ***Therapy stage*** Second-line ***Previous treatments*** Refractory to prior platinum, paclitaxel and topotecan therapy: 35/89 (39.3%) Refractory to prior platinum therapy: 89/89 (100.0%) Refractory to prior platinum and paclitaxel therapy: 82/89 (92.1%) **Number of prior regimens** Mean = 2.2 ***Disease present after first-line treatment*** Refractory ***Age*** Median = 61 years ***Inclusion criteria*** Not reported ***Exclusion criteria*** Not reported	***Intervention*** Pegylated liposomal doxorubicin hydrochloride **Route of administration** i.v. infusion over 1 hour **Dose** 50 mg/m^2. Mean cumulative dose = 211.6 mg/m^2 (range 50–808.4) **Number of cycles** Mean number of cycles = 4.4 **Length per cycle** 28 days	***Withdrawals*** No details reported ***Adverse events*** Interim results, unclear if based on ITT as absolute numbers were not always quoted 15/89 (16.9%) participants discontinued therapy due to adverse events, 10/89 (11.2%) were considered to be drug related **Grade 3/4 toxicities (unclear if these were ITT)** PPE: 20.2% Neutropenia: 15.7% Anaemia: 13.5% Toxicity was managed by dose reduction or delay, and occurred in 39/89 (43.8%) participants	***Authors' conclusions*** Pegylated liposomal doxorubicin hydrochloride was efficacious in this group of patients refractory to prior treatment regimens ***Comments*** Study only reported as an abstract so few details available. Same trial as reported in interim analysis by Gordon *et al.*, 1998[52] and Gordon *et al.*, 2000[54] Absolute numbers were not provided for the adverse events data so it was unclear if an ITT had been used QoL was not assessed as an outcome The period of follow-up was not stated Only age, performance status and previous therapies were described for the participants (not treatment-free interval, disease bulk and histology)

Results

Outcome 1 Survival	Outcome 2 Response (not defined)	Outcome 3 QoL
Not reported	Follow-up period not stated (interim results) based on ITT Complete response: 1/89 (1.1%) Partial response: 14/89 (15.7%) Total response: 15/89 (16.8%) All 15 responders were double refractory and six were triple refractory Median time to progression = 135 days (19.3 weeks) in the ITT group	Not reported

Appendix 10

Data extraction tables for economic evaluations

Study details and design	Data sources	Clinical outcome data and costs used	Statistical analysis and results	Sensitivity analysis	Authors' conclusions/ implications and comments
Schering-Plough Ltd[67] ***Title*** Caelyx in the treatment of recurrent ovarian cancer in the United Kingdom ***Source*** Company submission ***Language of publication*** English ***Type of intervention*** Treatment ***Study question*** To compare the costs of pegylated liposomal doxorubicin hydrochloride versus topotecan for the treatment of advanced epithelial ovarian cancer ***Economic study type*** CMA ***Study population*** 474 patients (ITT population) from the multicentre open-label RCT 30-49 (Schering-Plough Ltd).[47] All had advanced epithelial ovarian carcinoma (FIGO stage III/IV) and had failed first-line chemotherapy with a platinum-based regimen. The trial was based in multiple centres in both Europe and the USA. Patients were stratified prospectively for platinum sensitivity and bulky disease, and could have received no more that one prior platinum-based regimen	***Analysis of clinical effectiveness data*** Single trial (30-49 Schering-Plough Ltd)[47,48] The assumption of equivalence in the economic study was based on the results from the clinical study of pegylated liposomal doxorubicin hydrochloride versus topotecan (trial 30-49) The following outcomes were measured: 1. Time to progression 2. Overall survival 3. Response rates 4. Time to response 5. Duration of response 6. HRQoL 7. Adverse events (nine were included: sepsis, anaemia, stomatitis/ pharyngitis, PPE, nausea/vomiting, diarrhoea, thrombocytopenia, neutropenia and fever) These data favoured pegylated liposomal doxorubicin hydrochloride	***Clinical effectiveness*** Trial 30-49 was an equivalence trial and demonstrated that, for the outcomes considered, the treatments were statistically equivalent. The use of a CMA was, therefore, appropriate. However, all of the following clinical outcomes showed an advantage for pegylated liposomal doxorubicin hydrochloride over topotecan: 1. Time to progression (HR = 1.262, 90% CI, 1.062 to 1.500; $p = 0.026$) 2. Overall survival (HR = 1.116, 90% CI, 0.895 to 1.392; $p = 0.41$) 3. Response rates (overall response = 19.7% with intervention versus 17% with control; platinum-refractory response = 12% with intervention versus 7% with control) 4. HRQoL (QTWiST data showed pegylated liposomal doxorubicin hydrochloride had a significantly better QoL profile; at 12 weeks, an equal or higher % of patients showed improvement or maintained QoL scores with intervention with the exception of scales relating to emotional functioning and pain) 5. Adverse events (the events were graded according to a scale of increasing severity (grade 1–4) and the resources needed to manage the effects by grade were estimated by clinical experts) ***Adverse events per study group according to grade of severity*** **Stomatitis/pharyngitis** Grade 1: 202 (53%) with intervention, 91 (70%) with control Grade 2: 144 (38%) with intervention, 37 (28%) with control Grade 3: 31 (8%) with intervention, 2 (2%) with control Grade 4: 1 (< 1%) with intervention, 0 (0%) with control Total: 378 (100%) with intervention, 130 (100%) with control **PPE** Grade 1: 195 (51%) with intervention, 2 (100%) with control Grade 2: 120 (32%) with intervention, 0 (0%) with control Grade 3: 62 (16%) with intervention, 0 (0%) with control Grade 4: 2 (< 1%) with intervention, 0 (0%) with control Total: 379 (100%) with intervention, 2 (100%) with control **Nausea/vomiting** Grade 1: 236 (61%) with intervention, 333 (59%) with control Grade 2: 110 (28%) with intervention, 175 (31%) with control Grade 3: 37 (10%) with intervention, 51 (9%) with control Grade 4: 3 (< 1%) with intervention, 8 (1%) with control Total: 386 (100%) with intervention, 567 (100%) with control	***Statistical analysis used*** The use of study drugs was recorded as part of trial 30-49 Resources used in administration of drugs was estimated using expert opinion, as were the resources consumed in the treatment of adverse events Costs were then estimated by applying unit costs to resource use, and the sum of the costs for each drug summarised in terms of the total cost for the ITT population in trial 30-49 and the cost per person (95% CI). Costs were treated in a stochastic manner and bootstrapping was performed to check appropriateness of the statistical tests used More specifically, in order to estimate the costs incurred in each arm of the trial, the total amount of study drug used per patient was calculated by multiplying each dose (mg/m^2) administered by the patient's estimated body surface area and summing over all doses the patient used. The result was then multiplied by cost of the drug. For each dose administered,	The data were reanalysed in a sensitivity analysis using an extreme analysis that favoured topotecan. The hospitalisation length of stay and number of outpatient visits were varied. The highest estimated values (hospital length of stay or number of outpatient visits) were applied for the management of PPE and stomatitis/ pharyngitis, along with the lowest estimates for neutropenia, sepsis and fever. These parameters were chosen as they were the key drivers in the cost of treating the most common adverse events from the intervention and the control. Therefore, high cost estimates were used for the intervention adverse events (PPE and stomatitis/pharyngitis) and low cost estimates for the control adverse events (neutropenia, sepsis and fever)	***Authors' conclusions*** This analysis indicated that pegylated liposomal doxorubicin hydrochloride was the dominant therapy, that is, the effects were at least as good as topotecan but at a lower cost. This effect was apparent even with an extreme analysis that favoured topotecan, indicating that the finding was robust to some changes in resource use patterns ***Comments*** This study has been submitted for publication (Smith *et al.* – see below) The statistical analyses used were appropriate for the CMA (NHS/health service perspective) used The resources used in treating various adverse events were estimated using expert opinion (identity not stated). This was justified by the fact that the data required specialised data elements not normally collected in trials conducted to assess clinical efficacy (e.g. number, type and reason for hospitalisations; outpatient clinic visits; physician visits). Also, as the trial was an international multicentre trial, there would be variations in how adverse events were dealt with, e.g. patients in the USA are more likely to receive G-CSF (used to treat neutropenia, a common adverse effect of topotecan). However, using

