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Rapid review

A rapid and systematic review of the clinical effectiveness and cost-effectiveness of topotecan for ovarian cancer

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Health Technology Assessment
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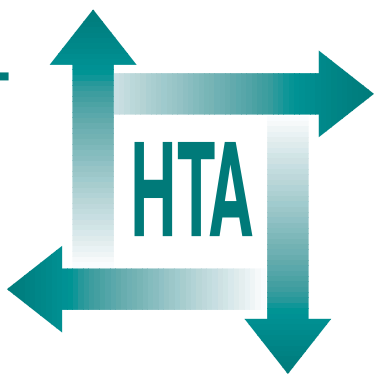

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Contents

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 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 change in the homeostasis of the organism or increases the susceptibility of the organism to other chemical or biological stress.

Alopecia Baldness/loss of body hair.

Anaemia Abnormally low level of red blood cells in the blood, which are responsible for carrying oxygen around the body.

Anthracyclines A group of antibiotics that have a tetrahydronaphthacenedione ring structure attached by a glycosidic linkage to a sugar molecule. These antibiotics have potent antineoplastic activity. They intercalate with DNA and 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.

Cost–benefit analysis (CBA) A form of economic evaluation where both costs and benefits are expressed in the same, usually monetary, units, that is, 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 because it is often difficult to determine the cost of health benefits.

Cost–consequences analysis (CCA) A form of cost-effectiveness analysis where costs and effectiveness (consequences) are presented separately and the decision-maker is left to make their own view about the relative importance of these factors.

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 a cost-effectiveness ratio, with the difference in cost in the numerator and the difference in survival in the denominator.

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

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.

continued

Glossary* *contd*

Complete response (CR) Total disappearance of all detectable malignant disease for at least 4 weeks.

Cost–utility analysis (CUA) A special form of CEA in which utility is measured and the units of effectiveness are quality-adjusted life-years. Utilities can be derived using various methods including the standard gamble and time trade-off techniques which are both based on utility theory. However, this form of economic evaluation has the disadvantage that utility data are often not collected in clinical trials because of the additional costs of data collection and the complex nature of the methods used in utility assessments. CUAs are important in the evaluation of cancer therapies because they are often associated with potentially serious or intolerable adverse effects.

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 effects 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 whilst 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) This is an organisation set up to conduct, develop, coordinate and stimulate laboratory and clinical research in Europe in order to improve the management of cancer and related problems by increasing survival and quality of life of patients.

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

Hazard ratio (HR) This is the hazard (the instantaneous risk of a patient 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.

Histological grade Degree of malignancy of a tumour as judged by histology.

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

Histology Examination of the cellular characteristics of a tissue.

Incremental CEA Analysis where estimates are made of the additional cost per year of life saved or gained. This type of analysis is often carried out to provide a more meaningful comparison of costs and consequences between different interventions.

International Federation of Gynaecologists and Obstetricians (FIGO) FIGO 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.

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

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

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

continued

Glossary* *contd*

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

Myalgia Muscle pain.

Neuropathy Term used to describe any disorder of the neurones or nerves of the body.

Neutropenia Abnormally low level of neutrophils in the blood. Neutrophils belong to a group of white blood cells known as granulocytes that 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.

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

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

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

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

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

Platinum (Pt)-based chemotherapy Treatment with Pt-based drugs such as cisplatin or carboplatin.

Pt-resistant disease Disease which is resistant to first-line Pt-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.

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

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 that might affect their physical, mental and social well-being.

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) as well as questions on six single items (dyspnoea, sleep disturbance, appetite loss, constipation, diarrhoea and financial impact). Higher scores on the function scales indicate better functioning and QoL, whereas higher scores on the symptom scales indicate the presence of more symptoms.

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

Recurrent-/disease-free survival 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.

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

Relative risk (RR)‡ Also called the 'risk ratio'. A common way of estimating the risk of experiencing a particular effect or result. An RR > 1.0 means a person is estimated to be at an increased risk, an RR < 1.0 means a person is apparently at decreased risk and

continued

Glossary* *contd*

an RR = 1.0 means there is no apparent effect on risk at all. For example, if the RR = 4.0 the result is about four times as likely to happen, and if it is 0.4 it is four times less likely to happen. The RR is usually expressed with confidence intervals (CIs), such as RR = 3.0 (95% CI, 2.5–3.8), which means the result is three times as likely to happen, and anything from 2.5 to 3.8 times as likely. It is statistically significant. In contrast, RR = 3.0 (95% CI, 0.5–8.9) means that the result is also estimated to be three times as likely, but it is not statistically significant, and the chances range from half as likely to happen (i.e. a decreased chance) to nearly nine times as likely to happen.

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† 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 or < 25% change in measurable lesions for at least 4–8 weeks with no new lesions appearing.

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

Stomatitis Inflammation/ulceration of the mouth.

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

Time to progression 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 involved in the replication of DNA, which 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 all of the health-related qualities of life. Hence, utility has been described as a global measure of health-related QoL.

Values Alternative measure of the strength of an individuals preference for a given health state or outcome. In contrast to utilities, values reflect preferences without risk (or uncertainty).

* Definitions adapted from references 1 and 2
† Definitions provided by the external expert panel
‡ Definition provided by Cochrane Collaboration Glossary

List of abbreviations

ASCO	American Society of Clinical Oncology
C	control*
CBA	cost–benefit analysis
CCA	cost–consequences analysis
CEA	cost-effectiveness analysis
CI	confidence interval
CMA	cost-minimisation analysis
CR	complete response
CUA	cost–utility analysis
EORTC	European Organisation for Research and Treatment of Cancer
FIGO	International Federation of Gynaecologists and Obstetricians
G-CSF	granulocyte colony-stimulating factor
HR	hazard ratio
I	intervention*
ITT	intention-to-treat
i.v.	intravenous
NA	not applicable*
NICE	National Institute for Clinical Excellence
PPE	Palmar–Plantar erythrodysesthesia
PR	partial response
Pt	platinum
Pt-r	platinum-refractory
Pt-s	platinum-sensitive
QALY	quality-adjusted life-year*
QLQ-C30	Quality of Life Questionnaire-C30
QoL	quality of life
RCT	randomised controlled trial
RR	relative risk
SD	standard deviation*
SE	standard error
TR	total response
TWIST	time without toxicity or symptoms

* Used in appendices and tables only

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. Due to the often asymptomatic nature of the early stages of the disease, most cases are not detected until the advanced stages. Consequently, the prognosis after diagnosis is poor and the 5-year survival rate in the UK is only about 30%. Current recommendations suggest that first-line chemotherapy for ovarian cancer should involve paclitaxel and platinum (Pt)-based therapy (cisplatin/carboplatin), however, most patients develop resistant or refractory disease and require second-line therapy. Patients may respond to re-challenge with Pt-agents if the treatment-free interval is > 6 months, but an alternative is often required. Topotecan is one of six drugs currently licensed in the UK for second-line therapy, and recent reviews suggest that it has modest efficacy in the treatment of advanced disease and performs favourably against paclitaxel. However, these reviews are based on a limited number of reports mainly consisting of non-randomised Phase I and II studies.

Objectives of the review

To examine the clinical effectiveness and cost-effectiveness of oral and intravenous topotecan (Hycamtin®, SmithKline Beecham, UK) for the treatment of all stages of ovarian cancer.

Methods

Search strategy

Sixteen electronic databases from inception to September 2000 and Internet resources were searched, in addition to the bibliographies of retrieved articles and submissions from pharmaceutical companies.

Inclusion and exclusion criteria

Two reviewers independently screened all titles/abstracts and included/excluded studies based on full copies of manuscripts. Any disagreements were resolved through discussion. Only randomised controlled trials (RCTs) and full economic evaluations comparing topotecan to non-topotecan regimens were included. All stages of therapy and disease were considered, and the outcomes included were survival, response, symptom relief, quality of life, adverse effects and costs.

Data extraction strategy

Data were extracted into an Access database by one reviewer and checked by a second. Any disagreements were resolved through discussion.

Quality assessment strategy

Two reviewers, using specified criteria, independently assessed the quality of the clinical effectiveness studies and the economic evaluations. Any disagreements were resolved through discussion.

Analysis strategy

Due to the limited number of studies included in the review and the fact that they compared topotecan with different comparators, the outcome data could not be pooled statistically. Clinical effectiveness data are discussed separately under the different outcome subheadings. For time-to-event data, hazard ratios with 95% confidence intervals are presented where available, and for the remaining outcomes, relative risks are reported or calculated where sufficient data were available. Relative risk data are also presented in the form of Forest plots without pooled estimates. Economic data are presented in the form of a summary and critique of the evidence, and a grading (A–I) assigned to each study indicating the direction and magnitude of the cost-effectiveness data.

Results

Included studies

A total of 568 titles/abstracts were identified and screened for relevance. Full copies of 72 papers were assessed and seven published manuscripts reporting details of two studies of clinical effectiveness and one economic evaluation were included. Further details of the two clinical effectiveness studies and two new economic evaluations were identified from confidential company submissions.

Overall, two international multicentre RCTs of effectiveness comparing topotecan with paclitaxel (trial 039) and topotecan with caelyx (trial 30-49) were included in the review. The three economic evaluations included in the review comprised one cost-minimisation analysis (CMA) comparing topotecan with caelyx, one cost–consequences analysis (CCA) comparing topotecan with paclitaxel, etoposide and altretamine and one cost-effectiveness analysis (CEA) comparing topotecan with paclitaxel.

Quality of clinical effectiveness data

Both clinical effectiveness studies (trial 30-49 and 039) were of reasonable quality, although it was unclear whether either performed valid intention-to-treat analyses. In addition, trial 30-49 failed to state whether the outcome assessors were blinded to treatment allocation.

Quality of economic evaluations

The CCA (comparing topotecan with three comparators) was of poor quality and of little relevance to the UK NHS. The CMA and CEA were of reasonable quality overall and relevant to the UK NHS. However, both, in particular the CEA, suffered from methodological problems, and thus their findings should be interpreted with caution.

Assessment of clinical effectiveness

The assessment of clinical effectiveness was based on limited data. Only two trials with a total of 709 participants were identified. In general, with a few minor exceptions, there were no statistically significant differences between topotecan and paclitaxel, or topotecan and caelyx in survival, response rate, median time to response, median duration of response and quality of life. Significant differences that were reported were mainly identified in subgroup analyses (Pt-sensitive disease and disease without ascites) of questionable validity and their relevance to a general advanced ovarian cancer patient population undergoing second-line chemotherapy is unclear. However, statistically significant differences were observed in the incidence of adverse effects. Topotecan was associated with increased incidences of haematological toxicities (including neutropenia, leukopenia, anaemia and thrombocytopenia), alopecia, nausea and vomiting. Caelyx-treated patients suffered from significantly increased incidences of Palmar–Plantar erythrodysesthesia, stomatitis, mucous membrane disorders and skin rashes. Paclitaxel was associated with significant increases in alopecia, arthralgia, myalgia, neuropathy, paraesthesiae, skeletal pain and flushing.

Assessment of cost-effectiveness

The assessment of cost-effectiveness was also based on limited data, with three evaluations identified, one of which was not relevant. The two remaining studies, comparing topotecan with paclitaxel (CEA) and topotecan with caelyx (CMA), both used effectiveness data from multicentre RCTs and based their costs on 1999/2000 UK sources. The evaluations were conducted from a UK NHS perspective and findings presented in £/Euros. Topotecan for the second-line treatment of advanced ovarian cancer was shown to be more cost-effective than paclitaxel (£32,513 versus £46,186 per person in terms of any response (complete or partial), incremental cost-effectiveness = £3065) in all respects except cost per time without toxicity or symptoms, but less cost-effective than caelyx (£14,023 versus £9979 per person regardless of whether the patient responded). However, direct comparisons of the cost findings between the two studies is difficult because they used different designs, different time horizons for the cost analyses and the findings were presented as costs per person for only patients who responded in one study (topotecan versus paclitaxel) and costs per person regardless of whether they responded in the other study (topotecan versus caelyx).

Conclusions

This review indicates that there is little evidence in the form of RCTs on which to base an assessment of the effectiveness of topotecan as second-line therapy for advanced ovarian cancer. The evidence suggests there were no statistically significant differences overall between topotecan and paclitaxel, or topotecan and caelyx in clinical outcomes. However, statistically significant differences were observed in the incidence of adverse effects. The clinical significance of the findings is not discussed. Overall, the effects of topotecan could at best be described as modest, but the alternative agents offer no real advantages except fewer side-effects and possibly improved cost-effectiveness. Both of the clinical effectiveness studies on which this evidence is based had methodological flaws, the most serious being the lack of a blinded assessor in the topotecan versus caelyx trial, which is important for unbiased assessment of response outcomes. The economic evaluations also suffered from a number of potential problems.

Recommendations for research

Further good quality RCTs and CEAs are required comparing topotecan with other licensed and

potentially useful (soon to be licensed) second-line treatments for ovarian cancer. At present, it is difficult to make any decisions about topotecan and other drugs for second-line therapy without good quality direct comparisons. In view of the ongoing studies identified, an update of the current review should be considered in approximately 18 months (Summer 2002) or possibly sooner if the recently commissioned National Institute for Clinical Excellence review of caelyx for ovarian cancer identifies additional data relevant to topotecan.

Chapter 1

Objectives and background

Objectives of the review

This review examines the clinical effectiveness and cost-effectiveness of intravenous formulations of the topoisomerase I inhibitor topotecan (Hycamtin®, SmithKline Beecham, UK) for ovarian cancer. All stages of disease and treatment are eligible for inclusion if topotecan is used alone or in combination with other chemotherapeutic agents. Only randomised controlled trials (RCTs) comparing topotecan-containing regimens with alternative non-topotecan-containing regimens are considered in the assessment of clinical effectiveness. The evaluation of cost-effectiveness includes cost-effectiveness analyses (CEAs), cost–consequences analyses (CCAs), cost–utility analyses (CUAs) and cost–benefit analyses (CBAs).

Background

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.[3] In 1996, there were 4580 deaths from the disease in the UK.[4] The value of screening remains the subject of ongoing clinical trials because many cases of ovarian cancer are not detected until the advanced stages of disease due to the often asymptomatic nature of the early stages. Consequently, the prognosis after diagnosis is poorer than for other gynaecological cancers and data suggest that the 5-year survival rate in the UK is only about 30%.[5,6]

There are three main types of ovarian cancer 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.[7] 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.[8,9] 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,[10] late menopause,[10] infertility,[11] the use of fertility drugs,[12,13] the use of talcum powder[14] 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 thus chemotherapeutic agents are used in addition to 'debulking' surgery. Currently, there are three main types of chemotherapy used for the first-line treatment of ovarian cancer: platinum (Pt) agents (e.g. cisplatin, carboplatin), non-Pt agents (e.g. cyclophosphamide, doxorubicin) 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 of > 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. Unfortunately, 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 the

stage of disease, the 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 may correlate 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/Pt 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 Pt-based therapy in recurrent (or resistant) ovarian cancer is not recommended. The choice of an alternative drug is then very much dependent on those previously used. No detailed recommendations or guidance have been issued about the choice of alternative second-line/salvage therapies for the treatment of ovarian cancer.

The Trent Development and Evaluation Committee has evaluated the use of topotecan after the failure of first-line or subsequent therapy in ovarian cancer and found that "topotecan is moderately effective in palliation of ovarian cancer refractory to other drugs".[23] The committee's report stated that "its usefulness in combination with other effective cytotoxic agents and/or in first-line treatment of ovarian cancer remains to be determined".

Description of the intervention

Topotecan is a water-soluble analogue of camptothecin, a drug derived from the oriental tree *Camptotheca acuminata*, which belongs to a class of drugs known as topoisomerase I inhibitors. These drugs target an essential step in cell growth by inhibiting an enzyme (topoisomerase I) involved in DNA replication. Topotecan is a relatively new drug, only launched in the UK in 1997, and is currently licensed for use in ovarian cancer. However, studies are also underway to investigate its potential in the treatment of lung cancer and colorectal cancer. Recent systematic reviews of topotecan suggest that the drug shows modest efficacy in the treatment of ovarian cancer and performs favourably against paclitaxel.[24,25] However, these findings were based on a limited number of studies, which included only one large randomised Phase III study. Therefore, there is a need to conduct an up-to-date review of the effectiveness of topotecan in order to incorporate any new evidence.

Current indications for topotecan

Topotecan is currently indicated for the treatment of patients with metastatic ovarian cancer after the failure of first-line or subsequent therapy.

Summary of current manufacturer's information provided for health professionals[26,27]

Recommended dosage

Prior to starting therapy with topotecan, patients must have a baseline neutrophil count of ≥ 1.5×10^9/l and a platelet count of ≥ 100×10^9/l. An initial dose of 1.5 mg/m^2 body surface area/day by intravenous infusion is recommended. This should be administered over a period of 30 minutes daily for 5 consecutive days with a 3-week interval between the start of each course. A minimum of four courses is recommended (7.6–11.6 weeks median time to response in clinical trials).

Subsequent doses of topotecan should not be re-administered unless the neutrophil count is ≥ 1×10^9/l, the platelet count is ≥ 100×10^9/l and the haemoglobin level is ≥ 9 g/dl (after transfusion if necessary).

Patients who experience severe neutropenia (neutrophil count < 0.5×10^9/l) for ≥ 7 days or severe neutropenia associated with fever or infection or who have had treatment delayed due to neutropenia should be given a reduced dose of topotecan or given granulocyte colony-stimulating factor (G-CSF) prophylactically. Doses should also be reduced if the platelet count falls below 25×10^9/l.

Contraindications

- A history of severe hypersensitivity reactions to topotecan and/or its excipients.
- Pregnancy or breastfeeding.
- Severe bone marrow depression (baseline neutrophils < 1.5×10^9/l and/or platelet count ≤ 100×10^9/l).

Special warnings and special precautions for use

- Topotecan should only be used by units specialised in the administration of cytotoxic chemotherapy and should only be administered

under the supervision of a physician experienced in the use of chemotherapy.
- Haematological toxicity is dose-related and full blood counts, including platelets, should be monitored regularly.
- There is no experience of topotecan use in patients with severe renal impairment (creatinine clearance < 20 ml/minute) or severe hepatic impairment due to cirrhosis (serum bilirubin ≥ 10 mg/dl), and its use is not recommended in these patient groups.

Adverse effects
- Haematological toxicity has been found to be dose-limiting, but predictable and reversible, with no evidence of cumulative toxicity.
- Severe neutropenia ($< 0.5 \times 10^9$/l) has been observed in 60% of patients during the initial course of therapy and 79% of patients (42% of courses) overall. In 13% of courses, neutropenia lasted beyond 7 days.
- Thrombocytopenia has been found to be severe (platelets $< 25.0 \times 10^9$/l) in 23% of patients (9% of courses) and moderate (platelets 25.0–29.9 $\times 10^9$/l) in 20% of patients (13% of courses).
- Anaemia has been found to be moderate to severe (haemoglobin ≤ 7.9 g/dl) in 36% of patients (15% of courses) and red cell transfusions required in 54% of patients (23% of courses).
- Non-haematological events have included nausea (68%), vomiting (44%), diarrhoea (26%), constipation (14%), stomatitis (20%), mild abdominal pain (8%), fatigue (about 33%), asthenia (about 20%), alopecia (total/pronounced 42%, partial 17%), anorexia (1%), malaise (1%) and hyperbilirubinaemia (1%).

Unit costs
The net price per 4 mg vial is £312.50.[27] The cost per course is £1562.50 based on open vials and £1054.68 based on weight (mg), with a minimum of four courses recommended.[23] A 1 mg vial was launched in March 2001 at the list price of £105 per vial.[28]

Comparator/alternative technologies
For those patients who require second-line therapy, guidance advises the use of Pt-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 (see *Table 1*).[22] Whichever agent is chosen, it is important to ensure that it does not exhibit cross-resistance with the first-line agent. At present, only topotecan, paclitaxel, carboplatin, treosulfan, caelyx and hexamethylmelamine are licensed for second-line therapy of ovarian cancer in the UK.

In the Trent Development and Evaluation Committee assessment, topotecan (as compared with paclitaxel) was highlighted as producing a better rate and longer duration of response with a greater delay in time to disease progression. However, topotecan was slightly more expensive than paclitaxel (£1562.50 versus £1372.69 per course, based on opened vials).[23]

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

Drug name (manufacturer)	Mode of action	Administration	Adverse effects
Carboplatin (Paraplatin®, Bristol-Myers Squibb)	Pt-based compound that binds to DNA to form inter-strand cross-links preventing DNA replication	400 mg/m^2 as a single intravenous dose administered by a 15–60-minute infusion. Licensed in the UK for first-line therapy and second-line therapy after other treatments have failed of advanced ovarian cancer	Myelosuppresssion, nephrotoxicity, nausea/vomiting
Docetaxel (Taxotere®, Aventis)	Prevents microtubule assembly and arrests the cell division cycle in phases G_2 and M	1-hour intravenous infusion after pre-medication with dexamethasone. Not yet licensed in the UK for ovarian cancer treatment	Hypersensitivity, fluid retention
Epirubicin (Ellence®, Pharmacia & Upjohn)	Anthracycline antibiotic that binds to DNA and inhibits nucleic acid synthesis	Intravenous administration. Not yet licensed in the UK for ovarian cancer treatment	Alopecia, skin rashes, diarrhoea, myelo-suppression, nausea/vomiting, mouth sores/ulcers, cardiac problems
Etoposide (Eposin®, Medac; Etopophos®/Vepesid®, Bristol-Myers Squibb)	Topoisomerase II inhibitor that inhibits DNA replication	Oral or intravenous administration. Not yet licensed in the UK for the treatment of ovarian cancer	Myelosuppression, alopecia, nausea/vomiting
Fluorouracil (injection non-proprietary, Faulding Pharmaceuticals) plus folinic acid (Refolinon®, Pharmacia & Upjohn)	Anti-metabolite that inhibits the enzyme thymidylate synthase, thereby blocking the synthesis of DNA	Oral or intravenous administration. Not yet licensed in the UK for ovarian cancer treatment	Neutropenia, thrombo-cytopenia, anaemia, diarrhoea, nausea/vomiting, mouth sores/ulcers
Gemcitabine (Gemzar®, Eli-Lilly)	Anti-metabolite nucleoside analogue that incorporates into replicating DNA causing DNA chain termination	30-minute intravenous infusion. Not yet licensed in the UK for ovarian cancer treatment	Mild gastrointestinal side-effects, skin rashes, renal impairment, pulmonary oedema, influenza-like symptoms
Goserelin (Zoladex®, Zeneca)	Gonadorelin analogue that 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 ovarian cancer treatment	Withdrawal bleeding, fibroid degeneration, ovarian cysts, transient changes in blood pressure
Hexamethylmelamine (Hexalen®, David Bull Laboratories)	Alkylating agent that damages DNA and interferes with DNA replication	Oral administration. Licensed in the UK for second-line treatment of ovarian cancer. Often given in combination with other agents, such as cyclophosphamide, doxorubicin and, if the patient can tolerate it, cisplatin	Neurotoxicity, myelosuppression, nausea/vomiting
Ifosfamide (Mitoxana®, ASTA Medica)	Alkylating agent that damages DNA and interferes with DNA replication	Intravenous administration. Not yet licensed in the UK for ovarian cancer treatment	Neutropenia, anaemia, thrombocytopenia, nausea/vomiting, alopecia

continued

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

Drug name (manufacturer)	Mode of action	Administration	Adverse effects
Oxaliplatin (Eloaxtin®, Sanofi-Synthelabo)	Diaminocyclohexane Pt-compound	Intravenous administration. Not yet licensed in the UK for ovarian cancer treatment	Sensory/peripheral neuropathy, bone marrow suppression, nausea/ vomiting, diarrhoea
Paclitaxel (Taxol®, Bristol-Myers Squibb)	Taxane, which promotes microtubule assembly and arrests the cell division cycle in phases G_2 and M	3–24-hour intravenous infusion after pre-medication with corticosteroid, antihistamine and histamine H_2-receptor antagonist. Licensed in the UK for metastatic ovarian cancer where standard Pt-containing therapy (cisplatin or carboplatin) has failed	Hypersensitivity, myelosuppression, peripheral neuropathy, cardiac conduction defects with arrhythmias, alopecia, myalgia, arthralgia
Tamoxifen (Nolvadex®, Zeneca; Oestrifen®, APS; Emblon®, Berk; Fentamox®, Cox; Tamofen®, Pharmacia & Upjohn; Soltamox®, Rosemont)	Oestrogen receptor antagonist	Oral administration. Not yet licensed in the UK for ovarian cancer treatment	Endometrial changes, leukopenia, skin rashes, alopecia, headaches, gastrointestinal disturbances
Treosulfan (Treosulfan®, Medac)	Alkylating agent that damages DNA and interferes with DNA replication	Oral or intravenous administration. Licensed in the UK for ovarian cancer treatment	Bone marrow suppression, skin rashes
Vinorelbine (Navelbine®, Burroughs Wellcome)	Vinca alkaloid that irreversibly inhibits cell division by binding to micro-tubule protein and inhibiting the formation of mitotic spindles	Intravenous administration. Not yet licensed in the UK for ovarian cancer treatment	Peripheral/autonomic neuropathy, abdominal pain, constipation, myelo-suppression, alopecia

Chapter 2
Methods

Search strategy

The following databases were searched for relevant published literature (details of the search strategy are given in appendix 1):

- MEDLINE
- EMBASE
- CANCERLIT
- BIOSIS
- Index to Scientific and Technical Proceedings
- Cochrane Controlled Trials Register
- Database of Abstracts of Reviews of Effectiveness
- NHS Economic Evaluation Database.

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

Research groups identified through searches of the registers listed below were also contacted for information about ongoing trials (see appendix 2):

- National Research Register
- UKCCCR 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 (ASCO) <http://www.asco.org/>
- National Cancer Institute of Canada <http://www.ctg.queensu.ca/>

All data submitted by the drug manufacturers were considered and included in the review if they met the inclusion criteria for the review.

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. Any discrepancies were resolved by consensus and, if necessary, a third reviewer was consulted.

Study design

The following study designs were eligible for inclusion:

- RCTs comparing topotecan-containing regimens with non-topotecan-containing regimens
- Cost-effectiveness evaluations including cost-minimisation analyses (CMAs) and CCAs
- CUAs
- CBAs.

Interventions

Oral or intravenous topotecan (Hycamtin, Smith-Kline Beecham, UK) used alone or in combination with other chemotherapeutic agents as part of the following stages of treatment were eligible for inclusion.

- First-line therapy – defined as the first chemotherapy regimen (usually administered with curative intent) given to patients who had been newly diagnosed with ovarian cancer or who had an early stage of the disease which had been previously treated with surgery alone but had since relapsed and required chemotherapy.
- Second-line therapy – defined as the second chemotherapy regimen administered either as a result of relapse after first-line therapy or immediately following on from first-line therapy in patients with progressive or stable disease. Depending on the circumstances, patients could have been treated with the same regimen again or a different regimen. In either case, this was defined as second-line therapy.
- Salvage therapy – defined as any therapy given in the hope of getting a response when the 'standard' therapy had failed. This could have overlapped with second-line therapy, but could have also included therapy given for patients with refractory disease, that is, disease that had never responded to first-line therapy.

Participants

Women with ovarian cancer, encompassing all stages of disease, were eligible for inclusion.

Where possible, the FIGO system was used throughout the report to define the stage of disease (see appendix 3).[29] Early ovarian cancer is used in reference to FIGO stage I disease 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 response (CR) and partial response (PR))
- symptom relief
- quality of life (QoL)
- adverse effects (haematological toxicity, including neutropenia, thrombocytopenia and anaemia; non-haematological toxicity, including nausea, diarrhoea, constipation, stomatitis, abdominal pain, fatigue, asthenia, alopecia, anorexia, malaise and hyperbilirubinaemia; and any other adverse effects judged to be appropriate)
- cost.

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 as a single study. Only the most recent publication was reported except in cases where only abstracts were available. In such instances, the abstract was included as well as any full reports of interim analyses. All of the publications identified as eligible for inclusion were published in English.

Quality assessment strategy

The quality of each individual study 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 NHS Centre for Reviews and Dissemination Report No. 4 (see appendix 5A),[30] and criteria based on the Drummond checklist[31] were used to assess the quality of cost-effectiveness studies (see appendix 5B). Details of individual study quality are presented both in table form and summarised within the text of the report.

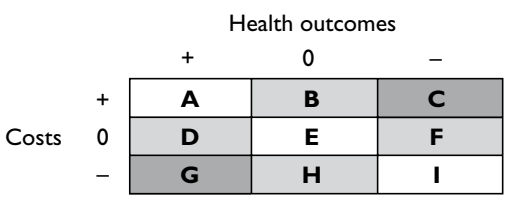
Analysis strategy

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 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, and, where data were not available, RRs and *p*-values have been presented.

Where RR estimates were not presented in the original trial report, they have been 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 have not been 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 companies and trialists concerned. These studies have not been included in the main body of the report but have been listed in appendix 6 as ongoing studies.

Details of each economic evaluation and the quality of the studies are presented in structured tables. A summary grading (A–I) based on the matrix shown in *Figure 1* has then been assigned to each study to indicate the direction and magnitude of cost-effectiveness data.[31,32] In addition, a narrative summary of the data is presented, which considers the quality of the evidence, the level of heterogeneity between studies, the sources of data and the methods of analysis used.



Comparison	Health outcomes	Costs
+ Intervention versus comparator	Better	Higher
0 Intervention versus comparator	Same	Same
– Intervention versus comparator	Poorer	Lower

Implication of findings

Code	Implication for intervention	Summary of the direction of the cost-effectiveness data and the magnitude of the effectiveness data
A	Trade-off	Higher costs but better outcomes (incremental analysis required)
B	Reject	Higher costs and no difference in outcomes
C	Reject	Higher costs and poorer outcomes
D	Accept	No difference in costs and improved outcomes (partial dominance)
E	Neutral	No difference in costs and no difference in outcomes
F	Reject	No difference in costs and poorer outcomes
G	Accept	Lower costs and improved outcomes (extended dominance)
H	Accept	Lower costs and no difference in outcomes (partial dominance)
I	Trade-off	Lower costs but poorer outcomes (incremental analysis required)

FIGURE 1 *Cost-effectiveness matrix. Adapted from Drummond and colleagues[31] and Birch and Gaffni[32]*

Chapter 3
Results

Quantity of research available

A total of 568 titles and abstracts were identified and screened for relevance, and 72 full articles were examined in further detail and assessed for inclusion in the review (see *Figure 2*).

Excluded studies

Of the 72 articles examined in further detail, a total of 66 were excluded from the review. Forty-three of the articles were literature reviews and background papers, and a further three publications were systematic reviews of topotecan

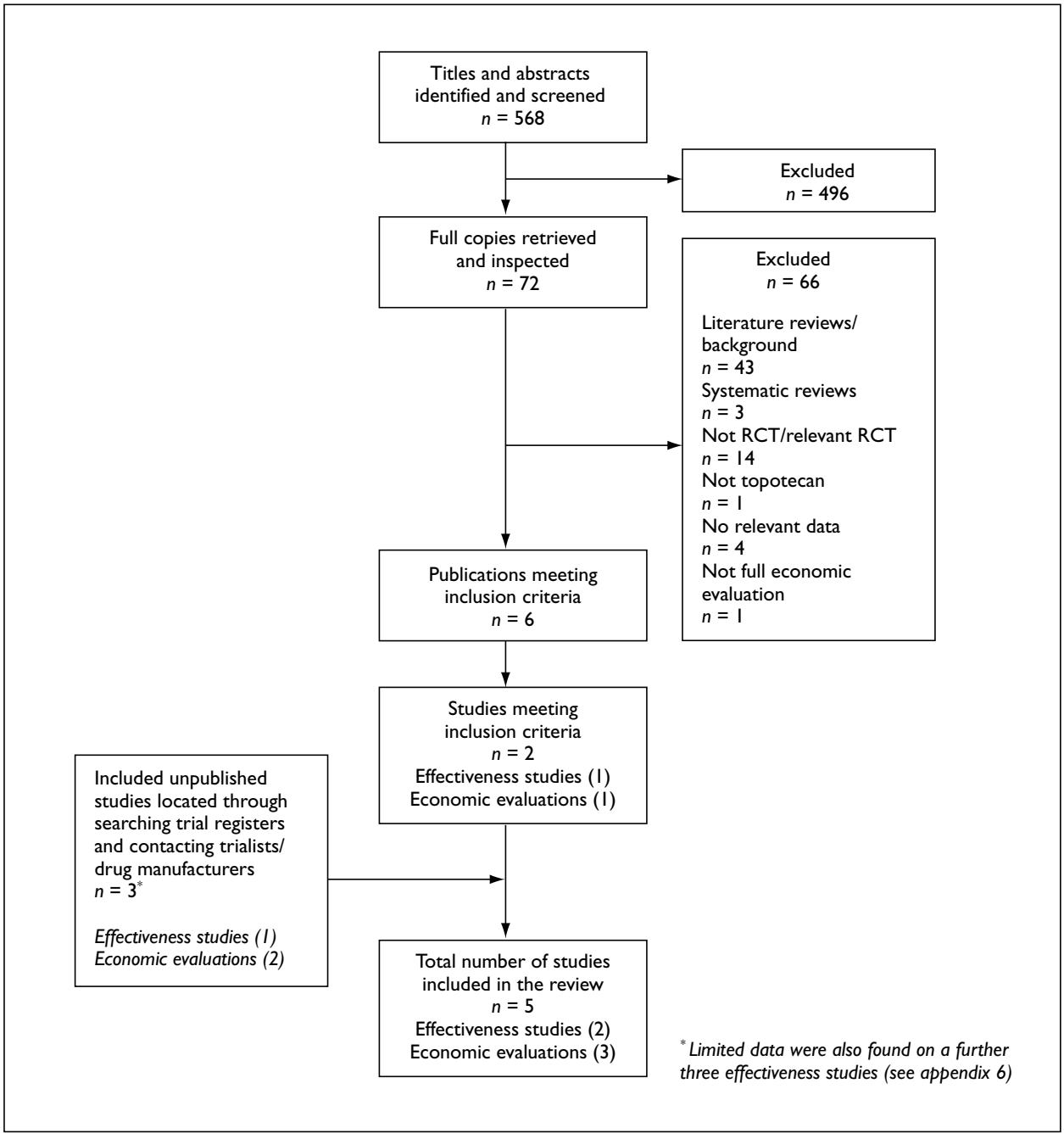


FIGURE 2 *Summary of study identification, retrieval and inclusion/exclusion*

studies.[24,25,33] The remaining publications were excluded for the following reasons: 14 did not use an RCT design comparing topotecan (or a combination including topotecan) with a non-topotecan comparator,[34–47] one did not consider topotecan as an intervention,[48] four presented no relevant outcome data[49–52] and the final study was not a full economic evaluation.[53] Details of these studies and the reasons for their exclusion are given in appendix 7.

Included studies

Of the five studies that met the criteria for inclusion in the review, two were clinical effectiveness studies (see *Table 2*) and three were economic evaluations of topotecan (see *Table 3*). The data from one of the economic evaluations were reported in two separate, almost identical, publications. Minimal information on a further three ongoing studies was also identified through searching trial registers. These studies appeared to fulfil the inclusion criteria and have, therefore, been highlighted in a table of ongoing studies (see appendix 6).

The two effectiveness studies were identified as trial 039 sponsored by SmithKline Beecham (235 participants) and trial 30-49 sponsored by Schering-Plough Ltd. (474 participants). Interim data from trial 039, which compared topotecan with paclitaxel, were published as a number of abstracts and one full manuscript.[54–56] However, the final trial analysis was only published in abstract form[54] and the full details were submitted as a partly confidential company submission (Smith-Kline Beecham).[28,57] Similarly, interim data from the other clinical effectiveness study (trial 30-49) were also only published in abstract form.[58] This study compared topotecan with a new drug, caelyx (pegylated liposomal doxorubicin hydrochoride, also known as doxil), which has recently received European approval (October 2000) for the second-line treatment of advanced ovarian cancer. The final analysis of this trial was again only available as part of a confidential company submission (Schering-Plough Ltd.).[59]

Both of the studies were international multicentre Phase III RCTs evaluating intravenous topotecan (1.5 mg/m^2/day as a 30-minute infusion daily for 5 consecutive days every 3 weeks) in advanced epithelial ovarian carcinoma (FIGO stage III/IV). Similarly, in both cases, patients had undergone prior first-line Pt-based chemotherapy, which had

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

Study	Status and source	Study design	Comparators
039 (SmithKline Beecham)	Completed and published.[54–56] Company submission[28,57]	Multicentre Phase III RCT, 235 participants analysed	Topotecan (1.5 mg/m^2/day as a 30-minute infusion for 5 consecutive days every 3 weeks) versus paclitaxel (175 mg/m^2/day as a 3-hour infusion every 21 days)
30-49 (Schering-Plough Ltd.)	Completed and interim results published as an abstract.[58] Final results submitted in confidence by Schering-Plough Ltd.[59]	Multicentre Phase III open-label RCT, 474 participants analysed	Topotecan (1.5 mg/m^2/day as a 30-minute infusion every day for 5 consecutive days every 3 weeks) versus caelyx (50 mg/m^2/day as a 1-hour infusion every 28 days)

TABLE 3 *Summary of the economic evaluations included in the review*

Evaluation	Source	Study design	Comparators
Bennett *et al.*, 1999 and Stinson *et al.*, 1999	Published[60,61]	Authors state that the study was a CMA, but it was, in fact, a CCA (participant numbers not stated)	Topotecan versus three comparators (paclitaxel, etoposide and altretamine)
SmithKline Beecham	Confidential data from SmithKline Beecham[28]	CEA based on hypothetical group of 1000 patients	Topotecan versus paclitaxel
Schering-Plough Ltd.	Confidential data from Schering-Plough Ltd.[62]	CMA based on the 474 participants in trial 30-49	Topotecan versus caelyx

failed. Patients in trial 039 were also reported as having undergone other forms of therapy, including radiotherapy and hormonal therapy. Although it would seem likely, it was not stated whether patients in trial 30-49 had undergone similar alternative forms of therapy. However, in terms of the clinical outcomes measured in the two trials, both included response rate, survival, time to response, time to progression, duration of response, QoL and adverse effects as outcomes. Further details of the two trials are given in appendix 8A.

The three economic evaluations included in the review all examined the use of topotecan (1.5 mg/m^2/day as a 30-minute infusion every day for 5 consecutive days every 3 weeks) in advanced ovarian cancer patients undergoing second-line chemotherapy after the failure of first-line Pt-based therapy. Two of the evaluations stated that they were CMAs, assuming equivalent or superior clinical effectiveness of one of the drugs under investigation. Consequently, only costs incurred were compared. However, the CMA that compared topotecan with a range of comparators (paclitaxel, etoposide and altretamine) was in fact a CCA as the drugs were not of equivalent clinical effectiveness. This evaluation was published in two almost identical publications.[60,61] Costs were examined from the perspective of the USA third-party payer system and patient out-of-pocket expenses.

The one true CMA was based on trial 30-49 comparing topotecan with caelyx. A comparison of costs from the perspective of the NHS was carried out based on the assumption that caelyx was at least of equivalent effectiveness compared with topotecan. The data from this analysis were submitted in confidence by Schering-Plough Ltd.[62] The final economic evaluation took the form of a CEA and was, again, part of a confidential company submission (SmithKline Beecham).[28] The clinical effectiveness data used in the analysis was based on the findings of trial 039 comparing topotecan with paclitaxel. The evaluation examined the cost-effectiveness of the two drugs from the perspective of the NHS. Further details of all the economic evaluations can be found in appendix 8B.

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

The quality of trial 039 (SmithKline Beecham) could be easily assessed using information obtained from several study publications (see *Table 4*).[54–56] Details of trial 30-49 (Schering-Plough Ltd.) were only published in abstract form and thus a full assessment of study quality relied on the use of confidential information contained within the company submission (see *Table 4*).[59]

Trial 039 used a centralised telephone method to randomly assign 235 participants to the two study groups and was, therefore, truly randomised. Participants were stratified according to Pt-sensitivity, age and ascites at baseline. Also implicit in this method of randomisation is the adequate concealment of the allocation procedure, which avoids the possibility of tampering and thus bias in treatment allocation. All of those patients originally included in the randomisation process were accounted for and the results of the trial were presented in terms of an intention-to-treat (ITT) analysis as well as a per protocol analysis. However, the ITT analysis used was not a true one because five patients from the topotecan group and four from the paclitaxel group who were included in the randomisation procedure were not included in the ITT analysis because they never received the treatment to which they were assigned. Of those assigned to receive topotecan, three participants subsequently refused treatment and withdrew their consent and two died (one from progressive disease and the other from pulmonary embolism). Three of the participants assigned to the paclitaxel group subsequently withdrew their consent and refused treatment and one had a performance status of 4 and thus did not fulfil the inclusion criteria for the trial. Not including these participants in the ITT analysis could introduce bias because these patients could have had a poorer prognosis (which was certainly true for the participant who died in the topotecan group). However, further trial withdrawals were included in the ITT analysis and reasons for their withdrawal were clearly stated.

The topotecan and paclitaxel study groups were similar at baseline in terms of the six characteristics stated in the quality checklist (identified by the external review panel). These factors were chosen for their potential importance in predicting disease progression and treatment response and included treatment-free interval, disease bulk, number of previous regimens, age, histology and performance status. The criteria used to select patients for inclusion in the trial were also stated, and appeared to be reasonable and

TABLE 4 *Quality of the clinical effectiveness studies*

Quality criteria	039 SmithKline Beecham[34,54–56]	30-49 Schering-Plough Ltd.[59]
Was the method used to assign participants to the treatment groups really random?	Yes	Not stated
Was the allocation of treatment concealed?	Yes	Not stated
Was the number of participants who were randomised stated?	Yes	No
Were details of baseline comparability presented in terms of treatment-free interval, disease bulk, number of previous regimens, age, histology and performance status?	Yes	Yes
Was baseline comparability achieved for treatment-free interval, disease bulk, number of previous regimens, age, histology and performance status?	Yes	Yes
Were the eligibility criteria for study entry specified?	Yes	Yes
Were any co-interventions identified that may have influenced the outcomes for each group?	No	No
Were the outcome assessors blinded to the treatment allocation?	Yes	Not stated
Were the individuals who administered the intervention blinded to the treatment allocation?	No	No
Were the participants who received the intervention blinded to the treatment allocation?	No	No
Was the success of the blinding procedure assessed?	Not stated	Not stated
Were ≥ 80% of the participants originally included in the randomisation process followed up in the final analysis?	Yes	Not stated
Were the reasons for any withdrawals stated?	Yes	Yes
Was an intention-to-treat (ITT) analysis included?	Yes	Yes

Yes, item adequately addressed; No, item not adequately addressed

comprehensive. For the duration of the trial, the patients used no other interventions apart from those under investigation and those used in the management of adverse effects (e.g. G-CSF). This reduced the possibility of confounding effects. To avoid further bias in the assessment of the clinical outcomes, an independent blinded radiological review was performed. Otherwise, the trial was conducted on an open-label basis, and all parties apart from the blinded independent assessor (e.g. patients, carers, physicians) were, therefore, aware of which of the two drugs the patients were receiving. However, it was not stated whether blinding of the independent assessors was successful or not. Overall, taking all of the above factors into account, the quality of trial 039 was good apart from the incomplete ITT analysis (see *Table 4*).

Based on the limited published information available for trial 30-49, it is not clear whether or not the trial participants were truly randomised, how many were included in the randomisation process and whether the allocation of treatment was adequately concealed. Unfortunately, this information was also absent from the confidential report supplied by the company. It is, therefore, difficult to make a proper assessment of the potential for bias in the design of the study, although the available information states that the trial was randomised. In addition, the two study groups would appear to be comparable in terms of the six potentially important factors outlined in the quality assessment. Information concerning the comparability of the two study groups was not made available in the published trial information, and the inclusion/exclusion criteria applied in the process of patient selection were also only available in the confidential submission. However, the criteria listed were fairly comprehensive and appeared to be reasonable. The comparability of the two study groups at baseline was difficult to assess from the published information, but the confidential submission confirmed that comparability was achieved in terms of the six identified factors. In addition, no other co-existing treatments, apart from those administered in the management of adverse effects, were identified.

Trial 30-49 was also an open-label trial implying that the patients, carers and physicians were all aware of the treatment received by the patient, but, unlike trial 039, it was not stated whether those individuals responsible for assessing the response outcomes of the study were blinded to the treatment allocation. Blinding is not important for outcomes such as survival where death is a clear outcome, but the outcomes may be biased if the assessor is not blinded for response outcomes. Knowledge of the drug under assessment may lead to the assessor providing a more or less favourable outcome 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.

The number of patients included in the randomisation process for trial 30-49 was also not stated, and it was, therefore, not possible to determine the percentage of patients that were included in the follow-up analysis. The information provided does state that an ITT analysis was performed, which implies that all patients included in the randomisation procedure were included in the final analysis, however, as trial 039 highlights, this may not necessarily be the case. Without knowing the original number of randomised participants, it is not possible to confirm if a true ITT analysis was performed and whether all of the participants were included in the final analysis. However, a number of patient withdrawals were highlighted in the confidential company submission and the reasons for these withdrawals were adequately described.[57] Overall, this trial would seem to be reasonable, although it was difficult to give a comprehensive assessment of the quality due to the lack of information provided (see *Table 4*). This may purely be due to inadequate reporting of the trial methodology or may highlight true inadequacies in the trial. The major concern centres on the potential absence of a blinded assessor for response outcomes, and a recent European Public Assessment Report of trial 30-49 suggested that the assessors were indeed not blinded.[63]

Further details of the studies and their quality are reported in appendix 8A.

Quality of economic evaluations

Only the quality of the economic evaluation by Stinson and Bennett and colleagues[60,61] could be determined from published information. The quality of the two evaluations included in the company submissions is derived from confidential information (see *Table 5*).

The major problem with the evaluation by Stinson and Bennett and colleagues[60,61] was the consideration of only costs based on the assumption of equivalent effectiveness. The authors stated that they were performing a CMA for this reason, and they obtained effectiveness data from a number of published studies (Sacketts grade A and B) identified through a literature search. The data from these studies were presented for a number of relevant outcomes, including response rate, the presence of progressive disease, median time to progression and median survival. However, the authors' assumption of equivalence was not supported by the data presented, which in fact showed a number of differences between the four drugs, and, therefore, a CCA was actually performed.

This evaluation clearly stated that it was conducted from the viewpoint of the USA third-party payer system and considered patient out-of-pocket expenses. This viewpoint would seem justified considering the aims and context of the evaluation, but is not relevant for the purposes of this review, that is, it is not applicable to the UK NHS setting. The comparators and patients considered in the evaluation were appropriate and relevant to the USA setting, with all of the drugs used for the second-line treatment of advanced ovarian cancer. However, etoposide and altretamine are not yet licensed for the treatment of ovarian cancer in the UK.

The sources of the costs used in the analysis were all given in US$ as were the final cost estimates for the comparators. The costs were based on 1996 figures from Medicare reimbursement protocols and USA average wholesale prices. The resources used took into account the level of adverse effects and the costs of appropriate support measures. Resource usage was derived from probability estimates, obtained from the published data, based on a number of defined assumptions. Many of these assumptions related to the use of other drugs and blood products to alleviate adverse effects. The authors also assumed that the patients would have a similar grade of disease and similar treatment histories across the studies. Without looking at the individual studies, it is difficult to comment on the validity of this assumption. However, the fact that the treatments were all second-line suggests that the patients were probably similar in that they would have had advanced stage disease and would have previously been treated with at least one chemotherapy regimen, which most likely would have been Pt-based.

TABLE 5 *Quality of the cost-effectiveness studies (quality assessments for the SmithKline Beecham and Schering-Plough Ltd. trials (last two columns) were mainly based on commercial in confidence material and the data are, therefore, omitted)*

Quality criteria	Bennett *et al.*[60] and Stinson *et al.*[61]	SmithKline Beecham[28]	Schering-Plough Ltd.[62]
The viewpoint(s) of the analysis were clearly stated and justified	Yes	Yes	Yes
Relevant alternatives were compared	Yes	Yes	Yes
The alternatives being compared were clearly described	Yes	Yes	Yes
The rationale for choosing the alternative programmes or interventions compared was stated	Yes	Yes	Yes
The choice of economic evaluation type was justified in relation to the questions addressed	Yes	Yes	Yes
The source(s) of effectiveness estimates used were stated	Yes	Yes	Yes
The source(s) of effectiveness estimates used were the Sackett grade A, B, C or D	B	A	A
Details of the method of synthesis or meta-analysis of estimates were given (if based on an overview of a number of effectiveness studies)	Not stated		
The primary outcome measure(s) for the economic evaluation were clearly stated	Yes		
Methods to value health states and other benefits were stated	NA		
Details of the individuals from whom valuations were obtained were given	Yes	Yes	Yes
The relevance of productivity changes to the study question was discussed	NA		
Productivity changes (if included) were reported separately	NA		
Quantities of resources were reported separately from their unit costs	Yes		
Methods for estimation of quantities were described	Yes		
Methods for estimation of unit costs were described	Yes	Yes	Yes
Currency and price data were reported	Yes	Yes	Yes
Details of currency of price adjustments for inflation or currency conversion were given	No		
Details of any model used were given	Yes		
The choice of model used and the key parameters on which it was based were justified	No		
Time horizon of costs and benefits was stated	No		Yes
The discount rate was stated	No		
The choice of rate was justified	NA		
A convincing explanation was given if cost or benefits were not discounted	No		
Details of statistical tests and confidence intervals (CIs) were given for stochastic data	No		
The approach to sensitivity analysis was given	No	Yes	
The choice of variables for sensitivity analysis was justified	No		
The ranges over which the variables were varied were stated	Yes		
Incremental analysis was reported	Unclear		
Major outcomes were presented in a disaggregated as well as an aggregated form	No		
The study was applicable to the NHS setting	No	Yes	Yes

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

The time horizon of the costs used in the analysis was not stated, although this is likely to be short considering the life-span of patients undergoing this form of therapy. Consequently, the absence of discounting is not a significant problem, although the authors do not justify this omission. The robustness of the final costings per drug was tested in a series of sensitivity analyses. A number of scenarios were used, including a 20% reduction in drug acquisition costs, alternative dosages and differences in the level of reported grade 3/4 neutropenia. However, the justification for examining these particular parameters and the ranges tested was not stated, and thus the appropriateness of the analyses is unclear. The authors also highlight a number of valid limitations in their analysis, including the possibility of heterogeneity between the studies under consideration and the fact that no one study examined all of the comparators simultaneously. Overall, this study was of questionable quality (see *Table 5*) and was of little relevance to this review.

The two remaining economic evaluations (one CEA[28] and one CMA[62]) included in the company submissions were both relevant to the UK setting and expressed their overall cost findings in terms of £ and Euros. Both clearly stated their aims and comparators and were based on RCTs (Sacketts evidence grade A) included in the assessment of clinical effectiveness (the CEA on trial 039 and the CMA on trial 30-49). Cost data from 1999/2000, based on relevant UK sources (e.g. MIMS, NHS/UK health service data) were used in both studies. However, further methodological details have been designated as confidential by the companies that sponsored them.

Overall, the studies were of reasonable quality although both unpublished studies suffered from methodological problems that warrant concern. In particular, our opinion is that the findings of the CEA of topotecan versus paclitaxel should be interpreted with caution.

Further details of all three evaluations and their quality are reported in appendix 8B.

Assessment of clinical effectiveness

The following section describes the clinical effectiveness data from trials 039 and 30-49. The trials gathered data relating to six main outcomes and each outcome is discussed separately. Due to the lack of included studies and the obvious heterogeneity between the two included studies (i.e. both looked at different comparators), it was not possible to pool the data.

The studies themselves did not present RR data and RRs have been calculated for the data relating to response rate, adverse effects and QoL where absolute numbers have been quoted. Where appropriate, the RR data has also been presented in the form of Forest plots, but, for the reasons outlined above, the estimates were not pooled. If the confidence intervals (CIs) crossed the line of no effect (i.e. 1.0), the RR estimate was considered not to be statistically significant (p-values ≤ 0.05 were considered significant). No comments have been made about the clinical significance of the findings and this issue was not addressed in the original trial reports.

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. This type of data requires 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 may be lost to the analysis. Where stated, the HRs (with CIs) given in the original trial reports have been used along with the median times estimated from Kaplan-Meier survival curves. Both of the trials presented Kaplan-Meier survival curves for the main time-to-event outcomes (i.e. survival and time to progression) and these have been directly reproduced in this report (*Figures 3* and *4*).[57,59] In addition, although trial 039 stated that HRs with 95% CIs had been calculated they were not reported and could not accurately be calculated from the data presented in the report. Only RRs with p-values were reported and these have been used in the following assessment. The risk ratio (or RR) is a common way of estimating the risk of experiencing a particular effect or result (e.g. producing a clinical response or death), and an RR > 1.0 means that a person is estimated to be at an increased risk, an RR < 1.0 means a person is apparently at decreased risk and an RR = 1.0 means there is no apparent effect on risk at all.

HRs were reported in trial 30-49, although only for the main time-to-event data and with 90% instead of 95% CIs. In the interim data for the trial, 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

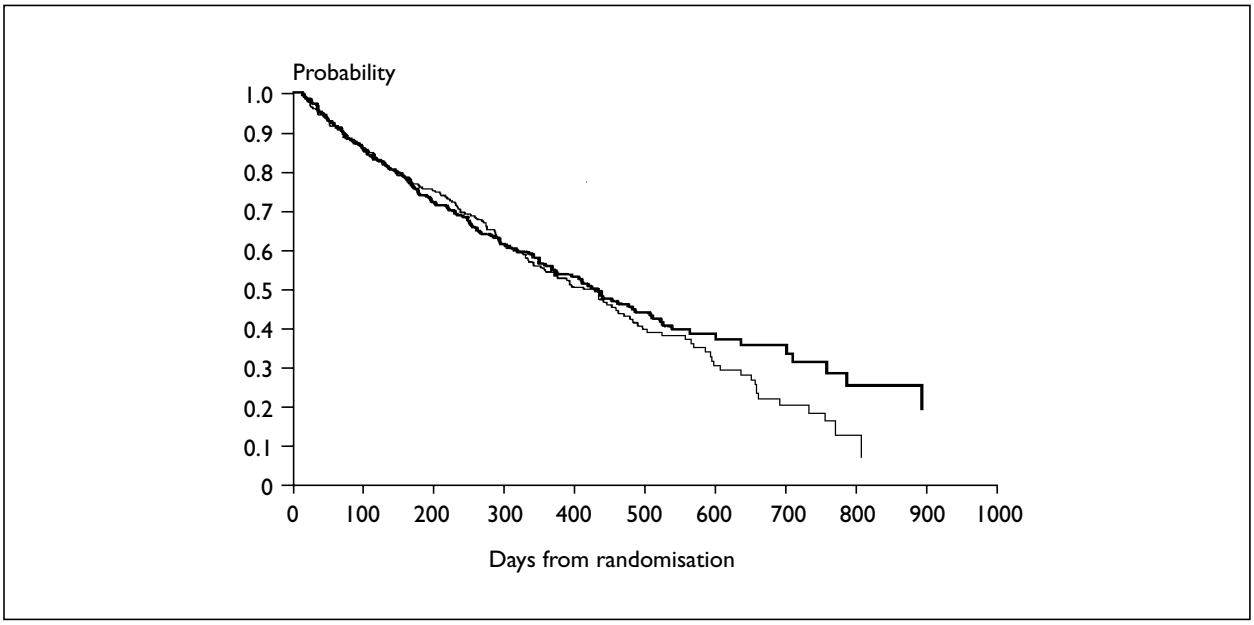


FIGURE 3 *Kaplan-Meier survival curves for topotecan (——) versus caelyx (▬). Reproduced from Schering-Plough Ltd.[59] with kind permission*

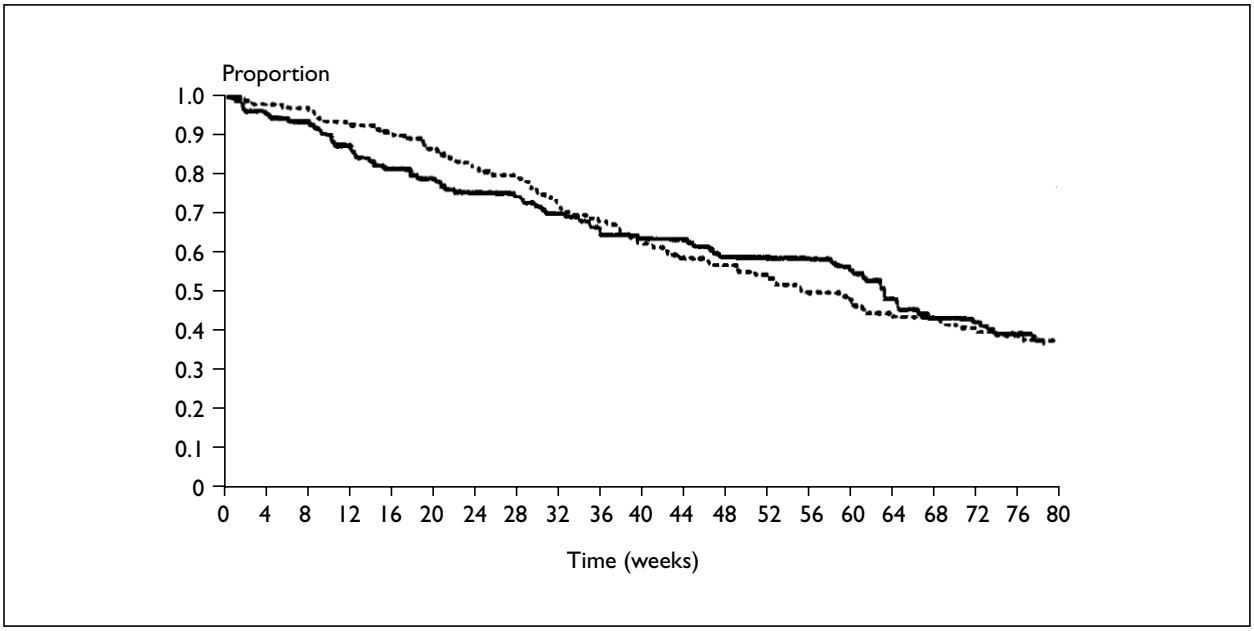


FIGURE 4 *Kaplan-Meier survival curve for topotecan (——) versus paclitaxel (- - - -). Reproduced from SmithKline Beecham[57] with kind permission*

and, where available, these have been quoted. However, the main findings of the trial were based on the 90% CIs, and these have been converted to 95% CIs using the following formula in order to present the data in a more usual form:

ln of lower 95% CI = ln HR – [1.96 × (ln of HR – ln of lower 90% CI)/1.645]

ln of upper 95% CI = ln HR + [1.96 × (ln of HR – ln of lower 90% CI)/1.645]

[Where 1.645 is the *Z*-value for 90%. The ln 95% CI values were then converted back to 95% CI values.]