continued

Study details and design	Data sources	Clinical outcome data and costs used	Statistical analysis and results	Sensitivity analysis	Authors' conclusions/ implications and comments
contd **Schering-Plough Ltd**[67] ***Setting*** The study was based in secondary care **Dates to which data relate** Effectiveness data from trial 30-49, study dates December 1996–February 1999. Resource use data on drug use from trial 30-49 (i.e. 1996–1999) Resource use data on, for example, outpatient attendances and treatment patterns for adverse events were from expert panel and the date was not stated, but presumably 1999/2000 Price data 1999–2000 ***Source of effectiveness data*** Single study ***Link between cost and effectiveness data*** Retrospective/disconnected. Retrospective costing carried out on a similar sample. Clinical trial used the evaluable population, which was a subsample of the ITT sample used in the economic analysis. The evaluable population	***Source of cost data*** 1. Cost of study drug (*BNF*, 1999[74]) 2. Cost of drug administration (e.g. outpatient visits from 1999 Chartered Institute of Public Finance and Accountancy Database, 1999) 3. Cost of managing adverse events (e.g. cost of medication from *BNF*, 1999[74]; cost of any associated hospital visits from tariffs at a UK cancer centre; cost of intensive care from UK study) ***Models used*** No model used	**Diarrhoea** Grade 1: 42 (57%) with intervention, 68 (54%) with control Grade 2: 26 (35%) with intervention, 47 (37%) with control Grade 3: 5 (7%) with intervention, 10 (8%) with control Grade 4: 1 (1%) with intervention, 1 (< 1%) with control Total: 74 (100%) with intervention, 126 (100%) with control **Anaemia** Grade 1: 199 (62%) with intervention, 363 (37%) with control Grade 2: 101 (32%) with intervention, 476 (48%) with control Grade 3: 18 (6%) with intervention, 134 (14%) with control Grade 4: 1 (< 1%) with intervention, 12 (1%) with control Total: 319 (100%) with intervention, 985 (100%) with control **Thrombocytopenia** Grade 1: 54 (76%) with intervention, 434 (46%) with control Grade 2: 14 (20%) with intervention, 272 (29%) with control Grade 3: 3 (4%) with intervention, 175 (19%) with control Grade 4: 0 (0%) with intervention, 63 (7%) with control Total: 71 (100%) with intervention, 944 (100%) with control **Neutropenia** Grade 1: 153 (48%) with intervention, 311 (20%) with control Grade 2: 110 (35%) with intervention, 394 (26%) with control Grade 3: 43 (14%) with intervention, 455 (30%) with control Grade 4: 11 (3%) with intervention, 358 (24%) with control (includes two fatal events in the topotecan arm) Total: 317 (100%) with intervention, 1518 (100%) with control **Sepsis** Grade 1: 0 (0%) with intervention, 0 (0%) with control Grade 2: 1 (25%) with intervention, 7 (35%) with control Grade 3: 3 (75%) with intervention, 3 (15%) with control Grade 4: 0 (0%) with intervention, 10 (50%) with control (includes three fatal events in the topotecan arm) Total: 4 (100%) with intervention, 20 (100%) with control **Fever** Grade 1: 38 (55%) with intervention, 51 (45%) with control Grade 2: 29 (42%) with intervention, 48 (42%) with control Grade 3: 2 (3%) with intervention, 9 (8%) with control Grade 4: 0 (0%) with intervention, 6 (5%) with control (includes one fatal event in the topotecan arm) Total: 69 (100%) with intervention, 114 (100%) with control	the cost for outpatient visits was also added. For each patient, the number of adverse events by type and severity level was counted. The estimated cost for each adverse event type was then added to obtain a total adverse event management cost. The estimated costs of managing adverse events at each level of severity were detailed 95% CIs around the mean per patient cost were also calculated based on a normal distribution assumption and checked with the bootstrap method ***Summary of results*** The total per person cost of the intervention was estimated to be £9970 while the per person cost of the control was estimated at £12,627. The 95% CIs were non-overlapping, indicating that this £2657 difference was statistically significant at the 5% level The costs of drug administration were much higher for	***Costs (n = 239 in the intervention group, n = 235 in the control group)*** Drug and administration: £2,195,614 (91.15%) with intervention, £2,173,107 (75.27%) with control Stomatitis/pharyngitis: £38,512 (1.60%) with intervention, £11,685 (0.40%) with control PPE: £41,126 (1.71%) with intervention, £171 (0.01%) with control Nausea/vomiting: £53,087 (2.20%) with intervention, £83,338 (2.89%) with control Diarrhoea: £8183 (0.34%) with intervention, £13,099 (0.45%) with control Anaemia: £59,677 (2.48%) with intervention, £319,886 (11.08%) with control Thrombocytopenia: £0 (0.00%) with intervention, £64,008 (2.22%) with control Neutropenia: £5135 (0.21%) with intervention, £149,579 (5.18%) with control Sepsis: £4029 (0.17%) with intervention, £37,338 (1.29%) with	expert opinion is open to bias, especially when the identity of the experts is not stated. It would have been better to use prospective resource data linked directly to trial 30-49 Pegylated liposomal doxorubicin hydrochloride has only recently (October 2000) received European approval for the second-line therapy of advanced ovarian cancer where first-line platinum-based therapy has failed The weakest point was the use of expert opinion to estimate resource use (especially as the identity of the experts was not revealed). The evaluation also used retrospective/disconnected costs. However, due to the relative newness of the intervention, there is a paucity of trial/study data and these estimates probably offer the best available assessment regarding the cost-effectiveness of these two interventions Overall, this was a clear analysis undertaken according to sound methodology

continued

Study details and design	Data sources	Clinical outcome data and costs used	Statistical analysis and results	Sensitivity analysis	Authors' conclusions/ implications and comments
contd **Schering-Plough Ltd**[67] referred to patients who met protocol-specified enrolment and received at least two cycles of the study drug ***Comparators*** Pegylated liposomal doxorubicin hydrochloride (50 mg/m^2 as a 1-hour infusion every 28 days) versus topotecan (1.5 mg/m^2/day as a 30-minute infusion for 5 days consecutively every 21 days) ***Country/currency*** UK, £ sterling ***Cost year*** 1999/2000 ***Perspective*** NHS/health service		***All relevant effects measured?*** Cardiotoxicity could still be a problem with pegylated liposomal doxorubicin hydrochloride ***Measure of benefit used in the economic analysis*** NA. The clinical equivalence trial justified the use of a CMA (because when two treatments are equally effective, the least cost option is the most efficient) ***Base-case total costs (n = 239 in the intervention group, n = 235 in the control group)*** Drug and administration: £2,198,556 (92.27%) with intervention, £2,176,052 (69.17%) with control Stomatitis/pharyngitis: £22,170 (0.93%) with intervention, £6206 (0.19%) with control PPE: £23,639 (0.99%) with intervention, £144 (0.00%) with control Nausea/vomiting: £53,151 (2.23%) with intervention, £83,444 (2.53%) with control Diarrhoea: £8222 (0.35%) with intervention, £13,137 (0.40%) with control Anaemia: £59,758 (2.51%) with intervention, £320,351 (9.71%) with control Thrombocytopenia: £0 (0.00%) with intervention, £64,099 (1.94%) with control Neutropenia: £8369 (0.35%) with intervention, £209,910 (7.08%) with control Sepsis: £5286 (0.22%) with intervention, £50,239 (1.69%) with control Fever: £3671 (0.15%) with intervention, £43,743 (1.48%) with control Total: £2,382,833 (100.00%) with intervention, £2,967,327 (100.00%) with control Per person: £9970 (95% CI, 9080 to 10,861) with intervention, £12,627 (95% CI, 11,527 to 13,727) with control ***Costing methodology*** **Direct costs** Discounting was inappropriate for the treatment period (< 1 year) and was, therefore, (correctly) not performed. The study did not consider differences between average and marginal costs. Quantities and costs were analysed separately, no cost components were excluded on the grounds that they were similar between the groups **Indirect costs** Not included in the analysis, but would have favoured pegylated liposomal doxorubicin hydrochloride even more than the base-case result ***All relevant costs considered?*** Cardiotoxicity could be associated with additional resource use for pegylated liposomal doxorubicin hydrochloride	topotecan due to the higher number of out-patient attendances to administer the drug. However, as pegylated liposomal doxorubicin hydrochloride is a much more expensive drug, the cost of the drug and its administration were similar in both arms. The costs associated with the treatment of adverse events were much greater with topotecan than with pegylated liposomal doxorubicin hydrochloride and it was this difference that drove the overall cost differential in the two treatments. The values applied in the analysis of extremes showed a smaller differential in per person costs between the two groups (£2208 versus £2657 in the base-case analysis), but still significant at the 5% level ***Applicable to the NHS*** Yes	control Fever: £3395 (0.14%) with intervention, £34,903 (1.21%) with control Total: £2,408,758 (100.00%) with intervention, £2,887,114 (100.00%) with control Per person: £10,078 (95% CI, 9176 to 10,980) with intervention, £12,286 (95% CI, 11,216 to 13,356) with control ***Synthesis of costs and effects*** NA for CMA. Incremental analysis of costs performed	