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. The significance of the findings should be interpreted with great caution where such analyses involve small numbers of participants, as is the case

in the two trials reported in this review. It is likely with such a large number of subgroups with small numbers of participants that effects that appear to be statistically significant are, in fact, purely the result of chance because statistical tests have reduced power in such circumstances. However, the results of the various subgroup analyses have been reported in the assessment of clinical effectiveness taking into account the aforementioned caveats. In addition, where an apparent significant difference in effect was observed a statistical test for interaction has been performed to assess whether there is a statistically significant interaction between the subgroup characteristic and the outcome of interest. This is achieved by calculating a value for delta (Δ) with 95% CIs and *p*-values as follows:

Δ = ln HR significant subgroup – ln HR other subgroup

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

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

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 Δ suggests that there is a significant interaction between the subgroup and the outcome.

In certain instances, particularly in trial 039, data were presented for both the evaluable patients and those patients included in the ITT population. Where possible, only ITT data has been used in the assessment of clinical effectiveness although, as previously discussed in the quality of clinical effectiveness studies section, it is not clear whether true ITT analyses were performed in either trial. 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 and not the groups to which they were finally assigned. ITT analyses should also include all dropouts and withdrawals that may have occurred. In this respect, they give more conservative estimates of clinical effects, which more closely resemble effects observed in clinical practice.

Further details of the individual trials and their outcomes are reported in appendix 8A.

Survival

Survival was reported in trial 039 in terms of median survival time (the time from initial drug administration to death), however, this is not the usual way to measure survival which is to use the time from randomisation. If there is a lag between randomisation and administration (which is often the case), this may introduce bias and consequently survival should not be measured in this way. Survival time was not defined in trial 30-49.

The median survival times from both trials are shown in *Table 6*. Both sets of data were based on Kaplan-Meier estimates and derived from the accompanying survival curves (see *Figures 3* and *4*). No statistically signficant differences in survival were reported for topotecan versus paclitaxel, or for topotecan versus caelyx. This is reflected in the Kaplan-Meier curves, which show little difference between the curves for the different drugs. A difference is observed in the curves in *Figure 3,* but this is only in the later stages of the curves where few participants remain in the analysis (i.e. > 600 days after randomisation). In *Figure 4,* paclitaxel appeared to have an improved survival rate compared with topotecan until about 36 weeks at which time the situation was reversed. After 64 weeks, there is little difference between the two drugs. The median survival times quoted in trial 039 are taken from the 50% survival point (the time (weeks) on the *x*-axis corresponding to 0.5 on the *y*-axis). This happens to be the point

TABLE 6 *Summary of the survival data based on ITT analyses*

Outcome	Topotecan versus paclitaxel[28]	Topotecan versus caelyx[59]
Median survival time (weeks) based on Kaplan-Meier estimates	Topotecan = 63.0 (95% CI, 46.6 to 71.9), paclitaxel = 53.0 (95% CI, 42.3 to 68.7); RR = 0.986, p = 0.931	Topotecan = 56.7, caelyx = 60.0; p = 0.34
HR	Not stated	HR = 1.121 (95% CI, 0.886 to 1.419)*

* *95% CIs were estimated from the original 90% CIs (quoted in the trial report) using the formula stated in the assessment of clinical effectiveness section*

at which the difference between the two drugs is at its maximum. However, as *Table 6* shows, this difference is still not statistically significant.

Trial 30-49 also performed a subgroup analysis (using Cox regression) of survival according to a variety of potentially important baseline patient characteristics, including age, Karnofsky performance status, treatment-free interval after first-line therapy, the presence/absence of bulky disease, Pt-sensitivity and the presence/absence of ascites (see *Table 7*). However, subgroup analyses can be very unreliable and misleading, particularly where the groups only contain small numbers of participants as in this instance, and should be thus treated with great caution.

Only one of the differences was significant as indicated by the CIs of the HR. This favoured caelyx over topotecan with respect to patients with Pt-sensitive (Pt-s) disease (108.0 weeks versus 71.1 weeks, respectively; HR = 1.720, 95% CI, 1.145 to 2.585), but, as already stressed, this finding should be interpreted with caution. The interaction test showed that $\Delta = 0.256$ (95% CI, 0.151 to 1.155, $p = 0.011$), suggesting that there is, however, a statistically significant interaction between Pt-sensitivity and survival, and consequently the observation that caelyx 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% CI, 0.886 to 1.419). The statistical significance of this adjusted HR was not stated although it is not likely to be

TABLE 7 *Summary of the subgroup analyses (using Cox regression) of the survival data based on the baseline characteristics for the topotecan versus caelyx trial*[59]

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

* *95% CIs were estimated from the original 90% CIs (quoted in the trial report) using the formula stated in the assessment of clinical effectiveness section*

significant considering the significance of the unadjusted HR. However, the adjusted HR does suggest that the general findings with regard to survival time were not significantly influenced by the identified baseline factors.

Response rate (including CR and PR)

Response rates can be a very subjective endpoint, particularly when the assessor is not blinded to the assigned intervention (as might be the case in trial 30-49). This is particularly the case in ovarian cancer trials where responses are very difficult to assess. Trial 039 does use independent blinded assessors and thus these data are potentially more reliable than the data gathered from trial 30-49. The subjective nature of response rates should be borne in mind when examining the following data. Response rates were defined similarly in both trials; a responder was a patient with at least a durable (complete or partial) response. A durable response was the patient's maximum confirmed response. A CR was defined as the complete disappearance of all known measurable and assessable disease on two separate measurements at least 4 weeks apart. A PR was defined as a 50% reduction in the sum of products of the perpendicular diameters of all measurable lesions for at least 4 weeks. Total response (TR) data included both CRs and PRs.

Figure 5 shows the data relating to the incidence of CR, PR and TR for both trial 039 (topotecan versus paclitaxel)[28,57] and trial 30-49 (topotecan versus caelyx).[59] RR data suggest that there are no statistically significant differences between topotecan and paclitaxel, or topotecan and caelyx with respect to the number of CRs, PRs and TRs. Trial 039 also reported TR data that took into account the nine patients who were randomised (five topotecan and four paclitaxel) but not included in the ITT analysis.[57] Again, this effect was not statistically significant (13.6% paclitaxel versus 18.8% topotecan; RR = 1.387, 95% CI, 0.776 to 2.492).

Response rate data were also presented in both trials according to the baseline response of the patients to first-line Pt therapy, that is, whether patients were Pt-s or Pt-refractory (Pt-r) (see *Figures 6* and *7*). This is thought to be an important factor in determining patients' response to treatment and their survival. *Figure 6* shows that there were no statistically significant differences between topotecan- and paclitaxel-treated patients

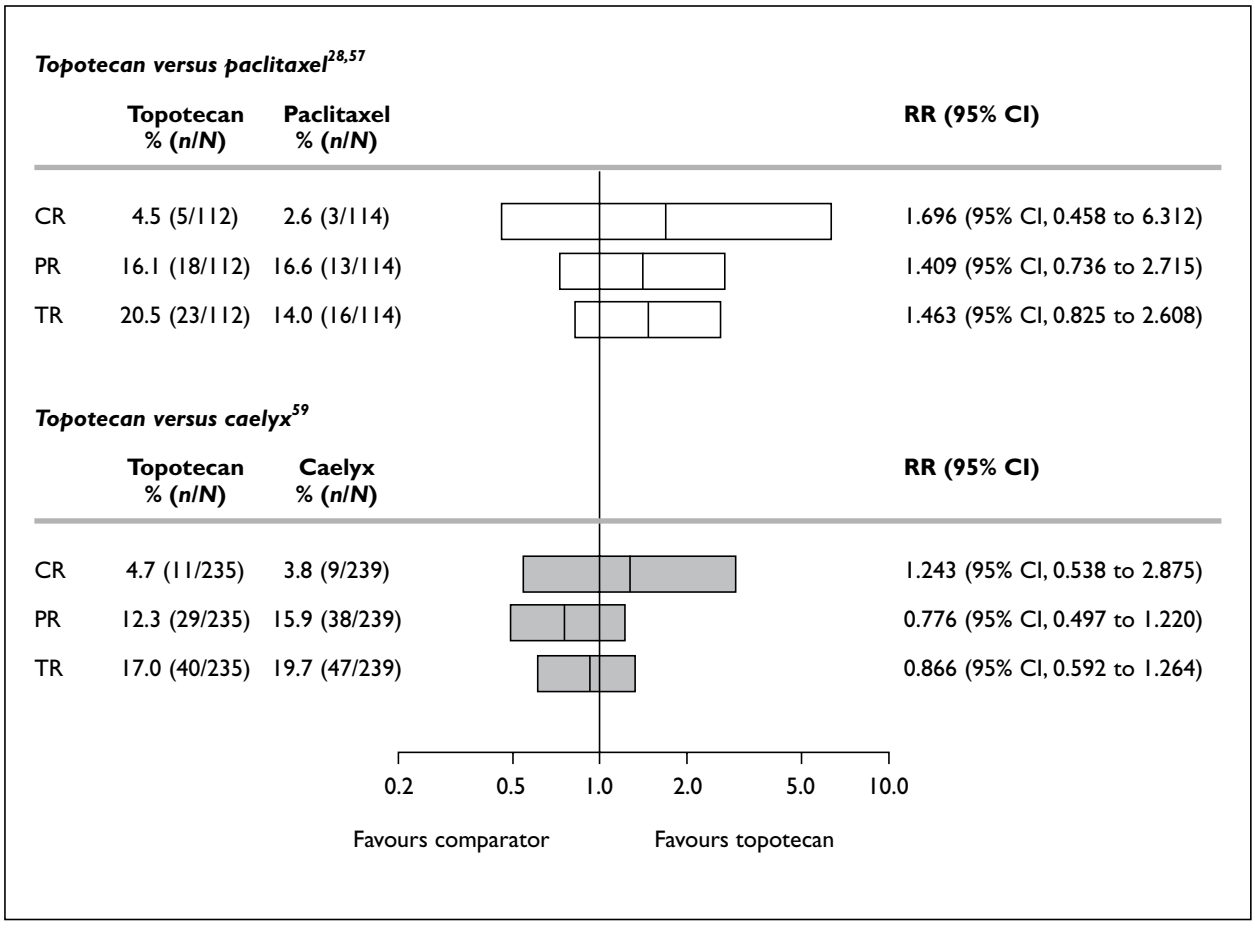


FIGURE 5 *RR of response rate*

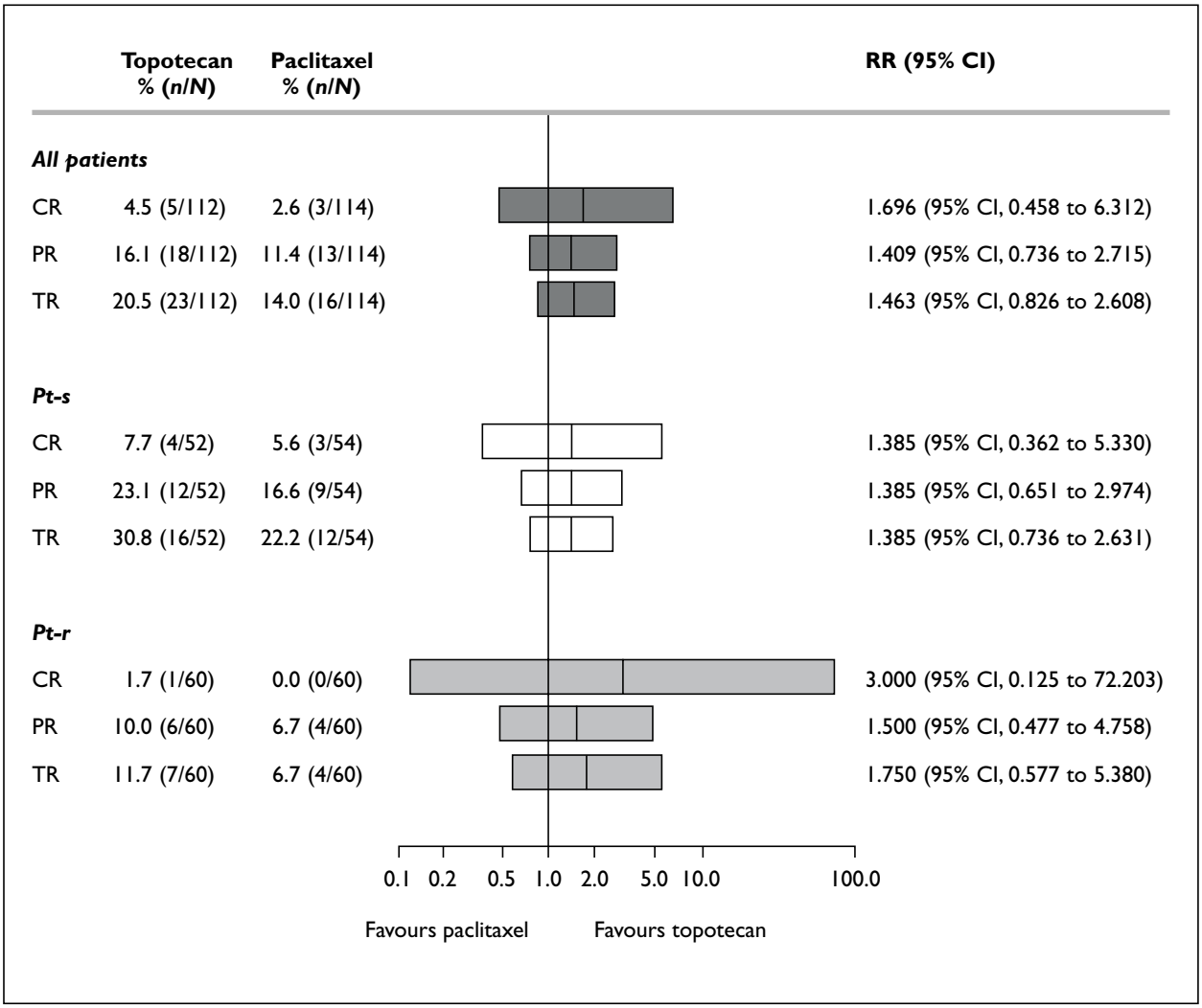


FIGURE 6 *RR of response rate for topotecan versus paclitaxel subgroup analysis (Pt-sensitivity).[28,57] Values were re-calculated from the classification used in trial 039 (refractory, early, interim and late relapse) to the traditionally used Pt-s and Pt-r subpopulations (i.e. refractory, early and interim relapse = refractory; late relapse = sensitive)*

in terms of CR, PR or TR for any of the patient groups (all patients, Pt-s and Pt-r) in trial 039, and *Figure 7* shows a similar lack of significant differences between topotecan and caelyx in trial 30-49.

In addition to carrying out subgroup analyses in terms of patients' baseline response to first-line Pt therapy, trial 039 also compared the CR, PR and TR rates of topotecan and paclitaxel in terms of other baseline characteristics relating to performance status and tumour size (see *Figures 8–10*). Both of these factors are potentially important in determining patients' response to treatment and survival. However, as previously mentioned, subgroup analyses should be interpreted with caution, particularly in this instance where the number of participants in the various subgroups is very small. *Figure 8* shows that there were no statistically significant differences between topotecan and paclitaxel in terms of CR rates in any of the subgroups analysed. Similarly, *Figure 9* showed that PR rates for the various different subgroups did not differ significantly between topotecan and paclitaxel. Finally, no statistically significant differences were again observed between topotecan and paclitaxel in terms of TR rate for any of the subgroups analysed in trial 039 (*Figure 10*).

Time to response

In both trials, time to response was considered a secondary and not a primary outcome measure and limited data were reported. Both trials used the median time to response. Trial 30-49 did not define how this outcome was measured. However, in trial 039, time to response was defined as the time from the first dose of study medication to the time of initial documented response. In the analysis reported here, trial 30-49 is assumed to have used an equivalent definition of time to

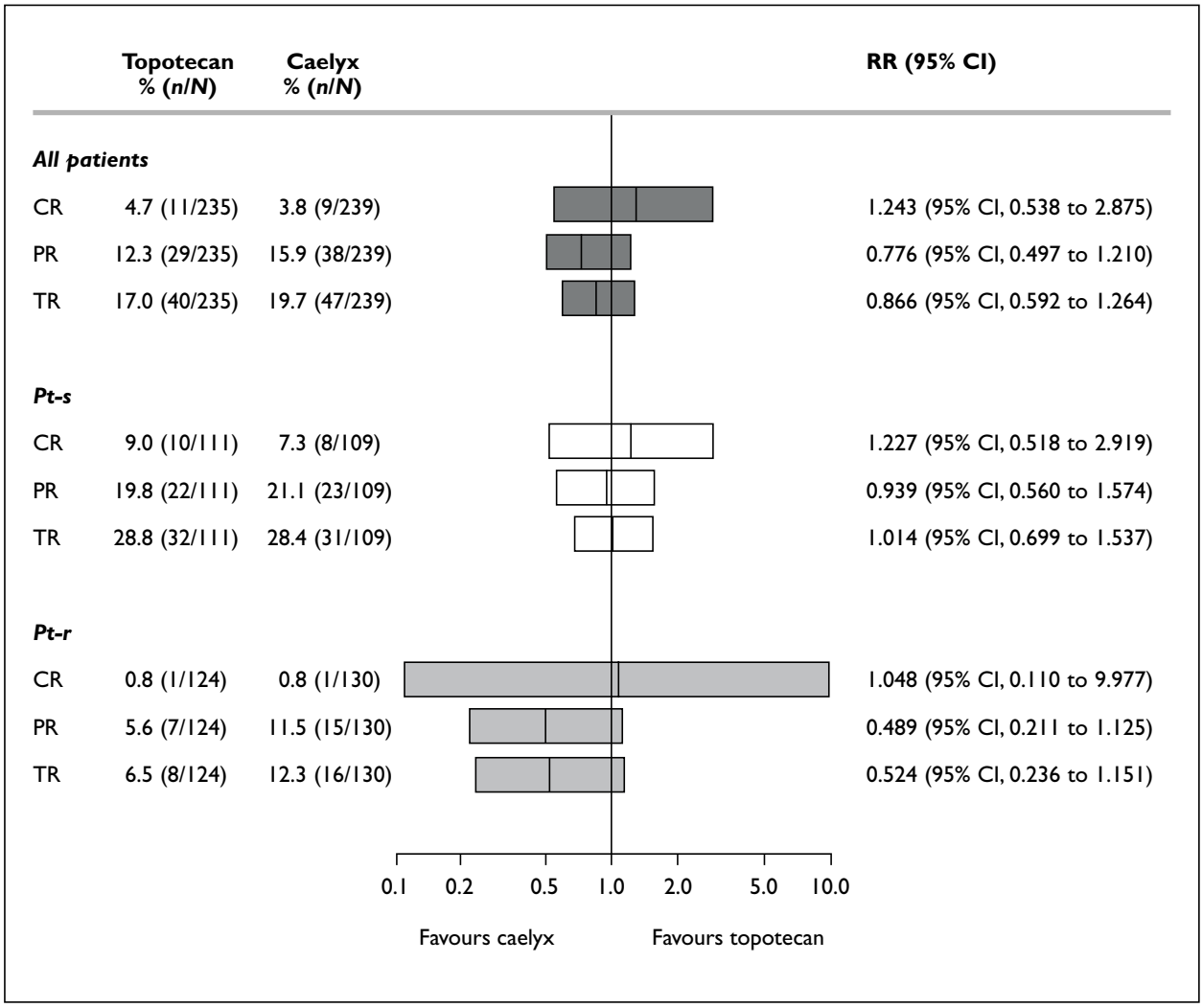


FIGURE 7 *RR of response rate for topotecan versus caelyx subgroup analysis (Pt-sensitivity)*[59]

response. A summary of the time to response data is presented in *Table 8*. Neither trial presented data in the form of HRs and survival curves. However, *p*-values indicated that there were no significant differences in median time to response for topotecan versus paclitaxel (trial 039) or topotecan versus caelyx (trial 30-49).

Duration of response

Duration of response was defined as the time from the initial documented response to the first sign of disease progression in trial 039. Progression was 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. Again, the values were expressed in the form of a median time and no outcome definition was provided in trial 30-49. In addition, few data were presented because this was not considered a major outcome. A summary of the duration of response data is presented in *Table 9*. Neither trial presented data in the form of survival curves and HRs. However, *p*-values indicated that no significant differences were observed between topotecan and paclitaxel, or between topotecan and caelyx in the median duration of response.

Time to progression

Time to progression was reported as the median time to progression and was considered a major outcome in both studies. In trial 30-49, median time to progression was defined as the primary outcome measure, although no specific definition of the term was provided. In trial 039, time to progression was defined as the time from first administration of the drug until the development of progressive disease or the administration of an alternate therapy, and progression was defined as

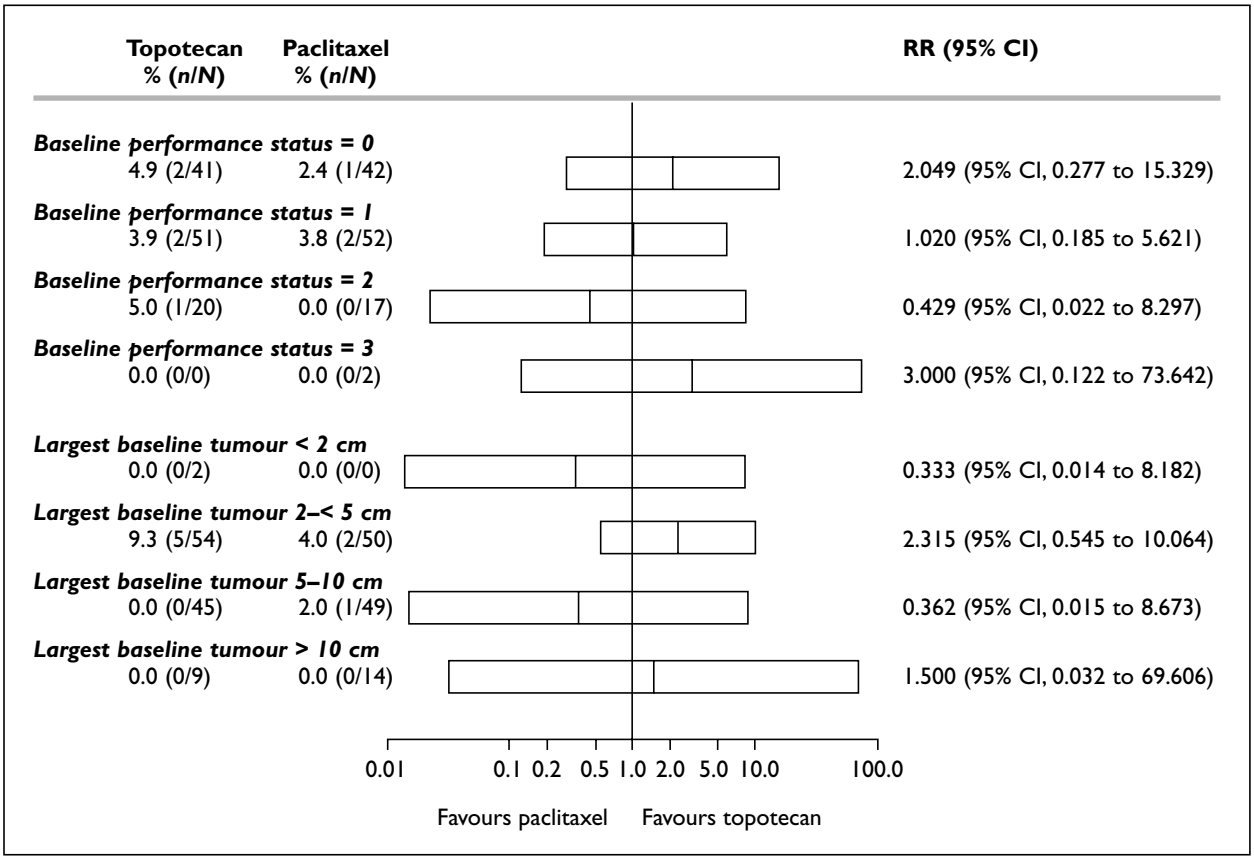


FIGURE 8 *RR of CR rate (subgroup analysis) of topotecan versus paclitaxel*[28,57]

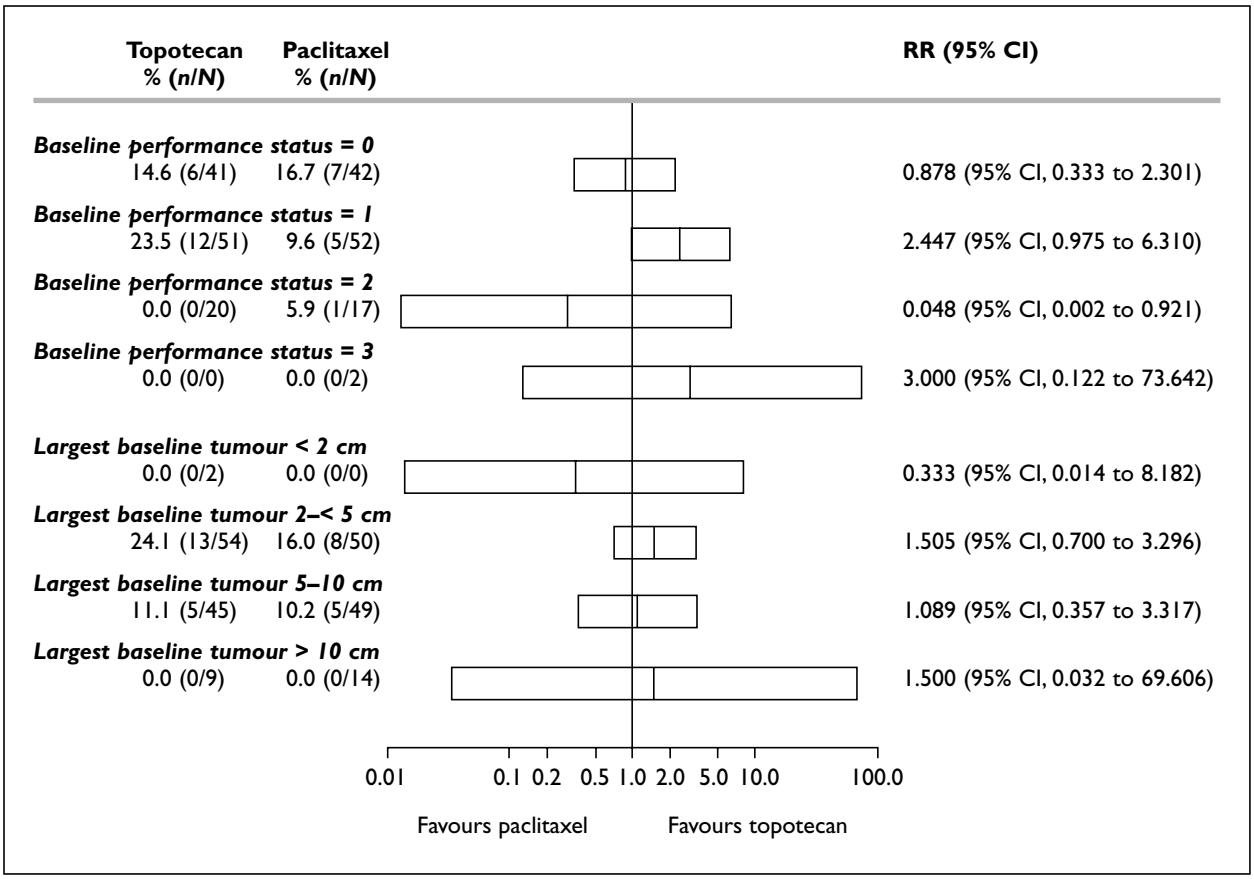


FIGURE 9 *RR of PR rate (subgroup analysis) of topotecan versus paclitaxel*[28,57]