Study details and design	Data sources	Clinical outcome data and costs used	Statistical analysis and results	Sensitivity analysis	Authors' conclusions/ implications and comments
Smith *et al.*, 2001[4] ***Title*** A comparative economic analysis of pegylated liposomal doxorubicin hydrochloride versus topotecan in ovarian cancer in the USA and UK ***Source*** Included with company submission Note, this paper was based on the same trial as the company submission. The authors of the economic evaluation of the company submission have subsequently submitted this paper to a peer-reviewed journal for publication ***Language of publication*** English ***Type of intervention*** Treatment ***Study question*** To compare the costs of pegylated liposomal doxorubicin hydrochloride versus topotecan for the treatment of advanced epithelial ovarian cancer ***Economic study type*** CMA	***Analysis of clinical effectiveness data*** Single trial (30-49 Schering-Plough Ltd)[47,48] The assumption of equivalence in the economic study was based on the results from the clinical study of pegylated liposomal doxorubicin hydrochloride versus topotecan (trial 30-49) Authors described results of the following clinical outcomes: 1. Time to progression 2. Overall survival 3. Response rates 4. Time to response 5. Duration of response 6. Adverse events (nine were included: sepsis, anaemia, stomatitis/ pharyngitis, PPE, nausea/ vomiting, diarrhoea, thrombocytopenia, neutropenia and fever) ***Source of cost data*** **UK** 1. Cost of study drug (*BNF*, 1999[74]) 2. Cost of drug administration (e.g. outpatient visits from 1999 Chartered Institute of Public Finance and Accountancy database, 1999) 3. Cost of managing adverse events (e.g. cost	***Clinical effectiveness*** Trial 30-49 was an equivalence trial and demonstrated that, for the outcomes considered, the treatments were statistically equivalent. The use of a CMA was, therefore, appropriate. However, all of the following clinical outcomes showed an advantage for pegylated liposomal doxorubicin hydrochloride: 1. Time to progression (HR = 1.176, 90% CI, 1.002 to 0.095; p = 0.095) 2. Overall survival (HR = 1.121, 90% CI, 0.92 to 1.367; p = 0.3407) 3. Response rates (Overall response = 19.7% with intervention versus 17% with control; platinum-refractory response = 12.3% with intervention versus 6.5% with control) 4. Time to response (mean = 47 days with intervention versus 40 days with control) 5. Duration of response (mean = 47 days with intervention versus 40 days with control) Note, that these values are different from those presented in the company submission (above) ***All relevant effects measured?*** Cardiotoxicity could have been included in the adverse events of pegylated liposomal doxorubicin hydrochloride ***Measure of benefit used in the economic analysis*** NA. The clinical equivalence trial justified the use of a CMA (because when two treatments are equally effective the least cost option is the most efficient) ***Base case per person costs (n = 239 in the intervention group, n = 235 in the control group)*** **UK** Drug: US$11,381 with intervention, US$7286 with control	***Statistical analysis used*** The use of study drugs was recorded as part of trial 30-49 Resources used in administration of drugs was estimated using expert opinion, as were the resources consumed in the treatment of adverse events. However, 83% of total costs were based on resource use data from the trial Costs were then estimated by applying unit costs to resource use, and the sum of the costs for each drug summarised in terms of the total cost for the ITT population in trial 30-49 and the cost per person (95% CI). Costs were treated in a stochastic manner and bootstrapping was performed to check appropriateness of the statistical tests used More specifically, in order to estimate the costs incurred in each arm of the trial, the total amount of study drug used per patient was calculated by multiplying each dose (mg/m^2) administered by the patient's estimated body surface area and summing over all doses the patient used. The result was then multiplied by the cost of the drug. For each dose administered, the cost for outpatient visits was also added. For each patient, the number of adverse events by type and severity level was counted. The estimated cost	The data were reanalysed in a sensitivity analysis using an extreme analysis that favoured topotecan. This appeared to be a two-way sensitivity with both extremes of resource use and unit costs employed The results in terms of mean costs and CIs around the difference in mean costs was not presented but 89% of 1000 bootstrap replicates showed pegylated liposomal doxorubicin hydrochloride to be cost saving ***Synthesis of costs and effects*** NA for CMA. Incremental analysis of costs performed	***Authors' conclusions*** Pegylated liposomal doxorubicin hydrochloride was less costly than topotecan in both the USA and UK, although the magnitude of the difference was considerable ***Authors' implications*** The results of this study are of use to clinicians and policy makers in the USA and UK ***Comments*** This study has been submitted for publication The statistical and sensitivity analyses were appropriate for the CMA used. The weaknesses in the model were acknowledged by the authors, which was partly dependent on the use of expert opinion and the difficulties of performing economic evaluations internationally. One weakness of the study was the merging of European data with UK data in the treatment of adverse events. The costs of cancer care vary greatly between the UK and the rest of Europe and it may have been inappropriate to merge these data. However, it is unlikely that this assumption has influenced the results The analysis for the USA provided a much clearer answer than that for the UK. In the UK, the analysis presented showed a reduction in costs of