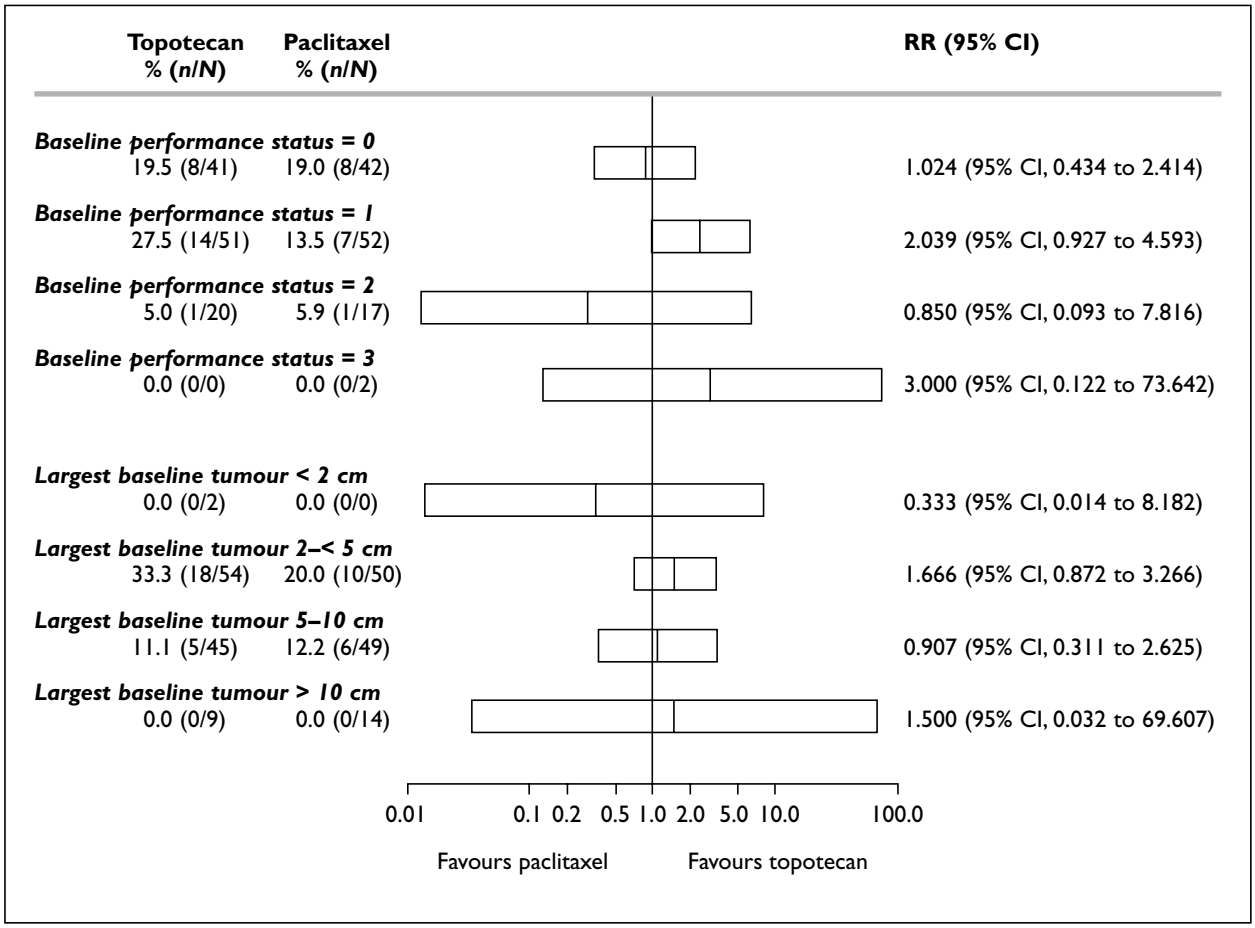


FIGURE 10 *RR of TR rate (subgroup analysis) of topotecan versus paclitaxel*[28,57]

TABLE 8 *Summary of the time-to-response data*

Outcome	Topotecan versus paclitaxel[57]	Topotecan versus caelyx[59]
Median time to response (weeks) based on Kaplan-Meier estimates	Topotecan = 7.6 (95% CI, 6.1 to 10.6; *n* = 23), paclitaxel = 6.0 (95% CI, 5.6 to 9.1; *n* = 16); RR = 0.615, *p* = 0.147	Topotecan = 8.1 (range 5.6–44.1), caelyx = 8.1 (range 4.0–28.4); *p* = 0.448*
HR	Not stated	Not stated

* *Log-rank test* p-*value*

TABLE 9 *Summary of the duration-of-response data*

Outcome	Topotecan versus paclitaxel[57]	Topotecan versus caelyx[59]*
Median duration of response (weeks) based on Kaplan-Meier estimates	Topotecan = 25.9 (95% CI, 22.1 to 32.9; *n* = 23), paclitaxel = 21.6 (95% CI, 16.0 to 34.0; *n* = 16); RR = 0.778; *p* = 0.476	Topotecan = 25.7 (range 7.0–55.1; *n* = 40), caelyx = 30.1 (range 5.0–90.4; *n* = 47); *p* = 0.891†
HR	Not stated	Not stated

* *Trial data as reported in trial report*[59]
† *Log-rank test* p-*value*

TABLE 10 *Summary of the time-to-progression data (ITT population)*

Outcome	Topotecan versus paclitaxel[57]	Topotecan versus caelyx[59]
Median time to progression (weeks) based on Kaplan-Meier estimates	Topotecan = 18.9 (95% CI, 12.1 to 23.6; *n* = 112), paclitaxel = 14.7 (95% CI, 11.9 to 18.3; *n* = 114); RR = 0.764, *p* = 0.072	Topotecan = 17.0 (*n* = 235), caelyx 16.1 (*n* = 239); *p* = 0.095*
HR	Not stated	1.176 (95% CI, 0.972 to 1.423)†

* *Log-rank test p-value*
† *95% CIs were estimated from the original 90% CIs (quoted in the trial report) using the formula stated in the assessment of clinical effectiveness section*

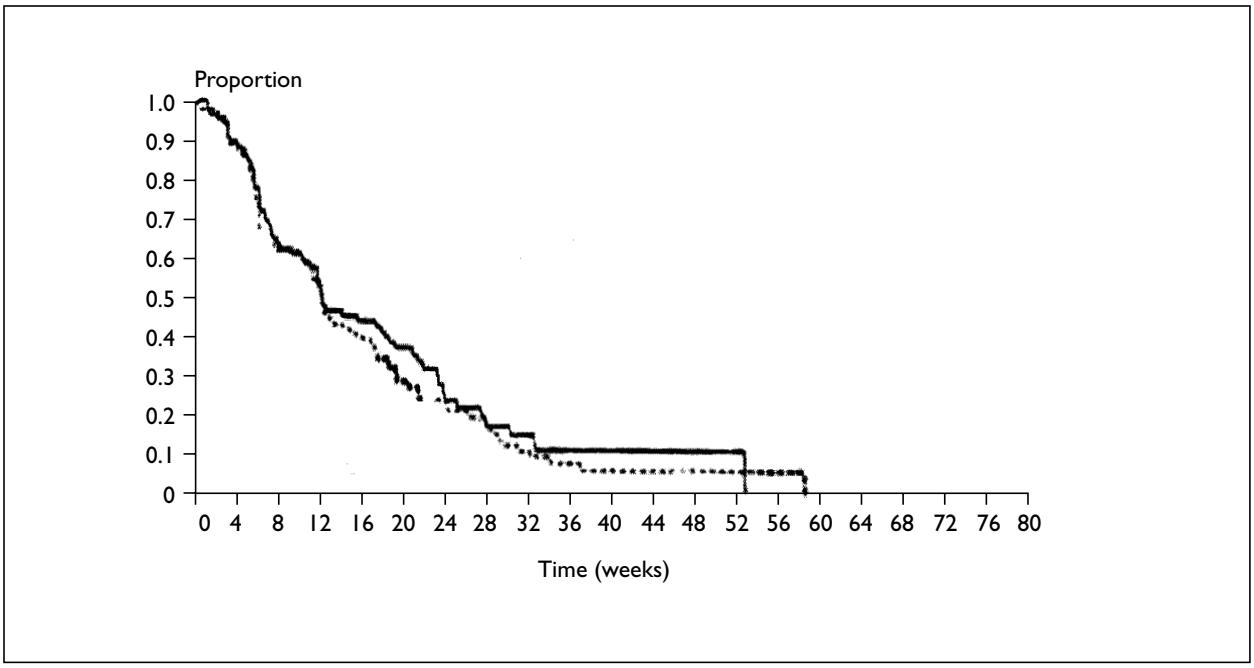


FIGURE 11 *Kaplan-Meier survival curves for time to progression for topotecan (——) versus paclitaxel (- - - -). Reproduced from SmithKline Beecham[57] with kind permission*

for the duration of response outcome. Measuring the time to progression from the administration of therapy and not from the time of randomisation may not be very reliable because it is subject to bias, especially since there is usually a variable lag period between the time of randomisation and the time of first drug administration in many cases. The results of trial 039 should, therefore, be interpreted with caution.

A summary of the median time-to-progression data is presented in *Table 10*. These data were based on Kaplan-Meier survival curves and the curve for trial 039 is shown in *Figure 11* (the curve for trial 30-49 was not provided). The *p*-values and 95% CIs (*Table 10*) showed no statistically significant differences in time to progression between topotecan and paclitaxel, or between topotecan and caelyx. Similarly, little difference is observed between the two Kaplan-Meier curves (*Figure 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, treatment-free interval after first-line therapy, the presence/absence of bulky disease, Pt-sensitivity and the presence/absence of ascites. These data are shown in *Table 11*. However, such subgroup analyses can be very unreliable and misleading, particularly when the groups contain only 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 topotecan and caelyx were

TABLE 11 *Subgroup analysis of time to progression for topotecan versus caelyx[59] (Cox regression analysis)*

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

* *95% CIs were estimated from the original 90% CIs (quoted in the trial report) using the formula stated in the assessment of clinical effectiveness section*

reported in the absence of ascites subgroup (22.4 versus 19.1 weeks; HR = 1.295, 95% CI, 1.026 to 1.635) and the Pt-s disease subgroup (28.8 versus 23.3 weeks; HR = 1.349, 95% CI, 1.018 to 1.788), and both results appeared to favour caelyx over topotecan. However, as already stressed, these findings should be interpreted with caution, and, indeed, the calculated interaction terms, that is, a measure of how independent the result is, suggest that neither the presence of Pt-s disease ($\Delta = 0.254$, 95% CI, –0.129 to 0.638; $p = 0.194$) nor the absence of ascites ($\Delta = 0.331$, 95% CI, –0.093 to 0.755; $p = 0.126$) were significantly associated with time to progression. The observed differences between topotecan and caelyx were, 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 it suggests that the general findings with regards to time to progression were not significantly influenced by the identified baseline factors.

QoL

Both of the effectiveness studies included QoL as an outcome using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-C30 (QLQ-C30). This questionnaire is self-administered and designed to measure health-related QoL. It consists of nine scales – one global QoL scale, five function scales (physical, role, emotional, cognitive and social) and three symptom scales

TABLE 12 *Changes in QLQ-C30 parameters from baseline to end of best response for trial 039[28] based on the patients who received randomised treatment*

QoL parameter	Topotecan			Paclitaxel		
	n	Median	Range	*n*	Median	Range
Physical functioning	93	0.0	–100– +80	98	0.0	–100– +80
Role functioning	93	0.0	–100– +100	97	0.0	–100– +100
Emotional functioning	85	8.0	–83– +75	91	8.0	–100– +75
Cognitive functioning	85	0.0	–67– +50	90	0.0	–67– +50
Social functioning	89	0.0	–83– +67	95	0.0	–100– +100
Global QoL	89	–8.0	–58– +83	95	0.0	–67– +50
Fatigue	90	0.0	–78– +89	94	0.0	–67– +67
Nausea/vomiting	90	0.0	–100– +100	94	0.0	–83– +50
Pain	91	0.0	–100– +67	93	0.0	–100– +67
Appetite loss	88	0.0	–100– +67	89	0.0	–67– +100
Constipation	89	0.0	–100– +67	91	0.0	–100– +67
Diarrhoea	88	0.0	–67– +100	94	0.0	–100– +33
Dyspnoea	89	0.0	–67– +67	94	0.0	–67– +67
Financial impact	89	0.0	–67– +100	94	0.0	–100– +67
Sleep disturbance	89	0.0	–100– +100	93	0.0	–100– +100

(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.

During trial 039, QoL data were collected at baseline and on days 8 and 15 of each course of treatment, as well as immediately prior to each subsequent dose of chemotherapy. Changes in QoL were estimated from baseline to the end of the best response (defined as within 7 days of a patient's lesion assessment date of best response) for each of the individual QLQ-C30 parameters. Very little change was observed from baseline to follow-up for topotecan or paclitaxel, and there was also little difference when comparing the two agents. The clinical relevance of the minimal changes that were observed is unclear, but is unlikely to be significant (see *Table 12*).

In trial 30-49, QoL was measured using the QLQ-C30 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 caelyx every 4 weeks), the first time point at which data could be gathered from the two study groups was week 12. At this point, no more than 50% of patients in either group provided QoL data. Scores were awarded for each of the individual QoL parameters and, in this case, the data were analysed overall and in terms of baseline Pt-sensitivity (i.e. Pt-r and Pt-s patients). However, the scores for the single QoL questions (dyspnoea, sleep disturbance, appetite loss, constipation, diarrhoea and financial impact) were not presented.

At 12 weeks of follow-up, 23.4% (55/235) of topotecan patients and 28.5% (68/239) of caelyx patients had improved or stable global QoL scores, and 20.4% (48/235) of topotecan- and 20.5% (49/239) of caelyx-treated patients 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 Pt-sensitivity at baseline is shown in *Figures 12–14*, along with the calculated corresponding RRs. Despite the minimal differences overall in patient QoL between topotecan and caelyx , 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 12*). This significant difference favouring topotecan was maintained in the Pt-s subgroup (RR = 1.54, 95% CI, 1.211

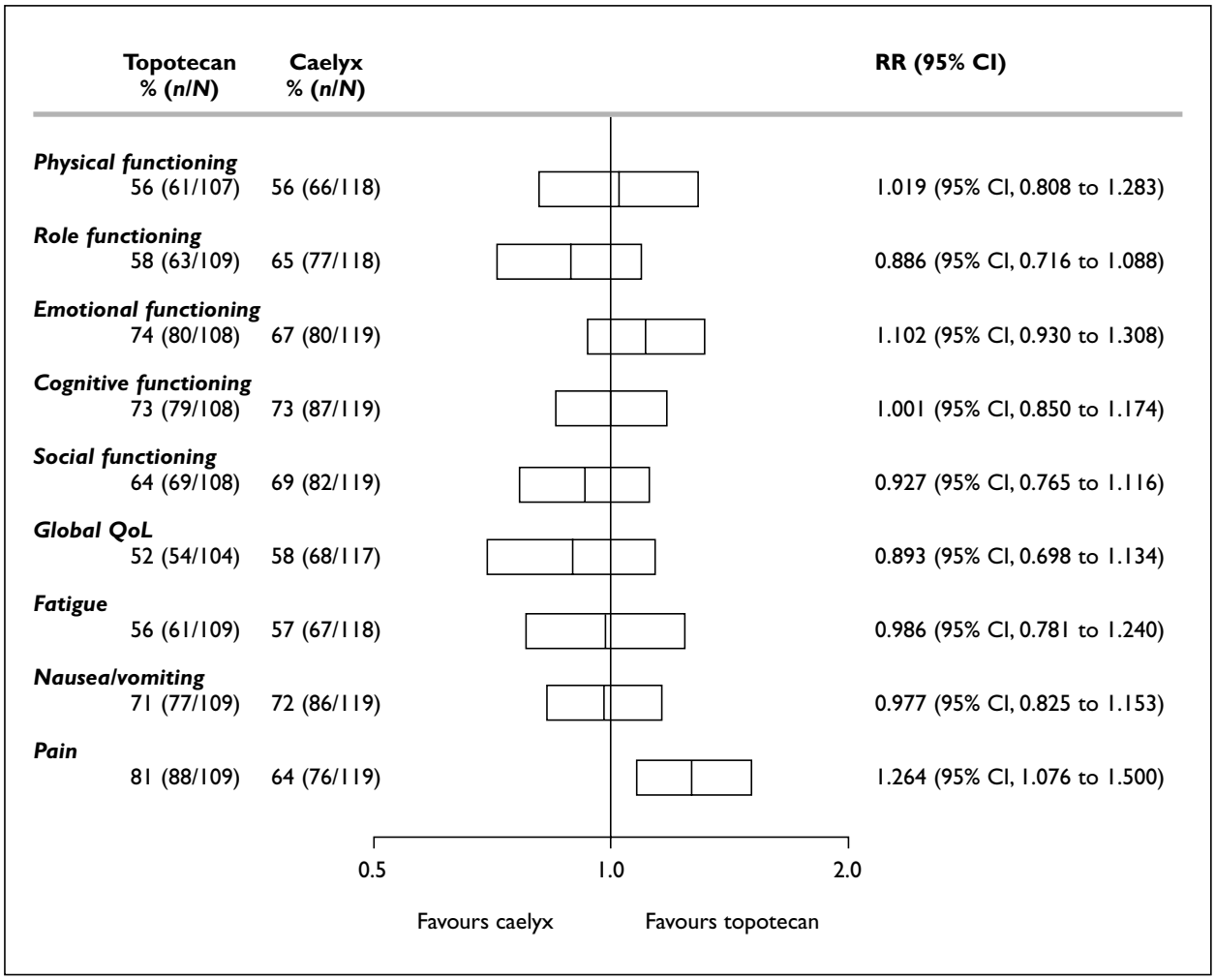


FIGURE 12 *RR of number of patients with a maintained or improved QoL score at 12 weeks of follow-up (based on number of patients remaining) – all patients, topotecan versus caelyx*[59]

to 2.023; see *Figure 13*). However, the clinical relevance of this observation was unclear.

Adverse effects

Extensive data on adverse effects were gathered in both studies. However, only those treatment-related effects experienced by at least 10% of patients are discussed in this review. In both cases, the data presented are based on the ITT populations as defined by the individual studies. Where absolute numbers of patients suffering from an effect were reported, this data has been used to calculate RRs with 95% CIs. Neither of the trials reported their own RRs and where absolute numbers were uncertain only percentage values have been quoted.

Trial 30-49 reported a number of adverse effects for both topotecan and caelyx.[58,59] The major adverse effects for topotecan were as previously reported in the British National Formulary,[27] mainly centring on haematological problems, such as neutropenia, thrombocytopenia and anaemia. All of these conditions relate to the reduction of specific blood cells within the body, such as neutrophils, thrombocytes and red blood cells/erythrocytes, which affects the body's ability to fight infection, coagulate blood and carry oxygen, respectively. In addition, alopecia was also a common adverse effect of topotecan treatment.

In contrast, haematological adverse effects were mild/moderate in caelyx-treated patients and Palmar–Plantar erythorodyseasthesia (PPE) was a major toxicity. 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 not known, but it is believed to be a result of microtrauma within tissue leading to leaky blood vessels.

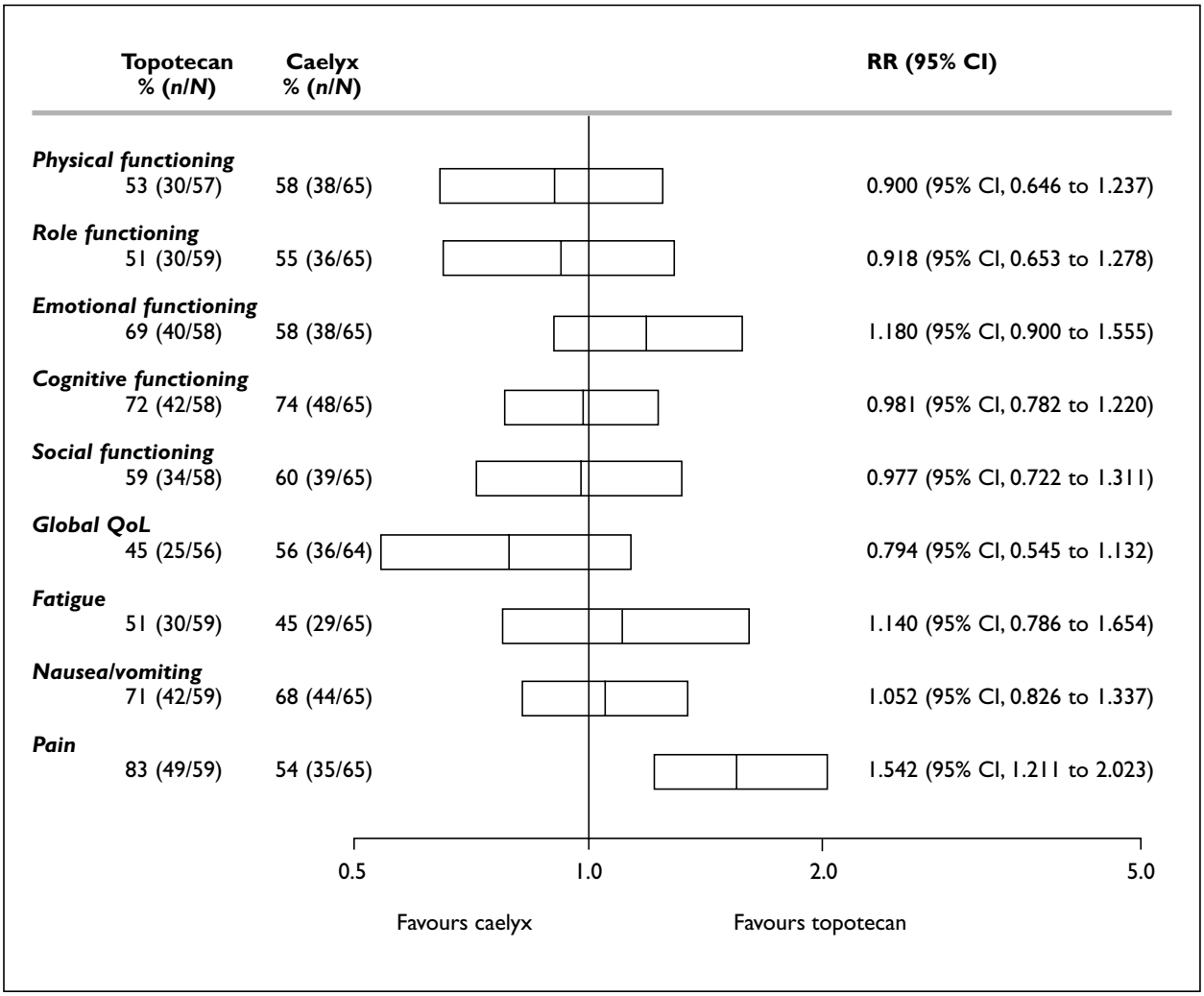


FIGURE 13 *RR of number of patients with a maintained or improved QoL score at 12 weeks of follow-up (based on number of patients remaining) – Pt-s patients, topotecan versus caelyx*[59]

Overall, in trial 30-49, 16% (39/239) of caelyx-treated patients and 12% (29/235) of topotecan-treated patients discontinued treatment due to adverse effects (RR = 0.756, 95% CI, 0.485 to 1.175). In addition, two patients treated with topotecan died as a result of treatment-related grade 3/4 neutropenia. No treatment-related deaths were recorded in those patients treated with caelyx. *Table 13* and *Figure 15* show further details of the adverse effects experienced in the two study groups.

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 caelyx-treated patients: 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%; 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). In the topotecan group, 29.1 and 57.8% of patients required G-CSF and transfusions, respectively, compared with 4.6 and 14.9% of patients in the caelyx group. In addition, constipation, diarrhoea, fever and asthenia were also significantly more frequent in the topotecan group.

In contrast, the main toxicities associated with caelyx were PPE, stomatitis, mucous membrane disorder and skin rashes. PPE and stomatitis represented the greatest problems with the incidences being significantly higher in the caelyx-treated compared with the topotecan-treated patients (PPE: 49 versus 1%; RR = 0.017,

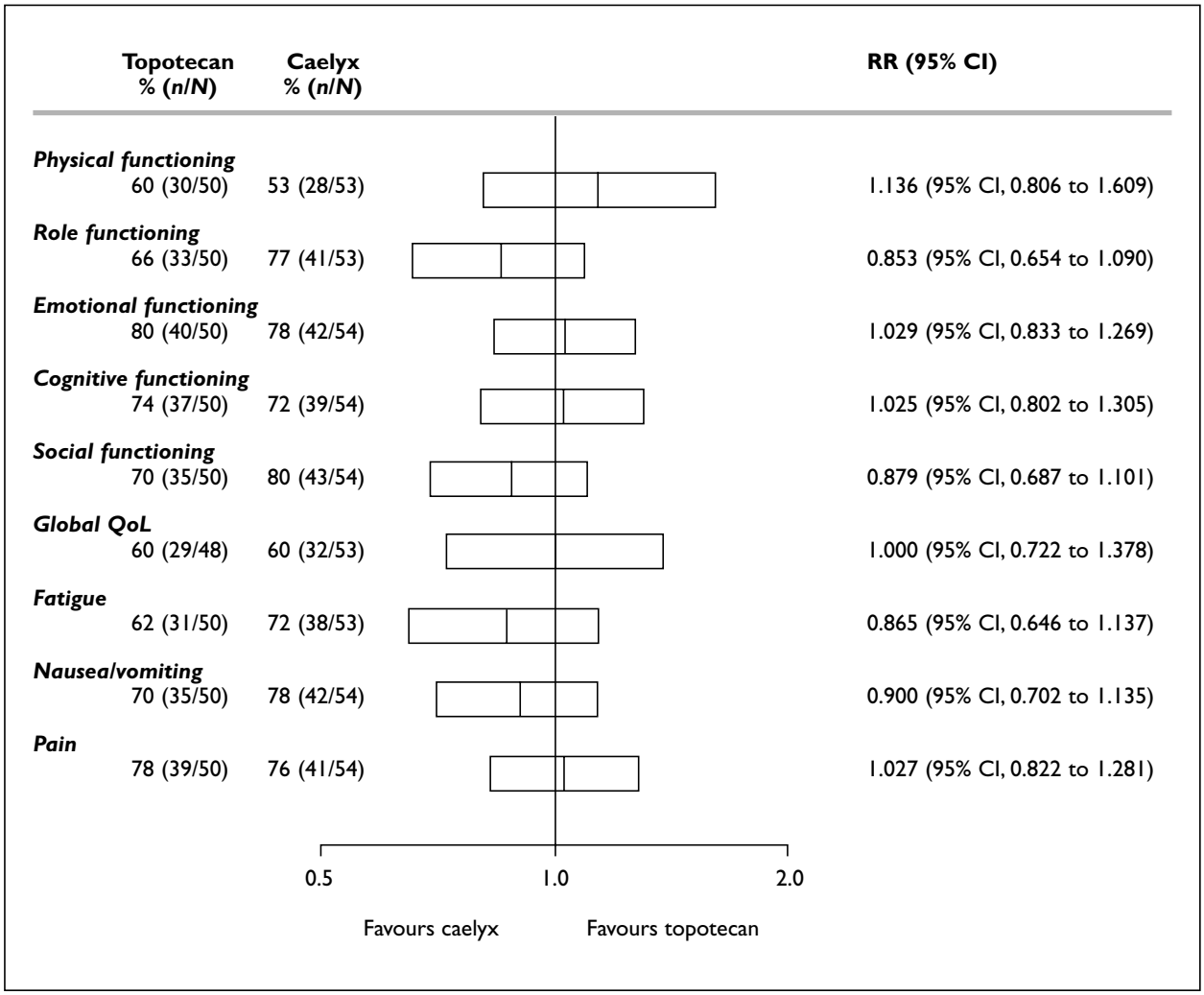


FIGURE 14 *RR of number of patients with a maintained or improved QoL score at 12 weeks of follow-up (based on number of patients remaining) – Pt-r patients, topotecan versus caelyx*[59]

95% CI, 0.005 to 0.063; stomatitis: 40 versus 15%; RR = 0.375, 95% CI, 0.265 to 0.525). PPE was classed as severe in 23% of caelyx-treated patients 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 disorder (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 caelyx-treated compared with topotecan-treated patients.

Data from trial 039 (see *Figure 16*) showed that, again, leukopenia, neutropenia, anaemia, thrombocytopenia and nausea/vomiting were common adverse effects of treatment with topotecan. These adverse effects were significantly more likely to occur in patients treated with topotecan than those treated with paclitaxel. In addition, constipation was more likely to occur in the topotecan-treated patients. Grade 4 events are classified as severe adverse events, and grade 4 neutropenia was experienced by 79% of patients in the topotecan group (23% in the paclitaxel group), grade 4 leukopenia by 34% (3% in the paclitaxel group) and grade 4 thrombocytopenia by 25% (2% in the paclitaxel group). The occurrence of grade 4 anaemia was similar in both groups (4 versus 3% with topotecan and paclitaxel, respectively).

Although a higher percentage of patients in the paclitaxel group suffered from abdominal pain, pain, alopecia and haematuria, alopecia (93 versus 77%; RR = 0.826, 95% CI, 0.728 to 0.920) was the only adverse effect that was significantly more likely to occur in paclitaxel-treated compared to topotecan-treated patients. In addition, a number of adverse effects were observed in the paclitaxel group that were only observed in < 10% of topotecan-treated patients, including myalgia, arthralgia, neuropathy and paraesthesiae. Due to the fact that absolute numbers of affected patients

were not reported for the topotecan group, RR estimates could not be calculated. However, it would appear that these toxic effects were more commonly associated with paclitaxel. In contrast, no absolute numbers were reported for skin rash and dyspnoea in the paclitaxel group because < 10% of the patients suffered from these adverse events. It could, again, be assumed that topotecan is more commonly associated with these effects compared with paclitaxel.

Summary of clinical effectiveness data

Only two clinical effectiveness studies were identified (709 participants in total) and both compared topotecan with different comparators. There was thus limited evidence available on which to base an assessment of clinical effectiveness. There was no clear evidence of any major statistically significant differences between topotecan and paclitaxel, or between topotecan and caelyx for median survival, response rate, median time to response, median duration of response and QoL (see *Table 14*). The only apparently statistically significant differences were observed in terms of subgroup analyses. However, the validity of these analyses is questionable given the small numbers of patients involved. Tests of interaction performed for the three statistically significant differences observed in the subgroup analyses revealed that only one was associated with a significant interaction between the subgroup characteristic and the effectiveness outcome, which was the improvement in survival of Pt-s patients treated with caelyx versus topotecan. However, this significant interaction was not borne out for the subgroup analyses. Caelyx did show a significantly greater response compared with topotecan for Pt-s 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 with only one of the QoL subscale scores: more patients in the topotecan group compared with the caelyx group had a maintained or improved pain score at 12 weeks of follow-up for all patients (81 versus 64%; RR = 1.264; 95% CI, 1.076 to 1.500) and Pt-s patients (83 versus 54%; RR = 1.54; 95% CI, 1.211 to 2.023). However, the clinical relevance of these differences is unclear.

Although no significant differences were found in the main effectiveness outcomes, differences were apparent in treatment-related adverse effects. Statistically significant differences were observed between topotecan and paclitaxel, or between topotecan and caelyx. Topotecan administration was commonly associated with haematological toxicities, including neutropenia, leukopenia, anaemia and thrombocytopenia. Alopecia and nausea/vomiting were also common adverse effects associated with topotecan. All of the aforementioned adverse effects were significantly associated with topotecan compared with caelyx: neutropenia (81 versus 35%; RR = 2.313, 95% CI, 1.938 to 2.793), anaemia (72 versus 36%; RR = 2.022, 95% CI, 1.683 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), 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). A similar significant increase in these adverse effects was also observed with topotecan compared to with paclitaxel: neutropenia (97 versus 85%; RR = 1.144, 95% CI, 1.060 to 1.261), anaemia (99 versus 88%; RR = 1.130, 95% CI, 1.063 to 1.233), thrombocytopenia (96 versus 18%; RR = 5.235, 95% CI, 3.628 to 7.803), leukopenia (98 versus 85%; RR = 1.154, 95% CI, 1.074 to 1.271), nausea (80 versus 34%; RR = 2.323, 95% CI, 1.794 to 3.082) and vomiting (65 versus 30%; RR = 2.123, 95% CI, 1.578 to 2.912). The only exception was the occurrence of alopecia, which was more frequently observed with paclitaxel (77 versus 93%; RR = 0.826, 95% CI, 0.728 to 0.920).

Caelyx-treated patients suffered from a significant increase in 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 disorder (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. Paclitaxel was associated with a significant increase in alopecia (93 versus 77%; RR = 0.826, 95% CI, 0.728 to 0.920), and arthralgia, myalgia, neuropathy, paraesthesiae, skeletal pain and flushing were also increased but the RRs could not be calculated.

In summary, there is no clear evidence of major differences in clinical effectiveness between topotecan and paclitaxel, or topotecan and caelyx overall, although there appear to be statistically significant differences between the drugs in terms of their adverse effects.

Assessment of cost-effectiveness

A brief summary of the three economic evaluations included in this review is given in *Table 15*. Only one of the evaluations was published (two publications) and the other evaluations were submitted as part of company submissions and were confidential. All three evaluations examined the use of topotecan in advanced ovarian cancer patients (FIGO stage III/IV) who had failed first-line therapy. The published study takes the form of a CCA (although the authors state that it is a CMA) from the perspective of the USA Medicare system (third-party payer) and out-of-pocket patient costs,[60,61] and topotecan is compared with paclitaxel, altretamine and epotoside. The two confidential evaluations are from the perspective of the UK NHS, and one is a CMA[62] and the other is a CEA.[28] Both evaluations compare topotecan with a single comparator, paclitaxel[28] or caelyx.[62]

The published study used a systematic review to identify a number of published studies, which were used as a source of clinical effectiveness data (see *Table 16*). Clinical outcomes included response rate (CR and PR), presence of progressive disease, median time to progression, median overall survival and the level of adverse effects. Data relating to these outcomes are presented in appendix 8B. On the basis of these data, equivalent clinical effectiveness was assumed. However, the data presented did not support this assumption of equivalence, which leads to a number of issues as have been previously discussed in the assessment of study quality (see the quality of economic evaluations section).

Overall, in terms of Medicare reimbursements per patient treated, topotecan was the most expensive of the four drugs ($18,598), followed by paclitaxel ($15,684), etoposide ($7655) and lastly altretamine ($0). Altretamine is an oral formulation and, as such, is not included by Medicare reimbursement policies, and consequently the out-of-pocket patient costs for this drug were the highest ($4477). The patient out-of-pocket expenses for the remaining drugs were $83 for paclitaxel, $66 for etoposide and $37 for topotecan. In summarising their findings, the authors concluded that intravenous agents may be used over more expensive oral agents where efficacy and toxicity are equivalent. However, the authors identify a patient preference for oral drug formulations. Overall, the matrix grading (see the analysis strategy section and *Figure 1*) used to indicate the direction and magnitude of the cost-effectiveness data reported in the evaluation was unclear.

The CMA based on trial 30-49 used clinical effectiveness data from the trial and 1999/2000 cost data from UK sources (MIMS, Chartered Institute of Public Finance and Accountancy and UK hospital/cancer centre tariffs; see *Table 16*). No discounting was applied due to the short time horizon because advanced ovarian cancer patients, even when treated with second-line therapy, have a poor survival rate. The details of the CEA were commercial in confidence and have, therefore, been excluded. However, the total cost of caelyx was estimated to be Euros 16,266 (£9979) per person (regardless of whether individuals responded to treatment) versus Euros 22,858 (£14,023) for topotecan.

The final economic evaluation from SmithKline Beecham conducted a modelled CEA using clinical effectiveness data from trial 039 and 2000 cost data from UK sources (MIMS and NHS trust data; see *Table 16*). See *Table 17* for further details. However, because the CEA and the sensitivity analysis for topotecan versus paclitaxel were considered to be commercial in confidence, the details are omitted.

Further details of all three evaluations are reported in appendix 8B.

Costs/savings to the NHS

The two main economic evaluations both reported budgetary implications for the NHS.[28,62] However, only one of the evaluations focused on the implications of treatment with topotecan,[28] but the details of this are commercial in confidence and thus omitted. It is unclear whether the authors' estimation of the numbers of eligible patients is reasonable, but the cost data on which the overall costs are based would appear to be reasonable.

Summary of economic data

Overall, of the three economic evaluations that were identified, two were based on confidential company submission data[28,62] and the third was published in two separate, almost identical, publications.[60,61] Two of the evaluations were described as CMAs, but one was, in fact, a CCA.[60,61] Both evaluations focused their findings only on costs[60–62] and the final evaluation was a CEA.[28] The published CCA compared topotecan, paclitaxel, etoposide and altretamine, implying equivalent effectiveness data. However, the effectiveness data did not reflect this position. In addition, the evaluation was based on the USA third-party payer system and costs were presented in US$, therefore, overall, the analysis was not relevant to the UK NHS or this review. The two remaining studies were relevant and compared topotecan with paclitaxel (CEA),[28] and topotecan to caelyx (CMA).[62]

In summary, topotecan was shown to be cost-effective compared with paclitaxel (£32,513 versus £46,186 per person in terms of any response (CR or PR), incremental cost-effectiveness = £3065) in all respects apart from cost per time without toxicity or symptoms (TWIST), but less cost-effective compared with caelyx (£14,023 versus £9979 per person regardless of whether the patient responded) for the second-line treatment of advanced ovarian cancer patients. Overall, however, it is difficult to make direct comparisons between the two studies in terms of their cost findings. The studies use different designs, different time horizons for the cost analyses and the findings are presented in terms of costs per person for only patients who respond in one study (topotecan versus paclitaxel) and costs per person regardless of whether they respond in the other study (topotecan versus caelyx).

TABLE 13 *RRs of treatment-related adverse effects based on the ITT populations (observed in ≥ 10% of patients)*

Adverse effect	Topotecan versus paclitaxel[57]		Topotecan versus caelyx[59]	
	Topotecan	Paclitaxel	Topotecan	Caelyx
Leukopenia (all grades)	110/112 (98%)	97/114 (85%)	149/235 (63%)	87/239 (36%)
Neutropenia (all grades)	109/112 (97%)	97/114 (85%)	191/235 (81%)	84/239 (35%)
Thrombocytopenia (all grades)	108/112 (96%)	21/114 (18%)	152/235 (65%)	31/239 (13%)
Anaemia (all grades)	111/112 (99%)	100/114 (88%)	169/235 (72%)	85/239 (36%)
Alopecia (all grades)	86/112 (77%)	106/114 (93%)	115/235 (49%)	38/239 (16%)
Stomatitis (all grades)	28/112 (25%)	17/114 (15%)	35/235 (15%)	95/239 (40%)
PPE (all grades)	Not stated	Not stated	2/235 (1%)	117/239 (49%)
Nausea (all grades)	89/112 (80%)	39/114 (34%)	127/235 (54%)	85/239 (36%)
Vomiting (all grades)	73/112 (65%)	35/114 (30%)	81/235 (35%)	58/239 (24%)
Fatigue (all grades)	47/112 (42%)	36/114 (32%)	Not stated	Not stated
Constipation (all grades)	50/112 (45%)	35/114 (31%)	58/235 (25%)	33/239 (14%)
Diarrhoea (all grades)	48/112 (43%)	44/114 (39%)	49/235 (21%)	28/239 (12%)
Fever (all grades)*	31/112 (28%)	21/114 (18%)	49/235 (21%)	28/239 (12%)
Asthenia (all grades)	26/112 (32%)	15/114 (13%)	104/235 (44%)	75/239 (31%)
Arthralgia (all grades)	Not stated	39/114 (34%)	Not stated	Not stated
Myalgia (all grades)	Not stated	33/114 (29%)	Not stated	Not stated
Neuropathy (all grades)	Not stated	20/114 (18%)	Not stated	Not stated
Paraesthesiae (all grades)	Not stated	36/114 (32%)	Not stated	Not stated
Abdominal pain (all grades)	34/112 (30%)	45/114 (40%)	29/235 (12%)	20/239 (8%)
Skeletal pain (all grades)	Not stated	19/114 (17%)	Not stated	Not stated
Flushing (all grades)	Not stated	16/114 (14%)	Not stated	Not stated
Mucous membrane disorder (all grades)	Not stated	Not stated	7/235 (3%)	33/239 (14%)
Anorexia (all grades)	20/112 (18%)	16/114 (14%)	32/235 (14%)	26/239 (11%)
Skin rash (all grades)	13/112 (12%)	Not stated	18/235 (8%)	58/239 (24%)
Dyspnoea (all grades)	27/112 (24%)	Not stated	Not stated	Not stated
Headache (all grades)	22/112 (20%)	16/114 (14%)	Not stated	Not stated
Back pain (all grades)	19/112 (17%)	17/114 (15%)	Not stated	Not stated
Urinary tract infections (all grades)	18/112 (16%)	Not stated	Not stated	Not stated
Pain (all grades)	17/112 (15%)	22/114 (19%)	Not stated	Not stated
Dyspepsia (all grades)	14/112 (13%)	13/114 (11%)	Not stated	Not stated
Anxiety (all grades)	13/112 (12%)	Not stated	Not stated	Not stated
Coughing (all grades)	13/112 (12%)	13/114 (11%)	Not stated	Not stated
Haematuria (all grades)	13/112 (12%)	15/114 (13%)	Not stated	Not stated
Upper respiratory tract infections (all grades)	13/112 (12%)	13/114 (11%)	Not stated	Not stated
Hypokalaemia	12/112 (10.7%)	Not stated	Not stated	Not stated

* *Excludes reports of the verbatim term febrile neutropenia*

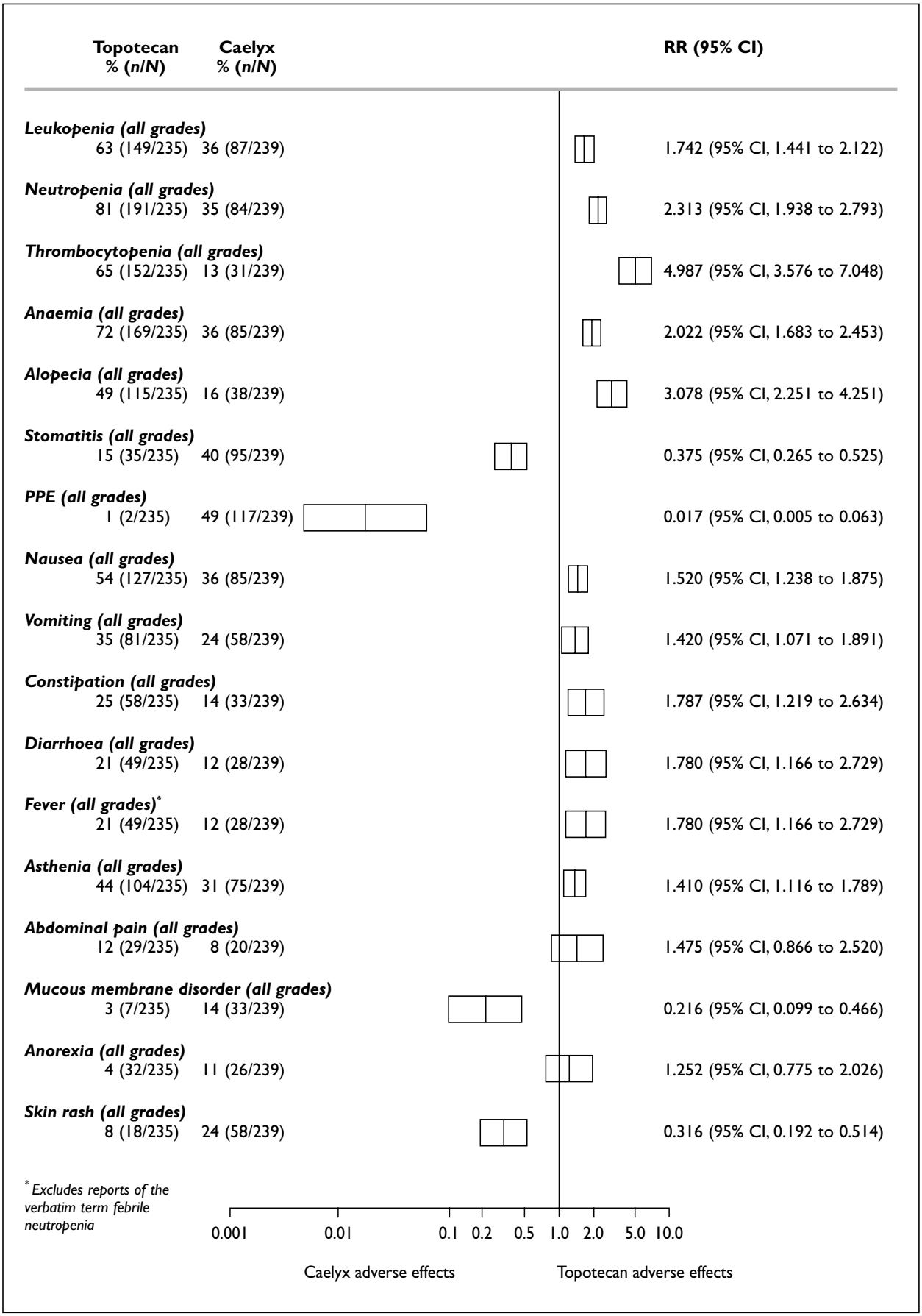


FIGURE 15 *RRs of treatment-related adverse effects for topotecan versus caelyx*[59]

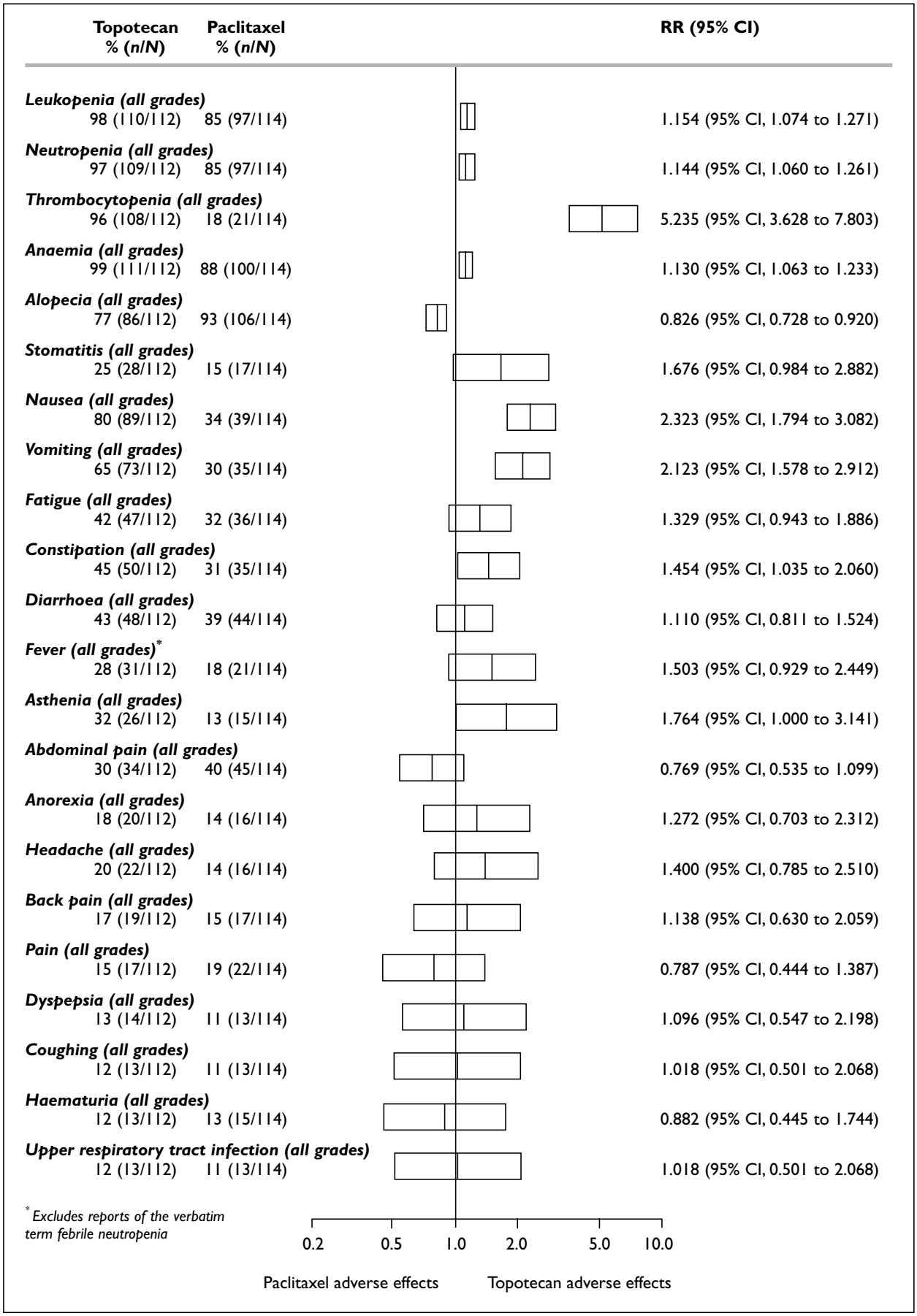


FIGURE 16 *RRs of treatment related adverse effects for topotecan versus paclitaxel*[57]

TABLE 14 *Summary of clinical effectiveness findings*

Outcome	Comparators	Result
Survival	Topotecan versus paclitaxel	No statistically significant differences
	Topotecan versus caelyx	No statistically significant differences except for the Pt-s subgroup, which favoured caelyx (108.0 weeks versus 71.1 weeks; HR = 1.720, 95% CI, 1.145 to 2.585; Δ = statistically significant)
Response rate	Topotecan versus paclitaxel	No statistically significant differences
	Topotecan versus caelyx	No statistically significant differences
Time to response	Topotecan versus paclitaxel	No statistically significant differences
	Topotecan versus caelyx	No statistically significant differences
Duration of response	Topotecan versus paclitaxel	No statistically significant differences
	Topotecan versus caelyx	No statistically significant differences
Time to progression	Topotecan versus paclitaxel	No statistically significant differences
	Topotecan versus caelyx	No statistically significant differences except for the Pt-s and the absence of ascites subgroups, which favoured caelyx, although the Δ values for these interactions were not statistically significant
QoL	Topotecan versus paclitaxel	No statistically significant differences
	Topotecan versus caelyx	Favoured topotecan over caelyx, with the percentage of patients with a maintained or improved pain subscale score at 12 weeks in all patients being 81 versus 64% (RR = 1.264, 95% CI, 1.076 to 1.500) and in Pt-s patients being 83 versus 54% (RR = 1.54, 95% CI, 1.211 to 2.023)
Adverse effects	Topotecan versus paclitaxel	***The following were reported as statistically significant:*** *Favoured topotecan over paclitaxel* Alopecia (77 versus 93%; RR = 0.826, 95% CI, 0.728 to 0.920). Also incidence of myalgia, arthalgia, neuropathy, and paraesthesiae (no RR calculated) *Favoured paclitaxel over topotecan* Neutropenia (97 versus 85%; RR = 1.144, 95% CI, 1.060 to 1.261); anaemia (99 versus 88%; RR = 1.130, 95% CI, 1.063 to 1.233); thrombocytopenia (96 versus 18%; RR = 5.235, 95% CI, 3.628 to 7.803); leukopenia (98 versus 85%; RR = 1.154, 95% CI, 1.074 to 1.271); nausea (80 versus 34%; RR = 2.323, 95% CI, 1.794 to 3.082); vomiting (65 versus 30%; RR = 2.123, 95% CI, 1.578 to 2.912)
	Topotecan versus caelyx	***The following were reported as statistically significant:*** *Favoured caelyx over topotecan* Neutropenia (81 versus 35%; RR = 2.313, 95% CI, 1.938 to 2.793); anaemia (72 versus 36%; RR = 2.022, 95% CI, 1.683 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); 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); vomiting (35 versus 24%; RR = 1.420, 95% CI, 1.071 to 1.891) *Favoured topotecan over caelyx* 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 disorder (14 versus 3%; RR = 0.216, 95% CI, 0.099 to 0.466); skin rashes (24 versus 8%; RR = 0.316, 95% CI, 0.192 to 0.514)

TABLE 15 *Summary details of the economic evaluations*

Study	Type	Perspective	Comparators	Patients
Bennett *et al.*[60] and Stinson *et al.*[61]	Stated that it was a CMA, but it was, in fact, a CCA	USA third-party payer and patient costs	Topotecan versus paclitaxel, altretamine and etoposide	Pt-r/-resistant advanced ovarian cancer (FIGO III/IV)
SmithKline Beecham[28]	CEA	UK NHS	Topotecan versus paclitaxel	Advanced ovarian cancer (FIGO III/IV) receiving second-line therapy
Schering-Plough Ltd.[62]	CMA	UK NHS	Topotecan versus caelyx	Advanced ovarian cancer (FIGO III/IV) after failing first-line Pt therapy

TABLE 16 *Summary of the data sources and results of the economic evaluations*

Study	Effectiveness source	Cost source	Results	Conclusion
Bennett *et al.*[60] and Stinson *et al.*[61]	Equal effectiveness assumed from multiple studies	USA Medicare reimbursement data. Cost year 1996	Matrix grading – unclear *Medicare costs*: paclitaxel $15,684; topotecan $18,598; altretamine $0; etoposide $7,655 *Patient costs*: paclitaxel $83; topotecan $37; altretamine $4,477; etoposide $66	Cost model suggested that when efficacy and toxicity were equal, more expensive intravenous agents may be used over less expensive oral alternatives due to concern over out-of-pocket costs to patients
Schering-Plough Ltd.[62]	Superior effectiveness of caelyx assumed from trial 30-49	MIMS and NHS trust data. Cost year 2000	Matrix grading G/H in favour of caelyx Total cost of caelyx was estimated to be Euros 16,266 (£9,979) per person (regardless of whether they responded) versus Euros 22,858 (£14,023) for topotecan	This analysis indicates that caelyx is the dominant therapy, that is, the effects are at least as good as topotecan, but at a lower cost
SmithKline Beecham[28]	Outcome data from trial 039 used in a decision model	MIMS, Chartered Institute of Public Finance and Accountancy database and UK cancer centre tariffs (resources were estimated using expert opinion). Cost year 1999/2000	Matrix grading A in favour of topotecan *Cost per patient with any response (CR + PR)*: topotecan = £32,513, paclitaxel £46,186; incremental cost-effectiveness ratio of topotecan = £3,065. *Cost per TWIST*: topotecan = £1,503, paclitaxel = £987; incremental cost-effectiveness ratio of topotecan = –£94	This analysis demonstrated that the use of topotecan in women who had relapsed after first-line therapies was a valuable cost-effective addition to the management options for these cases

TABLE 17 *Cost-effectiveness ratios of topotecan versus paclitaxel,[28] however, details of the CEA were commercial in confidence*

Cost description	Topotecan	Paclitaxel	Incremental cost-effectiveness ratio
Per week of survival	£106	£122	£20
Per patient with a CR	£148,115	£248,691	£10,485
Per patient with a PR	£41,399	£56,719	£4,238
Per patient with any response (CR + PR)	£32,513	£46,186	£3,065
Per time without toxicity or symptoms (TWIST)	£1,503	£987	–£94

Chapter 4

Relevance to the NHS

At present, paclitaxel, hexamethylmelamine, treosulfan, carboplatin, caelyx and topotecan are licensed for the second-line treatment of ovarian cancer. However, recent guidance issued by NICE in May 2000 recommends the use of paclitaxel in combination with Pt therapy (cisplatin/carboplatin) for the first-line treatment of ovarian cancer, leaving hexamethylmelamine, caelyx, treosulfan and topotecan as the only current options for second-line therapy. NICE has recommended "the use of paclitaxel/Pt 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 with drug resistance.[22] A number of alternative chemotherapy agents at various stages of development are currently under investigation, but the options for the treatment of recurrent/resistant ovarian cancer are currently limited.

Chapter 5

Discussion and conclusions

In summary, two international multicentre RCTs (trials 039 and 30-49) with a total of 709 participants were identified, which compared topotecan to paclitaxel (n = 235), and topotecan to caelyx (n = 474), respectively. Topotecan and paclitaxel are currently licensed in the UK for the second-line treatment of advanced ovarian cancer and caelyx has recently received European approval. In addition, three economic evaluations (one CCA, one CMA and one CEA) were identified.