continued

Study details and design	Data sources	Clinical outcome data and costs used	Statistical analysis and results	Sensitivity analysis and comments	Authors' conclusions/ implications
contd **Smith *et al.*, 2001**[4] ***Study population*** 474 patients (ITT population) from the multicentre open-label RCT 30-49 (Schering-Plough Ltd).[47] All had advanced epithelial ovarian carcinoma (FIGO stage III/IV) and had failed first-line chemotherapy with a platinum-based regimen. The trial was based in multiple centres in both Europe and the USA. Patients were stratified prospectively for platinum sensitivity and bulky disease, and could have received no more that one prior platinum-based regimen ***Setting*** The study was based in secondary care **Dates to which data relate** Effectiveness data from trial 30-49, study dates December 1996–February 1999. Resource use data on drug use from trial 30-49 (i.e. 1996–1999). Resource use data on, for example, outpatient attendances and treatment patterns for adverse events from expert panel, date not stated, but presumably 1999/2000 Price data 1999–2000	of medication from *BNF*, 1999;[74] cost of any associated hospital visits from tariffs at a UK cancer centre; cost of intensive care from UK study) **USA** 1. Cost of study drug based on USA *Red Book*, 2000 2. Hospital costs from fee lists at major academic centre 3. Cost of doctors' time based on Medicare reimbursement protocol ***Models used*** No model used	Administration: US$1513 with intervention, US$5701 with control Stomatitis/pharyngitis: US$175 with intervention, US$70 with control PPE: US$189 with intervention, US$1 with control Nausea/vomiting: US$151 with intervention, US$298 with control Diarrhoea: US$36 with intervention, US$60 with control Anaemia and thrombocytopenia: US$189 with intervention, US$1432 with control Neutropenia: US$36 with intervention, US$756 with control Sepsis and fever: US$46 with intervention, US$105 with control Hospital stays: US$280 with intervention, US$1197 with control Total per person: US$13,997 (95% CI, 12,863 to 15,392) with intervention, US$16,906 (95% CI, 15,617 to 18,847) with control **USA** Drug: US$12,962 with intervention, US$10,058 with control Administration: US$1438 with intervention, US$8377 with control Stomatitis/pharyngitis: US$101 with intervention, US$30 with control PPE: US$104 with intervention, US$0 with control Nausea/vomiting: US$49 with intervention, US$83 with control Diarrhoea: US$36 with intervention, US$58 with control Anaemia and thrombocytopenia: US$466 with intervention, US$5181 with control Neutropenia: US$497 with intervention, US$3756 with control Sepsis and fever: US$56 with intervention, US$111 with control Hospital stays: US$188 with intervention, US$566 with control	for each adverse event type was then added to obtain a total adverse event management cost. The estimated costs of managing adverse events at each level of severity were detailed 95% CIs around the mean per patient cost were also calculated based on a normal distribution assumption and checked with the bootstrap method ***Summary of results*** In the UK, mean cost per person was US$13,997 for pegylated liposomal doxorubicin hydrochloride and US$16,906 for topotecan. The 95% CI was US$770 to 3415 in favour of pegylated liposomal doxorubicin hydrochloride and was statistically significant at the 5% level The cost of drug administration was much higher for topotecan due to the higher number of outpatient attendances to administer the drug. However, as pegylated liposomal doxorubicin hydrochloride is a much more expensive drug, the cost of the drug and its administration were similar in both arms. The costs associated with the treatment of adverse events		borderline significance, while the clinical trial showed trends towards improved outcomes However, this was a clear paper using appropriate methodology and fairly extensive analysis to deal with uncertainty in the evaluation