Issues about the quality of the clinical effectiveness evidence

In terms of clinical effectiveness, the two RCTs appeared to be of reasonable quality, although trial 30-49 (topotecan versus caelyx) lacked some of the necessary information on which to base an assessment. The two main areas of concern were the analysis of ITT data and the blinding of individuals assessing the response outcomes, which is of particular concern because the assessment of therapy responses in ovarian cancer is very difficult and, therefore, open to bias. These quality issues should be borne in mind when interpreting the results of the trials. However, it is unclear whether these issues were related to poor reporting of the trial methodology or whether they are in fact real concerns, but a recent European Public Assessment Report of trial 30-49 does suggest that the assessors were not blinded.

ITT analyses represent a more conservative estimate of effects more closely resembling clinical practice, however, trial 039 failed to include all of the patients initially randomised to the trial in the final ITT analyses and thus they were not true ITT analyses. Trial 30-49 reported conducting ITT analyses, but did not state the number of participants originally included in the randomisation procedure and it was, therefore, not possible to confirm that a true ITT analysis had been performed.

Perhaps of more concern was the fact that it was unclear whether those assessing the response outcomes in trial 30-49 were blind to the drug allocation or independent from the sponsors of the trial (Schering-Plough Ltd.). There is some concern that responses may have been overestimated in favour of caelyx (manufactured by Schering-Plough Ltd.). Independent, blinded assessors were used in trial 039 and it was reported that investigators originally claimed 38 TRs (PR and CR) for topotecan and 28 for paclitaxel. However, these figures dropped to 23 and 16, respectively, after independent review, suggesting that independent verification of response outcomes is essential in order to avoid bias.

Summary and statistical significance of the clinical effectiveness data

The assessment of clinical effectiveness was based on only two trials, which compared topotecan with two different comparators, and was, therefore, based on limited data. The two RCTs used the outcomes of response rate, median survival time, median time to response, median time to progression, median duration of response, QoL and the incidence of adverse effects. No major statistically significant differences were observed in the main effectiveness outcomes (see *Table 14*). 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 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 and these tests were used in this report. These tests suggested that it is unlikely that the differences observed in the subgroup analyses were of any real relevance.

In a number of instances, the two trials failed to describe how various outcomes were measured. This was particularly the case for trial 30-49 where very few outcome definitions were reported. In addition, trial 039 measured survival and time to

progression from the first receipt of drug treatment and not from the time of randomisation, as is usually the case. This could have introduced bias into the measurement of these outcomes because there may have been a considerable and variable lag period between the time of randomisation and the point of first treatment. This potential for bias should be borne in mind when considering the data for these outcomes.

A considerable amount of data from both trials 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 cause a significant improvement in quality-adjusted survival and not just response.

Trial 039 (topotecan versus paclitaxel) stated that HRs and 95% CIs were calculated and survival curves plotted. These statistical parameters are important in the valid assessment of time-to-event data (e.g. duration of response, time to response). However, although survival curves were presented and median times based on the curves were reported, only RRs and not HRs were presented. It is possible to roughly estimate the HR from the survival curves, but sufficient data were not presented to allow more accurate estimation. However, the survival curves were reproduced as in the original trial reports. The omission of the HRs in trial 039 had little effect on the final results of the trial because the *p*-values of the RRs were not statistically significant, nevertheless, HRs should have been presented.

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 lowering these limits in the final analysis. Statistical data are usually presented with 95% CIs because the higher the interval the more confidence can be placed on the estimate. Using 90% CIs suggests that the HRs were less significant and, 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 differences in effects that are not statistically significant could be significant to the patients concerned, such as alleviating symptoms. However, in view of the fact that neither of the trials demonstrated many significant differences in QoL between the various patient groups, it seems unlikely that the differences in effect would make any real impact on patients' lives. Only two statistically significant differences in QoL were identified and these were limited to the pain subscale score. In patients in general and in Pt-s patients, significantly more had a maintained or improved QoL pain score at 12 weeks with topotecan than with caelyx.

Despite the lack of significant differences in response between topotecan and paclitaxel, or between topotecan and caelyx, differences in the incidence of adverse effects were found to be statistically significant. In both trials, topotecan was shown to be significantly associated with a higher incidence of neutropenia, leukopenia, thrombocytopenia, anaemia and nausea/vomiting. This haematological toxicity 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 caelyx, topotecan was also associated with a significantly higher incidence of alopecia. In trial 39-40, patients also died as a result of the haematological complications of topotecan and such adverse effects are, therefore, a serious concern. In contrast, caelyx was associated with a significantly higher incidence of PPE, stomatitis, mucous membrane disorder and skin rashes compared with topotecan. 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 pre-administration of dexamethasone may prevent the development of PPE. In terms of adverse effects, paclitaxel was significantly associated with a higher incidence of alopecia than topotecan. In addition, instances of myalgia, arthralgia, neuropathy and paraesthesiae were also increased, although RR estimates for these effects could not be calculated.

Summary and quality of the cost-effectiveness data

There was a limited amount of data on which to base an assessment of cost-effectiveness. Of the three economic evaluations that were identified, only two were of real relevance to the UK NHS

perspective of this review. The CCA only considered the USA third-party payer system and thus was not relevant. In addition, the evaluation was only valid if the drugs (paclitaxel, topotecan, etoposide and altretamine) were of equivalent clinical effectiveness, which, from the data presented, they were clearly not.

The two remaining evaluations used clinical effectiveness data from RCTs, however, the details were commercial in confidence and thus excluded. The CEA of topotecan versus paclitaxel demonstrated that topotecan had superior cost-effectiveness for all outcome measures except cost per TWIST. The CMA of topotecan versus caelyx suggested that the clinical effects of caelyx were at least as good as topotecan, and the drug was associated with lower costs. However, there were a number of methodological issues that warrant concern, particularly with respect to the CEA, which mean that the findings from both evaluations should be interpreted with caution. These issues centre on information designated as confidential and, therefore, cannot be discussed further in this review.

Comparison with other systematic reviews

Three systematic reviews of second-line therapy for ovarian cancer have been previously published.[24,25,33] One systematic review of topotecan for the treatment of various cancers, including ovarian cancer, concluded that topotecan appeared to be effective and may be at least as effective as paclitaxel as a second-line agent.[24] This finding was based on evidence from trial 039 and six other non-comparative Phase II studies, located through searching MEDLINE and other sources for English language publications. The authors also highlighted the need for additional studies.

Another similar systematic review of topotecan in ovarian cancer searched three electronic databases and additional published and unpublished sources for studies of any design with preference for controlled studies.[25] This review also concluded that topotecan showed modest activity in the treatment of ovarian cancer, with clinical activity similar to paclitaxel. Similarly, these findings were based on trial 039 and four non-comparative Phase II studies.

A German systematic review published in 2000 assessed second-line chemotherapies after Pt-based therapy for ovarian cancer.[33] Again, studies reported in the review included only one RCT (trial 039) and all the others were non-comparative studies. The authors concluded that disappointing clinical results and a lack of valid data indicated a need for more RCTs.

In conclusion, our review is consistent with previously published systematic reviews of second-line therapies for ovarian cancer in that only modest, non-significant differences between topotecan and the other second-line therapies (paclitaxel and caelyx) have been identified, and further RCTs are required in order to provide definitive conclusions.

Implications for further research

In view of the evidence presented in this review, there is a need both for basic research into new more effective agents for second-line chemotherapy and for more good quality RCTs comparing the effectiveness of existing agents, including topotecan. Future trials should ensure that data are gathered with respect to the range of outcomes 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 poor prognosis and limited survival of these patients at present. Ovarian cancer is a very difficult disease to treat and methods of prevention and detection are limited, and 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 included the absolute numbers of events and participants should be stated so as to allow others to calculate RR estimates.

With the advent of new data from RCTs, there will also be a need to carry out further good quality economic evaluations to ensure that an accurate representation of cost-effectiveness is maintained. These should take the form of full economic evaluations based on valid assumptions of clinical effectiveness, which are based on good quality data from clinical trials. Assumptions used in the evaluation should be made explicit and costs and benefits clearly reported in a disaggregrated and an aggregated form. Sensitivity analyses are also important and should take into account all possible variables in order to test the robustness of the findings. It would also be advisable to conduct a CUA in view of the adverse effects of topotecan and the other second-line therapies and their modest clinical effects. Evaluations should also be conducted from the perspective of the UK NHS and, where possible, gather concurrent cost data from clinical trials.

Updating the review

With respect to the limited number of trials and economic evaluations identified in this review, a number of ongoing RCTs of topotecan were identified (see appendix 6). However, little information and no outcome data were available. Unfortunately, no further ongoing economic evaluations were identified. In view of the ongoing studies found, an update of the current review should be considered in Summer 2002 or possibly sooner if the recently commissioned NICE review of caelyx for ovarian cancer (fifth wave of NICE appraisals due to be appraised in November 2001) identifies additional data relevant to topotecan.

Conclusions

This review suggests that there is little evidence in the form of RCTs on which to base an assessment of the effectiveness of topotecan in comparison to existing and new chemotherapy agents for the second-line treatment of advanced ovarian cancer. Only two clinical effectiveness studies both comparing topotecan to different comparators were identified with a total of 709 participants. In addition, only two economic evaluations relevant to the UK NHS setting were identified.

From the limited evidence available, it would appear that there are no statistically significant differences in the effects of topotecan and the two comparators considered in this review (paclitaxel and caelyx). The few statistically significant differences that were observed were limited to questionable subgroup analyses. However, there were statistically significant differences between the drugs in treatment-related adverse effects. The adverse effects of concern for topotecan were related to the haematological toxicity of the drug. In comparison, caelyx was associated with PPE and stomatitis and paclitaxel with alopecia, arthralgia, myalgia, neuropathy and paraesthesiae. Overall, the efficacy of topotecan could at best be described as modest, but the alternative agents offer no real advantages, apart from offering the benefit of fewer side-effects and possibly improved cost-effectiveness. Both of the trials on which this evaluation was based had methodological flaws, the most serious being the lack of a blinded assessor for response outcomes in the trial of topotecan versus caelyx.

It would appear that topotecan is more cost-effective than paclitaxel, apart from cost per TWIST, but less cost-effective compared with the new drug caelyx recently licensed in Europe. This evidence was derived from two reasonable quality evaluations. However, both studies had methodological problems that warrant concern, but cannot be detailed due to their designation as confidential. In particular, the findings from the topotecan versus paclitaxel evaluation should be treated with some degree of caution. Both evaluations were based on effectiveness data from RCTs. These findings might have been different had CUAs been considered, particularly in the case of topotecan versus paclitaxel. However, the comparison of topotecan and paclitaxel is somewhat redundant because paclitaxel has recently been recommended for use in first-line therapy and is, therefore, unlikely to be used for second-line therapy in future.

In conclusion, further good quality RCTs and prospective economic evaluations (CEAs and CUAs) are required comparing topotecan with other licensed and potentially useful (soon to be licensed) second-line chemotherapy agents for ovarian cancer. At present, it is difficult to make any choices about topotecan and other drugs for the second-line treatment of ovarian cancer without such good quality, direct comparisons.

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The views expressed in this report are those of the authors and not necessarily those of the NHS R&D Programme. Any errors are the responsibility of the authors.

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Appendix 1

Search strategy

MEDLINE

The search strategy was designed to find RCTs and cost-effectiveness studies and, therefore, used relevant methodological filters. Ovarian cancer terms and the drug names (topotecan, Hycamtin) were then added to the quality filters. The MEDLINE search covered the date range 1986 to August 2000. The search was carried out on 5th September 2000 and identified 87 records.

#1 randomized controlled trial in pt
#2 explode "randomized controlled trials"/ all subheadings
#3 "random allocation"/all subheadings
#4 "double blind method"/all subheadings
#5 "single blind method"/all subheadings
#6 clinical trial in pt
#7 explode "clinical trials"/all subheadings
#8 "controlled clinical trials"/all subheadings
#9 (clin* near3 trial*) in ti, ab
#10 ((singl* or doubl* or trebl* or tripl*) near3 (blind* or mask*)) in ti, ab
#11 placebo* in ti, ab
#12 "placebos"/all subheadings
#13 random* in ti, ab
#14 explode "research design"/all subheadings
#15 explode "Evaluation-Studies"/all subheadings
#16 "Follow-Up-Studies"/all subheadings
#17 "Prospective-Studies"/all subheadings
#18 (control* or prospectiv* or volunteer*) in ti, ab
#19 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18
#20 tg = animal
#21 tg = human
#22 #20 not (#20 and #21)
#23 #19 not #22
#24 explode "economics"/all subheadings
#25 (cost or costs or costed or costly or costing) in ti, ab
#26 (utilit* or benefit* or effective* or stud* or minimi* or analys*) in ti, ab
#27 #25 near #26
#28 (economic* or pharmacoeconomic* or price* or pricing) in ti, ab
#29 #24 or #27 or #28
#30 #23 or #29
#31 explode "ovarian neoplasms"/all subheadings
#32 (ovar* near4 (cancer* or tumo?r* or malignant*)) in ti, ab
#33 (ovar* near4 (oncolog* or carcinoma*)) in ti, ab
#34 #31 or #32 or #33
#35 "topotecan"/all subheadings
#36 topotecan in ti, ab, nm
#37 (hycamtin or hycamptamine) in ti, ab, nm
#38 #35 or #36 or #37
#39 #34 and #38
#40 #30 and #39

EMBASE

The MEDLINE search strategy above was translated and adapted to run in the EMBASE database. The EMBASE search covered the date range 1989 to July 2000. The search was carried out on 5th September 2000 and identified 195 records.

#1 "randomized-controlled-trial"/all subheadings
#2 "randomization"/all subheadings
#3 "double-blind-procedure"/all subheadings
#4 "single-blind-procedure"/all subheadings
#5 (random* near control* trial*) in ti, ab
#6 (clin* near3 trial*) in ti, ab
#7 explode "clinical trial"/all subheadings
#8 explode "controlled study"/all subheadings
#9 ((singl* or doubl* or trebl* or tripl*) near3 (blind* or mask*)) in ti, ab
#10 placebo* in ti, ab
#11 "placebo"/all subheadings
#12 "evaluation"/all subheadings
#13 "follow up"/ all subheadings
#14 "prospective study"/all subheadings
#15 (control* or prospective* or volunteer*) in ti, ab
#16 random* in ti, ab
#17 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16
#18 (explode "animal"/all subheadings) or (explode "animal experiment"/ all subheadings)
#19 (explode "human"/all subheadings) or (explode "human experiment"/ all subheadings)
#20 #18 not (#18 and #19)
#21 #17 not #20

#22 explode "economics"/all subheadings
#23 explode "health economics"/all subheadings
#24 (cost or costs or costed or costly or costing) in ti, ab
#25 (utilit* or benefit* or effective* or stud* or minimi* or analys*) in ti, ab
#26 #24 near #25
#27 #22 or #23 or #26
#28 #21 or #27
#29 explode "ovary cancer"/all subheadings
#30 (ovar* near4 (cancer* or tumo?r* or malignant*)) in ti, ab
#31 (ovar* near4 (oncolog* or carcinoma*)) in ti, ab
#32 #29 or #30 or #31
#33 "topotecan"/all subheadings
#34 topotecan in ti, ab
#35 (hycamtin or hycamptamine) in ti, ab, tn
#36 #33 or #34 or #35
#37 #32 and #36
#38 #28 and #37

CANCERLIT

The MEDLINE search strategy was translated and adapted to run in the CANCERLIT database. The CANCERLIT search covered the date range 1995 to June 2000. The search was carried out on 7th September 2000 and identified 124 records.

#1 randomized controlled trial in pt
#2 explode "randomized controlled trials"/ all subheadings
#3 "random allocation"/all subheadings
#4 "double blind method"/all subheadings
#5 "single blind method"/all subheadings
#6 clinical trial in pt
#7 explode "clinical trials"/all subheadings
#8 "controlled clinical trials"/all subheadings
#9 (clin* near3 trial*) in ti, ab
#10 ((singl* or doubl* or trebl* or tripl*) near3 (blind* or mask*)) in ti, ab
#11 placebo* in ti, ab
#12 "placebos"/all subheadings
#13 random* in ti, ab
#14 explode "research design"/all subheadings
#15 explode "Evaluation-Studies"/all subheadings
#16 "Follow-Up-Studies"/all subheadings
#17 "Prospective-Studies"/all subheadings
#18 (control* or prospectiv* or volunteer*) in ti, ab
#19 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18
#20 explode "economics"/all subheadings
#21 (cost or costs or costed or costly or costing) in ti, ab
#22 (utilit* or benefit* or effective* or stud* or minimi* or analys*) in ti, ab
#23 #21 near #22
#24 (economic* or pharmacoeconomic* or price* or pricing) in ti, ab
#25 #20 or #23 or #24
#26 #19 or #25
#27 explode "ovarian neoplasms"/all subheadings
#28 (ovar* near4 (cancer* or tumo?r* or malignant*)) in ti, ab
#29 (ovar* near4 (oncolog* or carcinoma*)) in ti, ab
#30 #27 or #28 or #29
#31 "topotecan"/all subheadings
#32 topotecan in ti, ab, nm
#33 (hycamtin or hycamptamine) in ti, ab, nm
#34 #31 or #32 or #33
#35 #30 and #34
#36 #26 and #35

BIOSIS

BIOSIS was searched via Edina on the Internet at <http://edina.ed.ac.uk/biosis/>. As this interface only accepts simple search strategies, the RCTs and cost-effectiveness studies filters were not used. A simple search strategy using the drug names (topotecan, Hycamtin) and ovarian cancer terms was used. The resulting references were then checked for duplication against those records already found. The BIOSIS search covered the date range 1993 to 2000. The search was carried out on 7th September 2000 and identified 136 records.

(topotecan or hycamtin) and ovar*

Index to Scientific and Technical Proceedings

The Web of Science interface was used to search Index to Scientific and Technical Proceedings at <http://wos.mimas.ac.uk/>. This interface only accepts simple search strategies and thus the RCTs and cost-effectiveness filters were not used. A simple search combining the drug names and ovarian cancer terms was implemented. This search was conducted on 11th September 2000 covering the date range 1990 to 2000, and identified 21 records.

(topotecan or hycamtin) and ovar*

Cochrane Controlled Trials Register

The Cochrane Library CD-ROM issue 2000; 3 of the Cochrane Controlled Trials Register was searched to find completed trials. A relatively simple search was used combining the drug names with terms for ovarian cancer. The search strategy did not require methodological filters for RCTs because the database only consists of such references. The search was carried out on 6th September 2000 and identified five records.

#1 OVARIAN-NEOPLASMS*: ME
#2 (OVAR* AND ((((CANCER*) or TUMOR*) OR TUMOUR*) OR MALIGNANT*))
#3 (OVAR* AND ((ONCOLOG*) or CARCINOMA*))
#4 ((#1 or #2) or #3)
#5 TOPOTECAN*: ME
#6 TOPOTECAN
#7 (HYCAMTIN or HYCAMPTAMINE)
#8 ((#5 or #6) or #7)
#9 (#4 and #8)

Database of Abstracts of Reviews of Effectiveness

The Cochrane Library CD-ROM issue 2000; 3 of the Database of Abstracts of Reviews of Effectiveness was searched to find completed trials. A simple search of the drug name was used. The search was carried out on 6th September 2000 and identified no additional records.

TOPOTECAN

NHS Economic Evaluation Database

The Cochrane Library CD-ROM issue 2000; 3 of the NHS Economic Evaluation Database was searched to find completed trials. Again, a simple search of the drug name was used. The search was carried out on 6th September 2000 and identified no additional records.

TOPOTECAN

National Research Register

The Cochrane Library CD-ROM issue 2000; 3 of the National Research Register was searched to find further ongoing and completed trials. A relatively simple search was used combining the drug names and terms for ovarian cancer. The search was carried out on 12th September 2000 and identified six ongoing and 19 completed trials.

#1 OVARIAN-NEOPLASMS*: ME
#2 (OVAR* AND ((((CANCER*) or TUMOR*) OR TUMOUR*) OR MALIGNANT*))
#3 (OVAR* AND ((ONCOLOG*) or CARCINOMA*))
#4 ((#1 or #2) or #3)
#5 TOPOTECAN*: ME
#6 TOPOTECAN
#7 (HYCAMTIN or HYCAMPTAMINE)
#8 ((#5 or #6) or #7)
#9 (#4 and #8)

Internet resources

A number of Internet sites were chosen to search for information about further ongoing trials. The sites included the main trials registers UKCCCR Register, National Institute of Health, Current Controlled Trials and CenterWatch Clinical Trials Listing Service. The trials register of the National Cancer Institute was also searched (Cancernet). In addition, the ASCO website was searched for abstracts from their annual conference proceedings.

The search strategy for all of the Internet sites consisted of the drug names only. The results were then browsed to find references dealing with ovarian cancer only.

TOPOTECAN
HYCAMTIN

UKCCCR Register

This site at <http://www.cto.mrc.ac.uk/ukcccr/text_only/search.html> was searched on the 14th September 2000 and identified two trials.

National Cancer Institute

The National Cancer Institute site at <http://cancernet.nci.nih.gov/trialsrch.shtml> was searched on the 14th September 2000 and identified 12 trials.

National Institute of Health

This site at <http://clinicaltrials.gov/ct/gui/c/r> was searched on the 14th September 2000 and identified 16 trials.

CenterWatch Clinical Trials Listing Service

This site at <http://www.centerwatch.com/main.htm> was searched on the 14th September 2000 and did not identify any trials.

Current Controlled Trials

This site at <http://www.controlled-trials.com/login. cfm?returnto=home_page.cfm> was searched on the 14th September 2000 and identified four trials.

ASCO

The ASCO site at <http://www.asco.org/> was searched on the 14th September 2000 and identified seven ASCO abstracts.

The National Cancer Institute of Canada

This site at <http://www.ncic.cancer.ca/> was searched on the 14th September 2000 and identified no additional trials.

The search results from MEDLINE, EMBASE, CANCERLIT, BIOSIS, Index to Scientific and Technical Proceedings and the Cochrane Controlled Trails Register were downloaded and imported into Endnote (ISI ReSearchSoft, USA) reference management software and duplicate records were deleted.

The search results from the National Research Register were downloaded in full into a text file.

The search results from the Internet were saved as HTML files.

Appendix 2

Trialists and organisations contacted for information on unpublished studies

Professor J Carmichael
CRC Academic Unit of Clinical Oncology
Nottingham City Hospital NHS Trust
Hucknall Road
Nottingham
UK

Dr M Crawford
Airedale NHS Trust
Airedale General Hospital
Steeton
Keighley
UK

Dr H Earl
Clinical Oncology Centre
Addenbrooke's NHS Trust
Cambridge
UK

EORTC
EORTC Central Office
Avenue Mounier
Brussels
Belgium

Dr C Gallagher
Medical Oncology Department
St Bartholomew's Hospital
West Smithfield
London
UK

Dr M Gore
Medicine Section
The Royal Marsden NHS Trust
Fulham Road
Chelsea
London
UK

HS Hochster
Kaplan Cancer Center
NYU School of Medicine
First Avenue
New York
USA

Dr A Hong
Department of Oncology
Royal Devon and Exeter Hospital
Barrack Road
Exeter
UK

Dr K O'Byrne
c/o Research and Development Office Clinical
Research Unit
Leicester Royal Infirmary NHS Trust
Infirmary Square
Leicester
UK

S Pignata
National Cancer Institute
Naples
Italy

Dr G Rustin
Cancer Centre
Mount Vernon Hospital
Rickmansworth Road
Northwood
Middlesex
UK

Appendix 3

Details about FIGO cancer staging[29]

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, capsule rupture and penetration.

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 therapy, 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$, £, …, 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 quality-adjusted life-years (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

Studies of clinical effectiveness were assessed using the following criteria based on the NHS Centre for Reviews and Dissemination Report No. 4:[30]

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 procedures with robust methods 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 in terms of Yes, item adequately addressed; No, item not adequately addressed; Yes/No, item partially addressed; Unclear, not enough information or unclear; NA, not applicable; or Not stated.

B. Studies of cost-effectiveness

Studies of cost-effectiveness were assessed using the following criteria based on the checklist developed by Drummond:[31]

Study question

1. The viewpoint(s) of the analysis were clearly stated and justified (provider institution, individual clinician, professional organisation, patient or patient group, purchaser or healthcare or society).

Selection of alternatives

2. Relevant alternatives were compared.
3. The alternatives being compared were clearly described (who did what, to whom, where and how often).
4. The rationale for choosing the alternative programmes or interventions compared was stated.

Type of evaluation

5. The choice of economic evaluation type was justified in relation to the questions addressed (a CBA to establish whether benefits were greater than costs for one intervention; a CMA if effects were equal to establish the less costly intervention; a CEA if costs and effects varied; a CUA to establish the best way to spend a given budget).

Effectiveness data

6. The source(s) of effectiveness estimates used were stated (single study, selection of studies, systematic review, delphi panel).

7. The source(s) of effectiveness estimates used were given the Sackett grade A, B, C or D (see appendix 10).
8. Details of the method of synthesis or meta-analysis of estimates were given (if based on an overview of a number of effectiveness studies).

Benefit measurement and valuation

9. The primary outcome measure(s) for the economic evaluation were clearly stated (such as cases detected, life-years, QALYs, willingness to pay).
10. Methods to value health states and other benefits were stated (such as time trade-off, standard gamble, willingness to pay, contingent valuation).
11. Details of the individuals from whom valuations were obtained were given (such as patients, members of the public, health-care professionals).
12. The relevance of productivity changes to the study question was discussed.
13. Productivity changes (if included) were reported separately.

Costing

14. Quantities of resources were reported separately from their unit costs (such as days in hospital).
15. Methods for estimation of quantities were described.
16. Methods for estimation of unit costs were described.
17. Currency and price data were reported.
18. Details of currency of price adjustments for inflation or currency conversion were given.

Modelling

19. Details of any model used were given (such as decisions tree model, epidemiology model, regression model).
20. The choice of model used and the key parameters on which it was based were justified (adjustments for timing of costs and benefits).
21. Time horizon of costs and benefits was stated.
22. The discount rate was stated.
23. The choice of rate was justified.
24. A convincing explanation was given if costs or benefits were not discounted (allowance for uncertainty).
25. Details of statistical tests and CIs were given for stochastic data.
26. The approach to sensitivity analysis was given (such as multivariate, univariate, threshold analysis).
27. The choice of variables for sensitivity analysis was justified.
28. The ranges over which the variables were varied were stated.

Presentation of results

29. Incremental analysis was reported.
30. Major outcomes were presented in a disaggregated as well as an aggregated form.
31. The study was applicable to the NHS setting.

All items (except item 7) were graded as either Yes, item adequately addressed; No, item not adequately addressed; Unclear, not enough information or unclear; NA, not applicable; or Not stated.