continued

Study details and design	Data sources	Clinical outcome data and costs used	Statistical analysis and results	Sensitivity analysis and comments	Authors' conclusions/ implications
contd **Smith *et al.*, 2001**[4] ***Source of effectiveness data*** Single study ***Link between cost and effectiveness data*** Retrospective/disconnected. Retrospective costing carried out on a similar sample. Clinical trial used the evaluable population, which was a subsample of the ITT sample used in the economic analysis. The evaluable population referred to patients who met protocol-specified enrolment and received at least two cycles of the study drug ***Comparators*** Pegylated liposomal doxorubicin hydrochloride (50 mg/m^2 as a 1-hour infusion every 28 days) versus topotecan (1.5 mg/m^2/day as a 30-minute infusion for 5 days consecutively every 21 days) ***Country/currency*** UK and USA, both costed in US$ ***Cost year*** 1999/2000 ***Perspective*** Not stated, but presumably the NHS in the UK and third-party payers in the USA		Total per person: US$15,895 (95% CI, 14,515 to 17,306) with intervention, US$28,220 (95% CI, 25,750 to 30,974) with control ***Costing methodology*** **Direct costs** Discounting was inappropriate for the treatment period (< 1 year) and was, therefore, (correctly) not performed. The study did not consider differences between average and marginal costs. Quantities and costs were analysed separately, no cost components were excluded on the grounds that they were similar between the groups **Indirect costs** Not included in the analysis, but would have favoured pegylated liposomal doxorubicin hydrochloride even more than the base-case result ***All relevant costs considered?*** Cardiotoxicity could still be a problem with pegylated liposomal doxorubicin hydrochloride and could lead to potentially significant resource use	were much greater for topotecan than for pegylated liposomal doxorubicin hydrochloride and it was this difference that drove the overall cost differential in the two treatments The USA results favoured pegylated liposomal doxorubicin hydrochloride considerably more. The mean difference between the two groups was $12,325 (95% CI, 9445 to 15,415). The difference between the UK and the USA (in terms of cost diferentials) was largely due to the higher resource use and, therefore, cost associated with treating adverse events ***Applicable to the NHS*** Yes		

Appendix 11

Transforming median survival to mean survival

The data provided in the company submission presented overall median survival for the evaluable population. The economic analysis within the company submission was based on mean costs in the ITT population. For the purposes of this economic review, mean survival was a more useful figure than median survival, and, therefore, median survival data were converted to mean survival data using the following equations.

Assuming exponential survival curves,

the cumulative probability of death at time t, $S(t) = 1 - e^{-\lambda t}$

where λ = HR.

Therefore, for median survival data, $0.5 = 1 - e^{-\lambda t}$

Re-arranging gives $\lambda = \frac{-\ln(0.5)}{t}$

Mean survival duration (area under curve) $= 1/\lambda$

$\text{Var}(\lambda) = \lambda^2/r$

where r = number of deaths per sample.

Using the delta method, $\text{Var}(1/\lambda) = \text{var}(\lambda) \times \left(\frac{dA}{d\lambda}\right)^2$

where $A = 1/\lambda = \lambda^{-1}$ $\frac{\lambda^2}{r} \times \left(-\lambda^{-2}\right)^2$

$= \frac{1}{r\lambda^2}$

so $\text{SE}(\lambda) = \frac{1}{\sqrt{r\lambda}}$

Health Technology Assessment Programme

Prioritisation Strategy Group

Members

Chair,
Professor Kent Woods,
Director,
NHS HTA Programme, &
Professor of Therapeutics
University of Leicester

Professor Bruce Campbell,
Consultant Vascular
& General Surgeon,
Royal Devon & Exeter Hospital

Professor Shah Ebrahim,
Professor in Epidemiology
of Ageing,
University of Bristol

Dr John Reynolds,
Clinical Director,
Acute General Medicine SDU,
Oxford Radcliffe Hospital

Dr Ron Zimmern,
Director, Public Health
Genetics Unit,
Strangeways Research
Laboratories, Cambridge

HTA Commissioning Board

Members

Programme Director,
Professor Kent Woods,
Director,
NHS HTA Programme, &
Professor of Therapeutics
University of Leicester

Chair,
Professor Shah Ebrahim,
Professor in Epidemiology
of Ageing,
University of Bristol

Deputy Chair,
Professor Jon Nicholl,
Director, Medical Care
Research Unit,
University of Sheffield

Professor Douglas Altman,
Director, ICRF Medical
Statistics Group,
University of Oxford

Professor John Bond,
Director, Centre for Health
Services Research, University
of Newcastle-upon-Tyne

Professor John Brazier,
Director of Health Economics,
University of Sheffield

Dr Andrew Briggs,
Research Fellow,
Institute of Health Sciences,
University of Oxford

Ms Christine Clark,
Freelance Medical Writer,
Bury, Lancs

Professor Martin Eccles,
Professor of
Clinical Effectiveness,
University of Newcastle-
upon-Tyne

Dr Andrew Farmer,
General Practitioner &
NHS R&D Clinical Scientist,
Institute of Health Sciences,
University of Oxford

Professor Adrian Grant,
Director, Health Services
Research Unit,
University of Aberdeen

Dr Alastair Gray,
Director, Health Economics
Research Centre,
Institute of Health Sciences,
University of Oxford

Professor Mark Haggard,
Director, MRC Institute
of Hearing Research,
University of Nottingham

Professor Jenny Hewison,
Academic Unit of Psychiatry
& Behavioural Sciences,
University of Leeds

Professor Peter Jones,
University Department
of Psychiatry,
University of Cambridge

Professor Alison Kitson,
Director, Royal College of
Nursing Institute, London

Professor Sarah Lamb,
Research Professor
in Physiotherapy,
University of Coventry

Dr Donna Lamping,
Head, Health Services
Research Unit,
London School of Hygiene
& Tropical Medicine