Appendix 6

List of ongoing multicentre RCTs of topotecan

Identification (company)	Comparators	Participants/therapy	Expected completion date
Open-label Phase II ROSE trial[64] (Sanofi Winthrop)	Topotecan versus oxaliplatin	Advanced ovarian cancer in non-responders to Pt-based/ second-line therapy	Accrual completed, abstract publication in May 2001
Multicentre Phase III Italian RCT (Contact: Francesco Perrone, Clinical Trials Office, National Cancer Institute, Naples)	Topotecan versus usual care (i.e. whether consecutive addition of topotecan in patients responding to usual care (surgery + carboplatin + paclitaxel) improves the outcomes compared with usual care alone)	Advanced ovarian cancer in patients who had previously been treated and responded to surgery + carboplatin + paclitaxel/second-line therapy immediately following a positive response to first-line therapy	Trial due to be completed summer 2002
Open-label Phase III trial (SmithKline Beecham)	Topotecan + cisplatin versus paclitaxel + cisplatin	Advanced ovarian cancer patients undergoing first-line therapy	Not known (only preliminary data and no published information available)

Appendix 7

List of excluded studies and reasons for exclusion

Study	Reason for exclusion
Akhtar *et al.*, 1999[35]	Not an RCT of topotecan therapy, but a Phase I, open-label, two-period crossover study investigating the bioavailability of topotecan in ovarian cancer patients
Anonymous, 1996[49]	Reports brief details of the protocols of two RCTs of topotecan sponsored by SmithKline Beecham (trial 039 and a trial of topotecan and cisplatin versus cisplatin alone in first-line therapy; see appendix 6), but did not report any outcome data
Bowman *et al.*, 1999[36]	Not an RCT of topotecan, but a Phase I/II dose-ranging study of 'reverse-schedule' topotecan and carboplatin in relapsed ovarian cancer patients
Cacciari *et al.*, 1999[37]	Not an RCT, but a Phase I dose-escalation study of topotecan added to a first-line carboplatin and paclitaxel regimen for advanced ovarian cancer patients
Cesano *et al.*, 1999[38]	Report of the usefulness of stabilisation of disease as a predictor of survival following second-line chemotherapy in small cell lung cancer and ovarian cancer. Included data from a number of trials, such as trial 039[28,54–57]
Doyle *et al.*, 1997[53]	Canadian study describing the costs and outcomes of palliative chemotherapy in recurrent and refractory ovarian cancer patients from the perspective of the healthcare provider, however, it did not include topotecan therapy
Eisenhauer *et al.*, 1997[39]	Phase II RCT of topotecan in previously treated ovarian cancer patients, however, it only compared two different topotecan regimens
Eisenkop *et al.*, 2000[48]	Not an RCT of topotecan therapy, but a cohort study of the role of secondary cytoreductive surgery in the treatment of patients with recurrent epithelial carcinoma
Goldwasser *et al.*, 1999[40]	Not an RCT, but a cohort study of topotecan in advanced ovarian cancer patients
Gore *et al.*, 1998[34]	Phase III RCT of topotecan in advanced ovarian cancer patients, but it compared intravenous and oral topotecan
Hoskins *et al.*, 1998[41]	Phase II RCT involving topotecan therapy in patients with recurrent epithelial ovarian cancer who had been treated with ≤ two prior chemotherapy regimens, however, it only compared two different treatment schedules of topotecan
Hoskins *et al.*, 1999[42]	Phase II study of sequential couplets of cisplatin/topotecan and cisplatin/paclitaxel as first-line therapy for advanced ovarian cancer, but did not appear to be randomised
Ieda *et al.*, 1999[43]	Abstract reporting details of a toxicity study of cisplatin/topotecan in second/third-line therapy of epithelial ovarian cancer. This study of only 19 women did not appear to be randomised and was designed to test the feasibility (toxicity) of using this combination of chemotherapy agents
Lane *et al.*, 1999[50]	Abstract looking at the relationship between tumour response and survival in small cell lung cancer and ovarian cancer patients treated with topotecan as a second-line therapy. It reported limited survival data for the topotecan groups in each case but did not report the equivalent data for the comparison groups
Lissoni *et al.,* 1999[44]	Abstract reporting data from an RCT of topotecan-based salvage therapy in advanced epithelial ovarian cancer, however, topotecan was compared with an alternative topotecan-containing regimen (topotecan and cisplatin) so it was not possible to assess the effects of topotecan

continued

continued

Study	Reason for exclusion
Malmström *et al*., 1996[45]	Abstract reporting data from a study of topotecan using patients from a previous RCT, however, this part of the trial did not appear to be randomised and all (*n* = 21) patients received topotecan
Ozols, 1997[51]	Reports minimal details of trials involving topotecan in ovarian cancer patients including trial 039,[28,54–57] but no outcome data were reported
Recio *et al*., 1998[46]	Not an RCT, but a cohort study of topotecan in the treatment of patients with advanced epithelial ovarian cancer who demonstrated progression while under treatment with cisplatin and paclitaxel
Rose *et al*., 1999[47]	Not an RCT, but an abstract reporting details of a Phase II pharmacokinetic study of topotecan in Pt- and paclitaxel-resistant ovarian cancer
Rustin *et al.,* 1997[52]	Based on an RCT (trial 039), but did not report any data on relevant outcomes

Appendix 8

Data extraction tables for included studies

A. Clinical effectiveness studies

Study design	Participants	Interventions	Follow-up/withdrawals and adverse events	Conclusion and comments
SmithKline Beecham[28] ***Source*** Company submission ***Objective*** To evaluate the clinical effectiveness of topotecan compared to paclitaxel ***Type of publication*** Summary of final analysis ***Trial identification*** 039 ***Phase*** Phase III ***Method of randomisation*** Not stated ***Concealed allocation*** Yes ***Blinding*** *Assessor*: blinded *Carer*: not stated *Patient*: not stated *Success of blinding checked*: not stated ***Length of follow-up*** Not stated ***ITT analysis performed*** Yes	***Number randomised*** Not stated ***Disease type*** Epithelial; advanced; occurrence of secondary spread – not stated ***Therapy stage*** Second-line ***Previous treatments*** Pt-based therapy ***Disease present after first-line treatment*** *Residual*: Yes *Refractory*: Yes ***Mean age/age range of participants*** Not stated ***Characteristics*** Not stated ***Inclusion/exclusion criteria*** Not stated	***Intervention (I) group*** *Type*: topotecan *Number randomised*: 112 (ITT) *Route of administration*: intravenous *Dose*: 1.5 mg/m^2/day for 5 days *Number of cycles*: not stated *Length per cycle*: 21 days ***Control (C) group*** *Type*: paclitaxel *Number randomised*: 114 (ITT) *Route of administration*: intravenous *Dose*: 175 mg/m^2/day as a 3-hour infusion *Number of cycles*: not stated *Length per cycle*: 21 days After the randomised phase of this trial, 61 patients switched from paclitaxel to topotecan and 49 from topotecan to paclitaxel. This part of the trial is referred to as the crossover trial but is not considered here. This abstract presents data based primarily on the ITT analysis	***Withdrawals from I*** Not stated ***Withdrawals from C*** Not stated ***Adverse events*** The figures below differ slightly from those in the confidential full trial report.[57] The figures from the confidential full trial report have been used in *Table 21* *Haematologic toxicity* *All grades of neutropenia*: I = 98%; C = 88% *Grade 4 neutrotpenia*: I = 79%; C = 23% *All grades of leukopenia*: I = 100%; C = 87% *Grade 4 leukopenia*: I = 34%; C = 3% *All grades of thrombocytopenia*: I = 97%; C = 18% *Grade 4 thrombocytopenia*: I = 25%; C = 2% *All grades of anaemia*: I = 100%; C = 90% *Grade 4 anaemia*: I = 4%; C = 3% *Non-haematological toxicity* *Alopecia*: I = 76.8%; C = 93.0% *Nausea*: I = 67.0%; C = 32.5% *Vomiting*: I = 50.0%; C = 16.7% *Fatigue*: I = 32.1%; C = 26.3% *Diarrhoea*: I = 23.2%; C = 21.9% *Stomatitis*: I = 21.4%; C = 14.0% *Asthenia*: I = 17.0%; C = 12.3% *Constipation*: I = 13.4%; C = not stated *Fever*: I = 11.6%; C = not stated *Anorexia*: I = 10.7%; C = not stated *Arthralgia*: I = not stated; C = 28.9% *Paraesthesiae*: I = not stated; C = 28.1% *Myalgia*: I = not stated; C = 26.3% *Peripheral neuropathy*: I = not stated; C = 14.9% *Pain*: I = not stated; C = 14.0% *Skeletal pain*: I = not stated; C = 14.0% *Abdominal pain*: I = not stated; C = 13.2% *Flushing*: I = not stated; C = 13.2%	***Authors' conclusions*** Topotecan demonstrated numerical superiority to paclitaxel on all clinical endpoints except QoL ***Comments*** These represent the final results from trial 039. The data in this report are a brief summary of those data presented in the confidential detailed trial report, which was also included in the industry submission from SmithKline Beecham[57] It is not clear if time-to-event data were based on Kaplan-Meier survival curves It is difficult to tell if true ITT analyses were performed as the number randomised was not stated. Other publications suggest that true ITT analyses were not performed There is very little detail in the report on the methodology of the trial and the characteristics of the patients

I, intervention; C, control

continued

A. Clinical effectiveness studies *contd*

Results		
Outcome 1: Response rate*	**Outcome 2: Response duration***	**Outcome 3: Time to progression***
Follow-up data *CR*: I = 5/112 (4.5%); C = 3/114 (2.6%) *PR*: I = 18/112 (16.1%); C = 13/114 (11.4%) *TR*: I = 23/112 (20.5%, 95% CI, 13.1 to 28.0), C = 16/114 (14.0%, 95% CI, 7.7 to 20.4); $p = 0.196$	***Follow-up data*** *Median*: I = 25.9 weeks (95% CI, 2.1 to 32.9), C = 21.6 weeks (95% CI, 16.0 to 34.0); $p = 0.476$	***Follow-up data*** *Median*: I = 18.9 weeks (95% CI, 12.1 to 23.6), C = 14.7 weeks (95% CI, 11.9 to 18.3); $p = 0.072$
Outcome 4: Survival*	**Outcome 5: QoL (EORTC QLQ-C30)**	
Follow-up data I = 63.0 weeks (95% CI, 46.6 to 71.9), C = 53.0 weeks (95% CI, 42.3 to 68.7); $p = 0.093$	***Follow-up data*** For I, median changes from baseline to end of best response were only observed for emotional function (8, range –83– +75) and global QoL (–8, range –58– +83). Overall, there were minimal changes between topotecan at baseline and end of best response, and between topotecan and paclitaxel For C, there were no median changes in any of the QoL scales from baseline to end of best response apart from emotional function (8, range –100– +75)	
I, intervention; C, control * *Based on standard World Health Organisation criteria*		

A. Clinical effectiveness studies *contd*

Study design	Participants	Interventions	Follow-up/withdrawals and adverse events	Conclusion and comments
Gordon *et al.*, 1998[54] ***Source*** Database ***Objective*** To compare the efficacy and toxicity of topotecan and paclitaxel in patients with advanced epithelial ovarian cancer who had progressed during or after treatment with one Pt-based chemotherapy regimen ***Type of publication*** Abstract of final report ***Trial identification*** 039 ***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 ***ITT analysis performed*** Yes	***Number randomised*** Not stated ***Disease type*** Epithelial; advanced; occurrence of secondary spread – not stated ***Therapy stage*** Second-line ***Previous treatments*** Pt-based therapy ***Disease present after first-line treatment*** *Residual*: yes *Refractory*: not stated ***Mean age/age range of participants*** Not stated ***Characteristics*** Patients had advanced epithelial ovarian cancer (bidimensionally measurable disease) and had failed one prior Pt-based therapy regimen ***Inclusion/exclusion criteria*** Women had to have advanced disease and have failed one prior Pt-based therapy regimen. Very few details of participants given in abstract	***I group*** *Type*: topotecan *Number randomised*: 112 (ITT) *Route of administration*: intravenous *Dose*: 1.5 mg/m^2/day for 5 days *Number of cycles*: not stated *Length per cycle*: 21 days ***C group*** *Type*: paclitaxel *Number randomised*: 114 (ITT) *Route of administration*: intravenous *Dose*: 175 mg/m^2/day as a 3-hour infusion *Number of cycles*: not stated *Length per cycle*: 21 days After the randomised phase of this trial, 61 switched from paclitaxel to topotecan and 49 from topotecan to paclitaxel. This part of the trial is referred to as the crossover trial but is not considered here. The data presented in this abstract was primarily based on the ITT analysis	***Withdrawals from I*** Not stated ***Withdrawals from C*** Not stated ***Adverse events*** *Grade 4 neutropenia*: I = 36% of courses, C = 9% of courses *Grade 4 thrombocytopenia*: I = 10% of courses, C = < 1% of courses *Grade 3/4 anaemia*: I = 16% of courses, C = 2% of courses *Grade 4 neutropenia associated with fever and/or infection*: I = 6% of courses, C = 1% of courses Non-haematological toxicity was mild for both groups	***Authors' conclusions*** Topotecan has comparable efficacy to paclitaxel with manageable and non-cumulative haematological toxicity ***Comments*** These represent the final results from trial 039. The data in this abstract were a very brief summary of those data presented in the confidential industry submission from SmithKline Beecham[28,57] It is difficult to tell if true ITT analyses were performed as the number randomised was not stated. Other publications suggest that true ITT analyses were not performed There is very little detail in the abstract on which to base quality assessment

continued

A. Clinical effectiveness studies *contd*

Results		
Outcome 1: Response rate (not defined)	**Outcome 2: Response duration (not defined)**	**Outcome 3: Time to progression (not defined)**
Follow-up data *TR*: I = 20.5%, C = 14.0%; RR = NA, p = 0.196	***Follow-up data*** I = 25.9 weeks, C = 21.6 weeks; RR = 0.778, p = 0.476	***Follow-up data*** I = 18.9 weeks, C = 14.7 weeks; RR = 0.764, p = 0.072
Outcome 4: Survival (not defined)	**Outcome 5: Response rate in the alternate arms (not defined)**	
Follow-up data I = 63.0 weeks, C = 53.0 weeks; RR = 0.974, p = 0.872	***Follow-up data*** I = 13.1%, C = 10.2%; RR = NA, p = 0.638	

A. Clinical effectiveness studies *contd*

Study design	Participants	Interventions	Follow-up/withdrawals and adverse events	Conclusion and comments
Gordon *et al.*, 2000[58] ***Source*** Database ***Objective*** To determine the effectiveness of caelyx 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*: not blinded *Patient*: not blinded *Success of blinding checked*: not stated ***Length of follow-up*** Not stated (interim analysis) ***ITT analysis performed*** Yes	***Number randomised*** Not stated, but 237 included in the ITT analyses ***Disease type*** Not stated; relapsed disease; incidence of secondary spread – not stated ***Therapy stage*** Second-line ***Previous treatments*** First-line Pt-based therapy ***Disease present after first-line treatment*** *Residual*: Yes *Refractory*: Yes ***Mean age/age range of participants*** Not stated ***Characteristics*** Not stated ***Inclusion/exclusion criteria*** Failure of first-line Pt-based therapy A total of 237 patients from 71 sites (I = 119, C = 118) included in interim analysis, of which 117 (I = 59, C = 58) had Pt-r disease	***I group*** *Type*: topotecan *Number randomised*: 119 (ITT) *Route of administration*: intravenous *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 ***C group*** *Type*: caelyx *Number randomised*: 118 (ITT) *Route of administration*: intravenous *Dose*: 50 mg/m^2/day as a 1-hour infusion *Number of cycles*: not stated *Length per cycle*: 28 days	***Withdrawals from I*** *Adverse events*: 16 (including five sepsis) *Treatment-related deaths*: 2 ***Withdrawals from C*** *Adverse events*: 14 (including four PPE) *Treatment-related deaths*: 0 ***Adverse events*** *Neutropenia*: I = 71%, C = 12% *Anaemia*: I = 33%, C = 5% *Thrombocytopenia*: I = 35%, C = 1% *PPE*: I = 0%, C = 25% *Alopecia*: I = 8%, C = 0%	***Authors' conclusions*** The differentiated safety profile combined with clinically equivalent efficacy supports the role of caelyx in patients failing first-line Pt-based therapy. 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 is unclear if discontinuations were included in the table of common adverse events The total number of patients randomised was not stated thus it was not possible to confirm that a true ITT analysis was performed Interim results were published in this abstract and final results were submitted in confidence by Schering-Plough Ltd.[59]

continued

A. Clinical effectiveness studies *contd*

Results		
Outcome 1: Median time to progression (not defined)	**Outcome 2: Overall survival (not defined)**	**Outcome 3: Response rate (not defined)**
Follow-up data I = 20.4 weeks, C = 22.4 weeks	***Follow-up data*** I = 56.3 weeks, C = 66.0 weeks	***Follow-up data*** *Confirmed objective*: I = 16.8% (20/119), C = 20.3% (24/118) *Objective*: I = 6.8% (4/59), C = 12.1% (7/58) in the Pt-r subgroup

A. Clinical effectiveness studies *contd*

Study design	Participants	Interventions	Follow-up/withdrawals and adverse events	Conclusion and comments
ten Bokkel Huinink *et al.*, 1997[55] ***Source*** Database ***Objective*** To compare the efficacy and toxicity of topotecan and paclitaxel in patients with advanced epithelial ovarian cancer who had progressed during or after treatment with one Pt-based therapy regimen ***Type of publication*** Interim report ***Trial identification*** 039 ***Phase*** Phase III ***Method of randomisation*** Centralised telephone randomisation ***Concealed allocation*** Yes ***Blinding*** *Assessor*: blinded *Carer*: not blinded *Patient*: not blinded *Success of blinding checked*: not stated	***Number randomised*** 235 ***Disease type*** Epithelial; advanced stage III/IV; occurrence of secondary spread – not stated ***Therapy stage*** Second-line ***Previous treatments*** *Radiotherapy*: I = 3, C = 4 *Immunotherapy*: I = 2, C = 1 *Hormonal therapy*: I = 0, C = 6 *Chemotherapy* *Cyclophosphamide*: I = 66.0%, C = 99.0% *Carboplatin*: I = 55.0%, C = 61.0% *Cisplatin*: I = 54.0%, C = 51.0% *Epirubicin*: I = 8.0%, C = 5.3% *Doxorubicin hydrochloride*: I = 4.5%, C = 6.1% *Doxorubicin*: I = 3.6%, C = 3.5% *Etoposide*: I = 1.8%, C = 0.9% *Mitoxantrone*: I = 1.8%, C = 0.9% *Ifosfamide*: I = 1.8%, C = 0.0% *Epirubicin hydrochloride*: I = 0.9%, C = 1.8% *Chlorambucil*: I = 0.9%, C = 0.9% *Prednimustine*: I = 0.9%, C = 0.0% *Fluorouracil*: I = 0.0%, C = 0.9% *Pirarubicin*: I = 0.0%, C = 0.9% ***Disease present after first-line treatment*** *Residual*: at least 4 weeks after previous treatment *Refractory*: Yes ***Mean age/age range of participants*** I = 59.2 years (range 29.0–85.0), C = 58.3 years (range 29.0–79.0)	***I group*** *Type*: topotecan *Number randomised*: 112 (ITT) *Route of administration*: intravenous *Dose*: 1.5 mg/m^2/day as a 30-minute infusion for 5 days *Number of cycles*: Dependent on response (see below), but 555 cyles in total for the whole group *Length per cycle*: 21 days ***C group*** *Type*: paclitaxel *Number randomised*: 114 (ITT) *Route of administration*: intravenous *Dose*: 175 mg/m^2/day as a 3-hour infusion *Number of cycles*: Dependent on response (see below), but 550 cyles in total for the whole group *Length per cycle*: 21 days Patients in the C group were pre-treated with dexamethasone, and both H_1- and H_2-receptor antagonists to prevent hypersensitivity reactions. Pre-medication was not given to the I	***Withdrawals from I*** Five randomised women did not receive treatment and were not included in the ITT population. Of the remaining 112, 16 were lost to follow-up for the response outcome (but included in the denominator for the ITT analysis) for the following reasons: *Withdrawal for adverse experience*: 7 *Lost to follow-up*: 2 *Patient refusal*: 2 *Protocol violation (no measureable disease at baseline)*: 2 *All lesions noted at screening were not assessed throughout the study*: 2 *Other (pulmonary embolism)*: 1 ***Withdrawals from C*** Four randomised women did not receive treatment and were not included in the ITT population. Of the remaining 114, nine were lost to follow-up for the response outcome (but included in the denominator for the ITT analysis) for the following reasons: *Withdrawal for adverse experience*: 3 *Patient refusal*: 1 *Protocol violation (no measureable disease at baseline)*: 1 *Protocol violation (indicator lesions)*: 1 *Previously irradiated*: 1 *Protocol violation (baseline performance status of 3)*: 1 *Entered study with renal failure*: 1 *Other*: 0 ***Adverse events*** 7% of the I group and 4% of the C group were withdrawn due to adverse events. The primary reasons for withdrawal were febrile neutropenia, infection and sepsis in the I group, and neurotoxicity in the C group	***Authors' conclusions*** Topotecan has efficacy at least equivalent to paclitaxel manifested by the higher response rate and significantly longer time to progression ***Comments*** These results are only interim. Final results are published as an abstract and a partly confidential industry submission[28,54,57] The methods section of the report stated that HRs with 95% CIs were calculated. Survival curves were presented for the duration of response, time to progression and survival, but no HRs were reported. HRs are the most appropriate representation of survival or time-to-event data. It was also not clear from the data presented whether the median times quoted were based on Kaplan-Meier estimates CR was defined as the complete disappearance of all known measurable and assessable disease on two separate measurements at least 4 weeks apart. PR was defined as a 50% reduction in the sum of products of the perpendicular diameters of all measurable lesions for at least 4 weeks Patients in the C group but not the I group routinely received pre-treatment consisting of dexamethasone and both H_1- and H_2-receptor antagonists

continued

A. Clinical effectiveness studies *contd*

Study design	Participants	Interventions	Follow-up/withdrawals and adverse events	Conclusion and comments
contd ten Bokkel Huinink *et al.*, 1997[55] ***Length of follow-up*** 60 weeks? ***ITT analysis performed*** Yes	***Characteristics*** *Performance status = 0*: I = 41/112 (36.6%), C = 42/114 (36.8%) *Performance status = 1*: I = 51/112 (45.5%), C = 53/114 (46.5%) *Performance status = 2*: I = 20/112 (17.9%), C = 17/114 (14.9%) *Performance status = 3*: I = 0/112 (0.0%), C = 2/114 (1.8%) *Mean weight*: I = 65.0 kg (range 1.3–2.3), C = 67.6 kg (range 1.4–2.4) *Tumour diameter < 5 cm*: I = 54/112 (48.2%), C = 53/114 (46.5%) *Tumour diameter ≥ 5 cm*: I = 56/112 (50.0%), C = 59/114 (51.8%) *Tumour diameter not determined*: I = 2/112 (1.8%), C = 2/114 (1.8%) *Tumour histology malignant serous*: I = 58/112 (51.8%), C = 59/114 (51.8%) *Tumour histology malignant mucinous*: I = 6/112 (5.4%), C = 6/114 (5.3%) *Tumour histology malignant endometriod*: I = 10/112 (8.9%), C = 15/114 (13.2%) *Tumour histology undifferentiated carcinoma*: I = 18/112 (16.1%), C = 8/114 (7.0%) *Tumour histology other*: I = 20/112 (17.9%), C = 26/114 (22.8%) *Histological grade 0–1*: I = 6/112 (5.0%), C = 8/114 (7.0%) *Histological grade 2*: I = 23/112 (20.5%), C = 29/114 (25.4%) (C) *Histological grade 3*: I = 56/112 (50.0%), C = 50/114 (43.9%) *Histological grade 4*: I = 10/112 (8.9%), C = 12/114 (10.5%) *Histological grade not determined*: I = 17/112 (15.2%), C = 15/114 (13.2%)	group unless nausea or vomiting occurred. However, prophylactic recombinant G-CSF was allowed after the first course of therapy to maintain dose intensity on day 6 for the I group and day 2 for the C group, if patients had experienced any of the following: grade 4 neutropenia with fever or infection, grade 4 neutropenia for > 7 days or grade 3 neutropenia that required a delay in treatment Dependent on toxicity, the doses of the two drugs could vary from 1.0 to 2.0 mg/m^2/day for I, and from 135 to 175 mg/m^2 for C The number of cycles for both I and C were determined by the patients' response. Patients with a CR/PR continued until progression or for 6 months after the maximal response. Patients who progressed during treatment were removed from the study. Those whose best response was stable disease after six courses were	Suspected or documented infection occurrred within 2 days of grade 4 neutropenia in 25% of I patients and 4% of C patients. In addition, 5% of the I group and 0.4 % of the C group developed sepsis. Two patients in the I group died due to topotecan-induced sepsis (one patient requested no aggressive treatment). There were no deaths attributed to myelopsuppression in the C group. Prophylactic G-CSF was administered to maintain dose intensity in 23% of I courses and 3% of C courses and platelet and red blood cell transfusions were given in 3 and 27% of I courses, respectively. *Haematologic toxicity (ITT)* *Grade 3 leukopenia*: I = 50.9%, C = 17.9% *Grade 4 leukopenia*: I = 33.6%, C = 2.7% *Grade 3 neutropenia*: I = 15.3%, C = 28.6% *Grade 4 neurotpenia*: I = 79.3%, C = 23.2% *Grade 3 thrombocytopenia*: I = 24.3%, C = 0.9% *Grade 4 thrombocytopenia*: I = 25.2%, C = 1.8% *Grade 3 anaemia*: I = 36.9%, C = 3.6% *Grade 4 anaemia*: I = 3.6%, C = 2.7% *Non-haematological toxicity (ITT)* *Grade 1/2 alopecia*: I = 75.9%, C = 92.1% *Grade 3/4 alopecia*: I = 0.0%, C = 0.9% *Grade 1/2 nausea*: I = 67.9%, C = 43.0% *Grade 3/4 nausea*: I = 9.8%, C = 1.8% *Grade 1/2 vomiting*: I = 53.6%, C = 28.1% *Grade 3/4 vomiting*: I = 9.9%, C = 2.7% *Grade 1/2 fatigue*: I = 33.1%, C = 25.4% *Grade 3/4 fatigue*: I = 8.0%, C = 6.1% *Grade 1/2 constipation*: I = 37.5%, C = 30.7% *Grade 3/4 constipation*: I = 5.4%, C = 0.0% *Grade 1/2 diarrhoea*: I = 33.9%, C = 37.8% *Grade 3/4 diarrhoea*: I = 6.3%, C = 0.9% *Grade 1/2 abdominal pain*: I = 21.5%, C = 36.0% *Grade 3/4 abdominal pain*: I = 5.4%, C = 3.5% *Grade 1/2 fever**: I = 27.7%, C = 17.7% *Grade 3/4 fever**: I = 0.9%, C = 0.0%	Progressive disease was defined as a 25% increase in a single measurable lesion, reappearance of measurable disease, clear worsening of assessable disease or the development of new metastatic disease. Stable disease was defined as any measurement not fulfilling the criteria for response or progression and lasting longer than 8 weeks. Non-assessable disease was defined as non-measurable lesions with an elevated CA-125 tumour marker All responses were subject to independent review and confirmation of scans by a radiologist, who was blind to the treatment assignment The response rates for the ITT population would have been conservative because the denominator included women who withdrew from the trial and were not evaluated for response. However, a true ITT analysis was not performed, as only 226 patients and not the total number randomised (235) were included Patients who progressed or whose best response was stable disease after six courses on one regimen were eligible to be switched to the other (alternate) regimen or were removed. A total of 110 (I = 49, C = 61) were entered into this alternate treatment phase. Efficacy analyses reported in this paper only included the ITT population for the randomised phase

continued

A. Clinical effectiveness studies *contd*

Study design	Participants	Interventions	Follow-up/withdrawals and adverse events	Conclusion and comments
contd ten Bokkel Huinink *et al.*, 1997[55]	***Inclusion/exclusion criteria*** Women were included if they had stage III/IV disease; histological diagnosis of epithelial ovarian carcinoma; failed first-line therapy with a Pt-based chemotherapy regimen; at least one bidimensionally measurable lesion as evidenced by computed tomography, magnetic resonance imaging, ultrasound or physical examination; at least a 4-week period between prior surgery, hormonal therapy, radiotherapy or chemo-therapy and treatment in the trial; an Eastern Cooperative Oncology Group performance status of ≤ 2; adequate bone marrow function (white blood cell count ≥ 3500/µl, neutrophil count ≥ 1500/µl and platelet count ≥ 100,000/µl); normal liver function (bilirubin level ≤ 2.0 mg/dl or creatinine clearance > 60 ml/minute). Patients who had received more than one prior chemotherapy regimen or who had received topotecan or paclitaxel previously were excluded Demographic and baseline disease characteristics in the ITT population were comparable between the two treatment groups Patients were stratified by age (< 65 or ≥ 65 years), ascites (present or absent) and response to prior Pt-based therapy (resistant, early, interim or late relapse)	removed or switched to the other treatment	*Grade 1/2 stomatitis*: I = 23.2%, C = 14.0% *Grade 3/4 stomatitis*: I = 0.9%, C = 0.9% *Grade 1/2 dyspnoea*: I = 17.8%, C = 13.2% *Grade 3/4 dyspnoea*: I = 6.3%, C = 5.3% *Grade 1/2 asthenia*: I = 17.0%, C = 9.6% *Grade 3/4 asthenia*: I = 5.4%, C = 3.5% *Grade 1/2 arthralgia*: I = 5.5%, C = 28.9% *Grade 3/4 arthralgia*: I = 0.9%, C = 2.6% *Grade 1/2 myalgia*: I = 3.6%, C = 25.4% *Grade 3/4 myalgia*: I = 0.0%, C = 2.6% *Grade 1/2 neuropathy*: I = 0.9%, C = 15.8% *Grade 3/4 neuropathy*: I = 0.0%, C = 0.0% *Grade 1/2 skeletal pain*: I = 4.5%, C = 11.4% *Grade 3/4 skeletal pain*: I = 0.0%, C = 5.3% *Grade 1/2 flushing*: I = 4.5%, C = 14.1% *Grade 3/4 flushing*: I = 0.0%, C = 0.0% *Grade 1/2 paraesthesiae*: I = 0.9%, C = 29.0% *Grade 3/4 paraesthesiae*: I = 0.0%, C = 0.0%	

continued

A. Clinical effectiveness studies *contd*

Results		
Outcome 1: Response rate	**Outcome 2: Response duration[†]**	**Outcome 3: Time to progression[‡]**
Follow-up data **Responders** *CR*: I = 5/112 (4.5%), C = 3/114 (2.6%) *PR*: I = 18/112 (16.1%), C = 12/114 (10.5%) *TR*: I = 23/112 (20.5%, 95% CI, 13.0 to 28.3), C = 15/114 (13.2%, 95% CI, 7.0 to 19.4); $p = 0.138$ *Subgroup analysis according to Pt-sensitivity* *Resistant disease* *CR*: I = 0/34 (0.0%), C = 0/33 (0.0%) *PR*: I = 3/34 (8.8%), C = 1/33 (3.0%) *TR*: I = 3/34 (8.8%), C = 1/33 (3.0%) *Early relapse* *CR*: I = 0/6 (0.0%), C = 0/10 (0.0%) *PR*: I = 1/6 (16.7%), C = 1/10 (10.0%) *TR*: I = 1/6 (16.7%), C = 1/10 (10.0%) *Interim relapse* *CR*: I = 1/20 (5.0%), C = 0/16 (0.0%) *PR*: I = 3/20 (15.0%), C = 2/16 (12.5%) *TR*: I = 4/20 (20.0%), C = 2/16 (12.5%) *Late relapse* *CR*: I = 4/52 (7.7%), C = 3/55 (5.5%) *PR*: I =11/52 (21.2%), C = 8/55 (14.5%) *TR*: I = 15/52 (28.8%), C = 11/55 (20.0%) *Overall* *CR*: I = 5/112 (4.5%), C = 3/114 (5.7%) *PR*: I = 18/112 (16.1%), C = 12/114 (10.7%) *TR*: I = 23/112 (20.5%), C = 15/114 (13.4%) *Response in relation to baseline disease status* *Age ≤ 40 years*: I = 0.0%, C = 0.0% *Age 41–64 years*: I = 19.7%, C = 12.0% *Age ≥ 65 years*: I = 23.7%, C = 16.7% *Ascites present*: I = 18.9%, C = 7.5% *Ascites absent*: I = 21.3%, C = 16.2% *Performance status = 0*: I = 22.0%, C = 14.3% *Performance status = 1*: I = 25.5%, C = 13.2% *Performance status = 2*: I = 5.0%, C = 11.8%	***Follow-up data*** *Median*: I = 32.1 weeks (range 5.4–53.1, *n* = 23), C = 19.7 (range 6.3–24.3, *n* = 15); RR = 0.416, $p = 0.222$	***Follow-up data*** *Median*: I = 23.1 weeks (range 0.7–62.1, *n* = 112), C = 14.0 weeks (range = 0.1–30.9, *n* = 114); RR = 0.578, $p = 0.021$

continued

A. Clinical effectiveness studies *contd*

***Results* contd**		
Outcome 1: Response rate	**Outcome 2: Response duration[†]**	**Outcome 3: Time to progression[‡]**
Follow-up data *Tumour burden < 5 cm*: I = 33.3%, C = 18.0% *Tumour burden 5–≤ 10 cm*: I = 10.9%, C = 12.5% *First-line therapy responder*: I = 15.2%, C = 10.5% *First-line therapy non-responder*: I = 5.4%, C = 2.6% ***Non-responders*** *Stable disease*: I = 33/112 (29.5%), C = 38/114 (33.3%) *Progressive disease*: I = 39/112 (34.8%), C = 56/114 (49.1%) *Not assessable*: I = 17/112 (15.2%), C = 5/114 (4.4%) *Total*: I = 89/112 (79.5%), C = 99/114 (86.8%)		
Outcome 4: Time to response[§]	**Outcome 5: Survival[¶]**	
Follow-up data *Median*: I = 9.0 weeks (range 3.1–19.0, *n* = 23), C = 6.0 (range 2.4–12.3, *n* = 15); RR = 0.476, *p* = 0.041	***Follow-up data*** *Median*: I = 61.3 weeks (range 0.7–62.1, *n* = 112), C = 42.6 weeks (range 0.1–75.3, *n* = 114); RR = 1.210, *p* = 0.515	