Professor David Neal,
Department of Surgery,
University of Newcastle-
upon-Tyne

Professor Tim Peters,
Social Medicine,
University of Bristol

Professor Martin Severs,
Professor in Elderly
Health Care,
University of Portsmouth

Dr Jonathan Shapiro,
Senior Fellow, Health Services
Management Centre,
Birmingham

Dr Sarah Stewart-Brown,
Director, Health Services
Research Unit,
University of Oxford

Dr Gillian Vivian, Consultant
in Nuclear Medicine &
Radiology, Royal Cornwall
Hospitals Trust, Truro

continued

continued

Diagnostic Technologies & Screening Panel

Members

Chair,
Dr Ron Zimmern,
Director, Public Health Genetics Unit, Strangeways Research Laboratories, Cambridge

Mrs Stella Burnside,
Chief Executive,
Altnagelvin Hospitals Health & Social Services Trust,
Londonderry

Dr Paul O Collinson,
Consultant Chemical Pathologist &
Senior Lecturer,
St George's Hospital,
London

Dr Barry Cookson,
Director, Laboratory of Hospital Infection, Public Health Laboratory Service,
London

Professor Howard Cuckle,
Professor of Reproductive Epidemiology,
University of Leeds

Professor Adrian K Dixon,
Professor of Radiology,
Addenbrooke's Hospital,
Cambridge

Dr David Elliman,
Consultant in Community Child Health,
St. George's Hospital, London

Dr Tom Fahey,
Senior Lecturer in General Practice,
University of Bristol

Dr Andrew Farmer,
General Practitioner & NHS R&D Clinical Scientist,
Institute of Health Sciences,
University of Oxford

Professor Jane Franklyn,
Professor of Medicine,
University of Birmingham

Dr Antony J Franks,
Deputy Medical Director,
The Leeds Teaching Hospitals NHS Trust

Dr J A Muir Gray,
Programmes Director,
National Screening Committee,
NHS Executive, Oxford

Dr Peter Howlett,
Executive Director – Planning,
Portsmouth Hospitals NHS Trust

Dr S M Ludgate,
Medical Director,
Medical Devices Agency,
London

Professor Jennie Popay,
Professor of Sociology & Public Health,
Institute for Health Research,
University of Lancaster

Dr Susan Schonfield,
CPHM Specialist Commissioning,
Public Health Directorate,
Croydon Primary Care Trust

Mrs Kathlyn Slack,
Professional Support,
Diagnostic Imaging & Radiation Protection Team,
Department of Health,
London

Mr Tony Tester,
Chief Officer,
South Bedfordshire Community Health Council,
Luton

Dr Andrew Walker,
Senior Lecturer in Health Economics,
University of Glasgow

Professor Martin J Whittle,
Head of Division of Reproductive & Child Health,
University of Birmingham

Pharmaceuticals Panel

Members

Chair,
Dr John Reynolds,
Clinical Director,
Acute General Medicine SDU,
Oxford Radcliffe Hospital

Professor Tony Avery,
Professor of Primary Health Care,
University of Nottingham

Professor Iain T Cameron,
Professor of Obstetrics & Gynaecology,
University of Southampton

Mr Peter Cardy,
Chief Executive,
Macmillan Cancer Relief,
London

Dr Christopher Cates,
GP & Cochrane Editor,
Bushey Health Centre,
Bushey, Herts

Dr Karen A Fitzgerald,
Pharmaceutical Adviser,
Bro Taf Health Authority,
Cardiff

Dr Felicity J Gabbay,
Managing Director,
Transcrip Ltd,
Milford-on-Sea, Hants

Mr Peter Golightly,
Director, Trent Medicines Information Services,
Leicester Royal Infirmary

Dr Alastair Gray,
Director, Health Economics Research Centre,
Institute of Health Sciences,
University of Oxford

Mrs Sharon Hart,
Managing Editor, *Drug & Therapeutics Bulletin*,
London

Dr Christine Hine,
Consultant in Public Health Medicine,
Bristol South & West Primary Care Trust

Mrs Jeannette Howe,
Deputy Chief Pharmacist,
Department of Health,
London

Professor Robert Peveler,
Professor of Liaison Psychiatry,
Royal South Hants Hospital,
Southampton

Dr Frances Rotblat,
CPMP Delegate,
Medicines Control Agency,
London

Dr Eamonn Sheridan,
Consultant in Clinical Genetics, St James's University Hospital, Leeds

Mrs Katrina Simister,
New Products Manager,
National Prescribing Centre,
Liverpool

Professor Terence Stephenson,
Professor of Child Health,
University of Nottingham

Dr Richard Tiner,
Medical Director,
Association of the British Pharmaceutical Industry,
London

Professor Jenifer Wilson-Barnett,
Head of Florence Nightingale School of Nursing & Midwifery,
King's College,
London

Therapeutic Procedures Panel

Members

Chair,
Professor Bruce Campbell,
Consultant Vascular & General Surgeon, Royal Devon & Exeter Hospital

Professor John Bond,
Professor of Health Services Research, Centre for Health Services Research, University of Newcastle-upon-Tyne

Ms Judith Brodie,
Head of Cancer Support Service, Cancer BACUP, London

Ms Tracy Bury,
Head of Research & Development, Chartered Society of Physiotherapy, London

Mr Michael Clancy,
Consultant in A & E Medicine, Southampton General Hospital

Professor Collette Clifford,
Professor of Nursing & Head of Research, School of Health Sciences, University of Birmingham

Dr Carl E Counsell,
Senior Lecturer in Neurology, University of Aberdeen

Dr Keith Dodd,
Consultant Paediatrician, Derbyshire Children's Hospital, Derby

Mr John Dunning,
Consultant Cardiothoracic Surgeon, Papworth Hospital NHS Trust, Cambridge

Mr Jonothan Earnshaw,
Consultant Vascular Surgeon, Gloucestershire Royal Hospital, Gloucester

Professor Gene Feder,
Professor of Primary Care R&D, St Bartholomew's & the London, Queen Mary's School of Medicine & Dentistry, University of London

Professor Richard Johanson,
Consultant & Senior Lecturer, North Staffordshire Infirmary NHS Trust, Stoke-on-Trent (deceased Feb 2002)

Dr Duncan Keeley,
General Practitioner, Thame, Oxon

Dr Phillip Leech,
Principal Medical Officer for Primary Care, Department of Health, London

Mr George Levvy,
Chief Executive, Motor Neurone Disease Association, Northampton

Professor James Lindesay,
Professor of Psychiatry for the Elderly, University of Leicester

Professor Rajan Madhok,
Medical Director & Director of Public Health, North & East Yorkshire & Northern Lincolnshire Strategic Health Authority, York

Dr Mike McGovern,
Senior Medical Officer, Heart Team, Department of Health, London

Dr John C Pounsford,
Consultant Physician, Frenchay Healthcare Trust, Bristol

Professor Mark Sculpher,
Professor of Health Economics, Institute for Research in the Social Services, University of York

Dr Ken Stein,
Senior Lecturer in Public Health, Peninsular Technology Assessment Group, University of Exeter

continued

continued

Expert Advisory Network

Members

Mr Gordon Aylward,
Chief Executive,
Association of British
Health-Care Industries,
London

Mr Shaun Brogan,
Chief Executive,
Ridgeway Primary Care Group,
Aylesbury, Bucks

Mr John A Cairns,
Reader in Health Economics,
Health Economics
Research Unit,
University of Aberdeen

Professor Nicky Cullum,
Director of Centre for
Evidence-Based Nursing,
University of York

Dr Katherine Darton,
Information Unit,
MIND – The Mental
Health Charity, London

Professor Carol Dezateux,
Professor of
Paediatric Epidemiology,
Institute of Child Health,
London

Professor Pam Enderby,
Dean of Faculty of Medicine
Institute of General Practice
& Primary Care,
University of Sheffield

Mr Leonard R Fenwick,
Chief Executive,
Freeman Hospital,
Newcastle-upon-Tyne

Professor David Field,
Professor of
Neonatal Medicine,
The Leicester Royal
Infirmary NHS Trust

Mrs Gillian Fletcher,
Antenatal Teacher &
Tutor & President,
National Childbirth
Trust, Henfield,
West Sussex

Ms Grace Gibbs,
Deputy Chief Executive
Director for Nursing,
Midwifery & Clinical
Support Services,
West Middlesex
University Hospital,
Isleworth, Middlesex

Dr Neville Goodman,
Consultant Anaesthetist,
Southmead Hospital, Bristol

Professor Robert E Hawkins,
CRC Professor & Director
of Medical Oncology,
Christie Hospital NHS Trust,
Manchester

Professor F D Richard Hobbs,
Professor of Primary Care
& General Practice,
University of Birmingham

Professor Allen Hutchinson,
Director of Public Health &
Deputy Dean of ScHARR,
University of Sheffield

Professor David Mant,
Professor of General Practice,
Institute of Health Sciences,
University of Oxford

Professor Alexander Markham,
Director,
Molecular Medicine Unit,
St James's University Hospital,
Leeds

Dr Chris McCall,
General Practitioner,
The Hadleigh Practice,
Corfe Mullen, Dorset

Professor Alistair McGuire,
Professor of Health Economics,
London School of Economics,
University of London

Dr Peter Moore,
Freelance Science Writer,
Ashtead, Surrey

Dr Andrew Mortimore,
Consultant in Public
Health Medicine,
Southampton City Primary
Care Trust

Dr Sue Moss,
Associate Director,
Cancer Screening
Evaluation Unit,
Institute of Cancer Research,
Sutton, Surrey

Mrs Julietta Patnick,
National Coordinator,
NHS Cancer
Screening Programmes,
Sheffield

Professor Chris Price,
Director of Clinical Research,
Bayer Diagnostics Europe,
Stoke Poges, Berks

Ms Marianne Rigge,
Director, College of Health,
London

Dr William Rosenberg,
Senior Lecturer &
Consultant in Medicine,
University of Southampton

Professor Ala Szczepura,
Director, Centre for
Health Services Studies,
University of Warwick

Dr Ross Taylor,
Senior Lecturer,
Department of General
Practice & Primary Care,
University of Aberdeen

Mrs Joan Webster,
Consumer member,
HTA – Expert
Advisory Network

Feedback

The HTA Programme and the authors would like to know your views about this report.

The Correspondence Page on the HTA website (http://www.ncchta.org) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

We look forward to hearing from you.

Copies of this report can be obtained from:

The National Coordinating Centre for Health Technology Assessment,
Mailpoint 728, Boldrewood,
University of Southampton,
Southampton, SO16 7PX, UK.
Fax: +44 (0) 23 8059 5639 Email: hta@soton.ac.uk
http://www.ncchta.org

ISSN 1366-5278