[*] *Excludes reports of the verbatim term febrile neutropenia*
[†] *Measured from the time of initial documented response to the first sign of disease progression*
[‡] *Measured from the time of first study drug administration to documented progressive disease or initiation of third-line therapy*
[§] *Measured from the time of initial drug administration to initial response*
[¶] *Measured from the time of initial drug administration to death*

A. Clinical effectiveness studies *contd*

Study design	Participants	Interventions	Follow-up/withdrawals and adverse events	Conclusion and comments
Schering-Plough Ltd., 2000[59] ***Source*** Company submission ***Objective*** To compare the efficacy and safety of caelyx versus topotecan in patients with epithelial ovarian carcinoma following failure of first-line Pt-based therapy ***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, but 474 included in the ITT analyses ***Disease type*** Epithelial; advanced; occurrence of secondary spread – not stated ***Therapy stage*** Second-line ***Previous treatments*** Pt-based therapy ***Disease present after first-line treatment*** *Residual*: Yes *Refractory*: Yes ***Mean age/age range of participants*** I = 60 years (median = 60, range 25–85), C = 59 years (median = 60, range 27–87) ***Characteristics*** *Mean drug-free interval*: I = 10 months (standard deviation (SD) = 14, median = 6.7, range < 1–110); C = 10 months (SD = 12, median = 7.0, range < 1–82) *Mean CA-125 level at baseline*: I = 932 U/ml (*n* = 224/239; SD = 2455, median = 178, range 3–29,330); C = 900 U/ml (*n* = 224/239; SD = 1933, median = 199, range 3–18,801)	***I group*** *Type*: topotecan *Number randomised*: not stated (but 235 ITT and 209 evaluable) *Route of administration*: intravenous *Dose*: 1.5 mg/m^2 (median = 7, range 3–10) as a 30-minute infusion for 5 days starting on day 1 *Number of cycles*: most patients received 4–5 cycles (estimated by dividing cumulative dose by cycle dose) *Length per cycle*: 21 days (median = 24, range 20–38) ***C group*** *Type*: caelyx *Number randomised*: not stated (but 239 ITT and 207 evaluable) *Route of administration*: intravenous *Dose*: 50 mg/m^2 (median = 50, range 34–58) as a 1-hour infusion *Number of cycles*: most patients received 4–5 cycles (estimated by dividing cumulative dose by cycle dose) *Length per cycle*: 28 days (median = 30, range 27–56) Participants were stratified according to Pt-sensitivity and bulky disease. The authors stated that the demographic characteristics of the participants were repre-	***Withdrawals from I*** *Reasons for discontinuation (ITT population)* *Disease progression*: 110 (46.8%) *Adverse event*: 29 (12.3%) *Death*: 18 (7.7%) *Non-compliance*: 1 (0.4%) *Inappropriate enrollment*: 1 (0.4%) *Other/unknown*: 35 (14.9%) *Protocol-completed (6 months of treatment)*: 39 (16.6%) *Ongoing*: 2 (0.9%) ***Withdrawals from C*** *Reasons for discontinuation (ITT population)* *Disease progression*: 114 (48.0%) *Adverse event*: 39 (16.3%) *Death*: 15 (6.3%) *Non-compliance*: 1 (0.4%); Inappropriate enrollment: 0 (0.0%) *Other/unknown*: 31 (13.0%) *Protocol-completed (6 months of treatment)*: 34 (14.2%) *Ongoing*: 5 (2.1%) ***Adverse events*** Any grade of events were reported by 232/235 (98.7%) of the I group and 222/239 (92.9%) of the C group. Grade 3 events were reported by 176/235 (74.9%) of I patients and 132/239 (55.2%) of C patients, and 158/235 (67.2%) and 20/239 (8.4%) reported grade 4 events, respectively The most common adverse events related to topotecan were haematological (neutropenia, anaemia, thrombocytopenia, leukopenia), nausea and alopecia. Haematological events, nausea and alopecia were less frequent in the C group. Most adverse events in the	***Authors' conclusions*** This final analysis confirms that caelyx 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 caelyx compared with topotecan together with its ease of administration support the role of caelyx as a valuable therapeutic option for patients failing first-line Pt-based treatment ***Comments*** ITT results were mainly presented, and where these were not available evaluable patient results were presented. However, as the total number of patients randomised was not stated, it was not possible to confirm that true ITT analyses were performed

continued

A. Clinical effectiveness studies *contd*

Study design	Participants	Interventions	Follow-up/withdrawals and adverse events	Conclusion and comments
contd Schering-Plough Ltd., 2000[59]	*FIGO stage I at diagnosis*: I = 15/235 (6.4%), C = 11/239 (4.6%) *FIGO stage II at diagnosis*: I = 8/235 (3.4%), C = 13/239 (5.4%) *FIGO stage III at diagnosis*: I = 164/235 (69.8%), C = 175/239 (73.2%) *FIGO stage IV at diagnosis*: I = 48/235 (20.4%), C = 40/239 (16.7%) *Karnofsky performance status < 80*: I = 37/235 (15.7%), C = 39/239 (16.3%) *Karnofsky performance status ≥ 80*: I = 195/235 (83.0%), C = 199/239 (83.3%) Mean sum of lesions at baseline: I = 34 (SD = 39), C = 39 (SD = 54) *Bulky disease (tumour mass > 5 cm) present*: I = 111/235 (47.2%), C = 111/239 (46.4%) *Bulky disease (tumour mass > 5 cm) absent*: I = 124/235 (52.8%), C = 128/239 (53.6%) *Pt-sensitivity/bulky disease – refractory/ present*: I = 64/235 (27.2%), C = 64/239 (26.8%) *Pt-sensitivity/bulky disease – refractory/ absent*: I = 60/235 (25.5%), C = 66/239 (27.6%) *Pt-sensitivity/bulky disease – sensitive/ present*: I = 47/235 (20.0%), C = 47/239 (19.7%) *Pt-sensitivity/bulky disease – sensitve/ absent*: I = 64/235 (27.2%), C = 62/239 (25.9%)	sentative of patients with advanced epithelial ovarian carcinoma and were similar between treatment groups	C group were mild–moderate in severity with the exception of PPE, which was severe in 23%, and stomatitis, which was severe in 8% *All grades of stomatitis*: I = 35/235 (14.9%), C = 95/239 (39.7%) *Grade 3/4 stomatitis*: I = 1/235 (0.4%), C = 20/239 (8.4%) *All grades of neutropenia*: I = 191/235 (81.3%), C = 84/239 (35.1%) *Grade 3/4 neutropenia*: I = 180/235 (76.6%)*, C = 29/239 (12.1%) *All grades of leukopenia*: I = 149/235 (63.4%), C = 87/239 (36.4%) *Grade 3/4 leukopenia*: I = 117/235 (49.8%), C = 24/239 (10.0%) *All grades of anaemia*: I = 169/235 (71.9%), C = 85/239 (35.6%) *Grade 3/4 anaemia*: I = 66/235 (28.1%), C = 13/239 (5.4%) *All grades of thrombocytopenia*: I = 152/235 (64.7%), C = 31/239 (13.0%) *Grade 3/4 thrombocytopenia*: I = 80/235 (34.0%), C = 3/239 (1.3%) *All grades of PPE*: I = 2/235 (0.9%), C = 117/239 (49.0%) *Grade 3/4 PPE*: I = 0/235 (0.0%), C = 55/239 (23.0%) *All grades of alopecia*: I = 115/235 (48.9%), C = 38/239 (15.9%) *Grade 3/4 alopecia*: I = 14/235 (6.0%), C = 3/239 (1.3%)	

continued

A. Clinical effectiveness studies *contd*

Study design	Participants	Interventions	Follow-up/withdrawals and adverse events	Conclusion and comments
contd Schering-Plough Ltd., 2000[59]	*Histological tumour grade well differentiated*: I = 3/235 (1.3%), C = 4/239 (1.7%) *Histological tumour grade moderately differentiated*: I = 13/235 (5.5%), C = 16/239 (6.7%) *Histological tumour grade poorly differentiated*: I = 72/235 (30.6%), C = 53/239 (22.2%) *Histological tumour grade unspecified differentiation*: I = 110/235 (46.8%), C = 125/239 (52.3%) *Histological tumour grade not specified*: I = 37/235 (15.7%), C = 41/239 (17.2%) ***Inclusion/exclusion criteria*** Women were included if they had documented clinically measurable recurrent or persistent epithelial ovarian cancer that was resistant to first-line Pt-based therapy			

continued

A. Clinical effectiveness studies *contd*

Results		
Outcome 1: Time to progression (not defined)	**Outcome 2: Overall survival (not defined)**	**Outcome 3: Response rate[†]**
Follow-up data *ITT population* *Number progressed*: I = 222/235, C = 217/239 *Number censored*: I = 13/235, C = 22/239 *Median time to progression (Kaplan-Meier estimate)*: I = 119 days, C = 113 days; *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* *Number progressed*: I = 197/209, C = 185/207 Number censored: I = 12/209, C = 22/207 *Median time to progression (Kaplan-Meier estimate)*: I = 134 days, C = 148 days; *p* (stratified log-rank test) = 0.026, 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* *Age < 65 years*: I = 138/235, median time to progression = 119 days; C = 156/239, median time to progression = 121 days; HR = 1.176 (90% CI, 1.002 to 1.381) *Age ≥ 65 years*: I = 97/235, median time to progression = 128 days; C = 83/239, median time to progression = 103 days; HR = 1.147 (90% CI, 0.879 to 1.498) *Karnofsky performance status score < 80*: I = 37/235, median time to progression = 71 days; C = 39/239, median time to progression = 53 days; HR = 0.867 (90% CI, 0.567 to 1.327) *Karnofsky performance status score ≥ 80*: I = 194/235, median time to progression = 134 days; C = 200/239, median time to progression = 131 days; HR = 1.157 (90% CI, 0.971 to 1.379)	***Follow-up data*** *ITT population* *Number dead*: I = 149/235, C = 136/239 *Number alive*: I = 86/235, C = 103/239 *Median survival (based on Kaplan-Meier estimates)*: I = 397 days, C = 420 days; *p* (stratifed log-rank test) = 0.340, HR = 1.121 (90% CI, 0.920 to 1.367; 91.6% CI, 0.911 to 1.381) *Evaluable patients only* *Number dead*: I = 123/209, C = 108/207 *Number alive*: I = 86/209, C = 99/207 *Median survival (based on Kaplan-Meier estimates)*: I = 454 days, C = 483 days; *p* (stratifed log-rank test) = 0.410, 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* *Age < 65 years*: I = 138/235, median survival = 394 days; C = 156/239, median survival = 439 days; HR = 1.143 (90% CI, 0.886 to 1.474) *Age ≥ 65 years*: I = 97/235, median survival = 435 days; C = 83/239, median survival = 407 days; HR = 1.008 (90% CI, 0.728 to 1.396) *Karnofsky performance status score < 80*: I = 37/235, median survival = 144 days; C = 39/239, median survival = 137 days; HR = 0.847 (90% CI, 0.544 to 1.319) *Karnofsky performance status score ≥ 80*: I = 194/235, median survival = 460 days; C = 200/239, median survival = 462 days; HR = 1.147 (90% CI, 0.915 to 1.437)	***Baseline data*** Not stated ***Follow-up data*** *ITT population* *Overall CR*: I = 11/235 (4.7%), C = 9/239 (3.8%) *Pt-s CR*: I = 10/111 (9.0%), C = 8/109 (7.3%) *Pt-r CR*: I = 1/124 (0.8%), C = 1/130 (0.8%) *Overall PR*: I = 29/235 (12.3%), C = 38/239 (15.9%) *Pt-s PR*: I = 22/111 (19.8%), C = 23/109 (21.1%) *Pt-r PR*: I = 7/124 (5.6%), C = 15/130 (11.5%) *Overall TR*: I = 40/235 (17%), C = 47/239 (19.7%) *Pt-s TR*: I = 32/111 (28.8%), C = 31/109 (28.4%) *Pt-r TR*: I = 8/124 (6.5%), C = 16/130 (12.3%) *Evaluable patients only* *Responders*: I = 40/209 (19.1%), C = 47/207 (22.7%); *p* (Cochran-Mantel-Haenszel) = 0.332 *CR*: I = 11/209 (5.3%), C = 9/207 (4.3%) *PR*: I = 29/209 (13.9%; 95% CI, 13.8 to 24.5), C = 38/209 (18.4%; 95% CI, 17.0 to 28.4) 95% CI for treatment difference, –4.2 to 11.4 *Non-responders*: I = 169/209 (80.9%), C = 160/207 (77.3%) *Unconfirmed CR*: I = 3/209 (1.4%), C = 1/207 (0.5%) *Unconfirmed PR*: I = 18/209 (8.6%), C = 11/207 (5.3%) *Stable disease*: I = 91/209 (43.5%), C = 73/207 (35.5%) *Progressive disease*: I = 50/209 (23.9%), C = 70/207 (33.8%) *No data available*: I = 7/209 (3.3%), C = 5/207 (2.4%)

continued

A. Clinical effectiveness studies *contd*

***Results* contd**		
Outcome 1: Time to progression (not defined)	**Outcome 2: Overall survival (not defined)**	**Outcome 3: Response rate[†]**
Drug-free interval after first-line therapy ≤ 6 months: I = 109/235, median time to progression = 94 days; C = 102/239, median time to progression = 57 days; HR = 1.095 (90% CI, 0.855 to 1.401) *Drug-free interval after first-line therapy > 6– ≤ 18 months*: I = 94/235, median time to progression = 131 days; C = 107/239, median time to progression = 148 days; HR = 1.170 (90% CI, 0.916 to 1.496) *Drug-free interval after first-line therapy > 18 months*: I = 32/235, median time to progression = 228 days; C = 30/239, median time to progression = 290 days; HR = 1.530 (90% CI, 0.918 to 2.549)	*Drug-free interval after first-line therapy ≤ 6 months*: I = 109/235, median survival = 276 days; C = 102/239, median survival = 249 days; HR = 1.017 (90% CI, 0.777 to 1.332) *Drug-free interval after first-line therapy > 6--≤ 18 months*: I = 94/235, median survival = 491 days; C = 107/239, median survival = 523 days; HR = 1.126 (90% CI, 0.815 to 1.557) *Drug-free interval after first-line therapy > 18 months*: I = 32/235, median survival = 661 days; C = 30/239, median survival = 785 days; HR = 1.782 (90% CI, 0.795 to 3.992)	
Bulky disease present: I = 111/235, median time to progression = 110 days; C = 111/239, median time to progression = 92 days; HR = 1.143 (90% CI, 0.903 to 1.447) *Bulky disease absent*: I = 124/235, median time to progression = 128 days; C = 128/239, median time to progression = 131 days; HR = 1.206 (90% CI, 0.969 to 1.500)	*Bulky disease present*: I = 111/235, median survival = 343 days; C = 111/239, median survival = 376 days; HR = 1.093 (90% CI, 0.833 to 1.436) *Bulky disease absent*: I = 124/235, median survival = 463 days; C = 128/239, median survival = 523 days; HR = 1.154 (90% CI, 0.865 to 1.539)	
Pt-s: I = 111/235, median time to progression = 163 days; C = 109/239, median time to progression = 202 days; HR = 1.349 (90% CI, 1.065 to 1.709) *Pt-r*: I = 124/235, median time to progression = 95 days; C = 130/239, median time to progression = 66 days; HR = 1.046 (90% CI, 0.841 to 1.301)	*Pt-s*: I = 111/235, median survival = 498 days; C = 109/239, median survival = 756 days; HR = 1.720 (90% CI, 1.222 to 2.422) *Pt-r*: I = 124/235, median survival = 289 days; C = 130/239, media n survival = 249 days; HR = 0.895 (90% CI, 0.700 to 1.143)	
Ascites present: I = 65/235, median time to progression = 102 days; C = 77/239, median time to progression = 63 days; HR = 0.930 (90% CI, 0.691 to 1.254) *Ascites absent*: I = 168/235, median time to progression = 134 days; C = 162/239, median time to progression = 157 days; HR = 1.295 (90% CI, 1.065 to 1.575)	*Ascites present*: I = 65/235, median survival = 276 days; C = 77/239, median survival = 197 days; HR = 0.982 (90% CI, 0.708 to 1.361) *Ascites absent*: I = 168/235, median survival = 447 days; C = 162/239, median survival = 539 days; HR = 1.330 (90% CI, 1.025 to 1.726)	

continued

A. Clinical effectiveness studies *contd*

***Results* contd**

Outcome 4: Time to response (not defined)	Outcome 5: Duration of response (not defined)	Outcome 6: QoL[‡]
Follow-up data *ITT population* Data not provided *Evaluable patients only* (I = 40, C = 47) *Median (Kaplan-Meier estimate)*: I = 8.1 (range 5.6–44.1), C = 8.1 (range 4.0–28.4); *p* (log-rank test) = 0.448	***Follow-up data*** *ITT population* Data not provided *Evaluable patients only* (I = 40, C = 47) *Percentage censored*: I = 62.5, C = 57.4 *Median (Kaplan-Meier estimate)*: I = 25.7 (range 7.0–55.1; both censored observations), C = 30.1 (range 5.0–90.4; both censored observations); *p* (log-rank test) = 0.891	***Baseline data*** Not stated, but function and symptom scale scores were similar for both the I and C groups ***Follow-up data*** Patients with maintained or improved QoL scores at 12 weeks (based on number of patients remaining after 12 weeks) *Total physical functioning*: I = 61/107 (57.0%), C = 66/118 (55.9%) *Pt-s physical functioning*: I = 30/57 (52.6%), C = 38/65 (58.5%) *Pt-r physical functioning*: I = 30/50 (60.0%), C = 28/53 (52.8%) *Total role functioning*: I = 63/109 (57.8%), C = 77/118 (65.3%) *Pt-s role functioning*: I = 30/59 (50.8%), C = 36/65 (55.4%) *Pt-r role functioning*: I = 33/50 (66.0%), C = 41/53 (77.4%) *Total emotional functioning*: I = 80/108 (74.1%), C = 80/119 (67.2%) *Pt-s emotional functioning*: I = 40/58 (69.0%), C = 38/65 (58.5%) *Pt-r emotional functioning*: I = 40/50 (80.0%), C = 42/54 (77.8%) *Total cognitive functioning*: I = 79/108 (73.1%), C = 87/119 (73.1%) *Pt-s cognitive functioning*: I = 42/58 (72.4%), C = 48/65 (73.8%) *Pt-r cognitive functioning*: I = 37/50 (74.0%), C = 39/54 (72.2%) *Total social functioning*: I = 69/108 (63.9%), C = 82/119 (68.9%) *Pt-s social functioning*: I = 34/58 (58.6%), C = 39/65 (60.0%) *Pt-r social functioning*: I = 35/50 (70.0%), C = 43/54 (79.6%) *Total global QoL*: I = 54/104 (51.9%), C = 68/117 (58.1%) *Pt-s global QoL*: I = 25/56 (44.6%), C = 36/64 (56.3%) *Pt-r global QoL*: I = 29/48 (60.4%), C = 32/53 (60.4%) *Total fatigue*: I = 61/109 (56.0%), C = 67/118 (56.8%) *Pt-s fatigue*: I = 30/59 (50.8%), C = 29/65 (44.6%) *Pt-r fatigue*: I = 31/50 (62.0%), C = 38/53 (71.7%) *Total nausea/vomiting*: I = 77/109 (70.6%), C = 86/119 (72.3%) *Pt-s nausea/vomiting*: I = 42/59 (71.2%), C = 44/65 (67.7%) *Pt-r nausea/vomiting*: I = 35/50 (70.0%), C = 42/54 (77.8%) *Total pain*: I = 88/109 (80.7%), C = 76/119 (63.9%) *Pt-s pain*: I = 49/59 (83.1%), C = 35/65 (53.8%) *Pt-r pain*: I = 39/50 (78%), C = 41/54 (75.9%)

continued

A. Clinical effectiveness studies *contd*

***Results* contd**		
Outcome 4: Time to response (not defined)	**Outcome 5: Duration of response (not defined)**	**Outcome 6: QoL[‡]**
		% of patients (ITT population) with global QoL (no other scales) *Week 3* *Improved/stable score*: I = 39.6% *Worsened score*: I = 31.9% *Week 4* *Improved/stable score*: C = 40.2% *Worsened score*: C = 32.6% *Week 6* *Improved/stable score*: I = 33.6% *Worsened score*: I = 29.4% *Week 8* *Improved/stable score*: C = 33.5% *Worsened score*: C = 28.9% *Week 9* *Improved/stable score*: I = 27.2% *Worsened score*: I = 23.0% *Week 12* *Improved/stable score*: I = 23.4%, C = 28.5% *Worsened score*: I = 20.4%, C = 20.5% *Week 15* *Improved/stable score*: I = 20.0% *Worsened score*: I = 17.4% *Week 16* *Improved/stable score*: C = 21.8% *Worsened score*: C = 19.2% *Week 18* *Improved/stable score*: I = 20.0% *Worsened score*: I = 13.2% *Week 20* *Improved/stable score*: C = 18.0% *Worsened score*: C = 16.7% *Week 21* *Improved/stable score*: I = 11.9% *Worsened score*: I = 10.6% *Week 24* *Improved/stable score*: I = 10.2%, C = 12.1% *Worsened score*: I = 9.4%, C = 14.6%

[*] *Includes two deaths*
[†] *A responder was defined as a patient with at least a durable response (CR or PR). The durable response was the patient's maximum confirmed response*
[‡] *Assessed using the self-administered EORTC QLQ-C30 questionnaire at 12 weeks*

A. Clinical effectiveness studies *contd*

Study design	Participants	Interventions	Follow-up/withdrawals and adverse events	Conclusion and comments
Fields 2000[57] ***Source*** Company submission ***Objective*** To compare the efficacy and toxicity of topotecan and paclitaxel in patients with advanced epithelial ovarian cancer who had progressed during or after treatment with one Pt-based therapy regimen ***Type of publication*** Final report ***Trial identification*** 039 ***Phase*** Phase III ***Method of randomisation*** Centralised telephone randomisation ***Concealed allocation*** Yes ***Blinding*** *Assessor*: yes *Carer*: not stated *Patient*: not stated *Success of blinding checked*: not stated	***Number randomised*** 235, but 226 included in the ITT analyses ***Disease type*** Epithelial; stage III/IV; occurrence of secondary spread – yes ***Therapy stage*** Second-line ***Previous treatments*** *Radiotherapy*: I = 3, C = 4 *Immunotherapy*: I = 2, C = 1 *Hormonal therapy*: I = 0, C = 6 *Prior chemotherapy* *Cyclophosphamide*: I = 67.0%, C = 69.0% *Carboplatin*: I = 55.0%, C = 61.0% *Cisplatin*: I = 54.0%, C = 51.0% *Epirubicin*: I = 8.0%, C = 5.3% *Doxorubicin hydrochloride*: I = 4.5%, C = 6.1% *Doxorubicin*: I = 3.6%, C = 3.5% *Etoposide*: I = 1.8%, C = 0.9% *Mitoxantrone*: I = 1.8%, C = 0.9% *Ifosfamide*: I = 1.8%, C = 0.0% *Epirubicin hydrochloride*: I = 0.9%, C = 1.8% *Chlorambucil*: I = 0.9%, C = 0.9% *Prednimustine*: I = 0.9%, C = 0.0% *Fluorouracil*: I = 0.0%, C = 0.9% *Pirarubicin*: I = 0.0%, C = 0.9% ***Disease present after first-line treatment*** *Residual*: yes *Refractory*: yes ***Mean age/age range of participants*** I = 59.2 years (range 29–85), C = 58.3 years (range 29–79)	***I group*** *Type*: topotecan *Number randomised*: 117; 112 (ITT), 85 evaluable *Route of administration*: intravenous *Dose*: 1.5 mg/m^2/day for 5 days *Number of cycles*: median per participant = 6 (range 1–20) *Length per cycle*: 21 days ***C group*** *Type*: paclitaxel *Number randomised*: 118; 114 (ITT), 99 evaluable *Route of administration*: intravenous Dose: 175 mg/m^2/days as a 3-hour infusion *Number of cycles*: median per participant = 5.5 (range 1–18) *Length per cycle*: 21 days After the randomised phase, 61 switched from paclitaxel to topotecan and 49 from topotecan to paclitaxel. This part of the trial is referred to as the crossover trial, but is not considered here. The data presented in this abstract was analysed on an ITT basis	***Withdrawals from I*** Five participants did not receive topotecan and were not included in the ITT population. Of these 112, 85 completed the trial and 27 (24.1%) were withdrawn (but included in the ITT) for the following reasons: *Adverse experience*: 13 (11.6%) *Protocol violation*: 1 (0.9%) *Lost to follow-up*: 2 (1.8%) *Other*: 11 (9.8%) ***Withdrawals from C*** Four participants did not receive paclitaxel and were not included in the ITT population. Of these 114, 99 completed the trial and 15 (13.2%) were withdrawn (but included in the ITT) for the following reasons: *Adverse experience*: 8 (7.0%) *Protocol violation*: 0 (0.0%) *Lost to follow-up*: 2 (1.8%) *Other*: 5 (4.4%) ***Adverse events*** 56/112 (50.0%) I group patients experienced serious side-effects compared with 34/114 (29.8%) C group patients 11/112 patients randomised to I died within 30 days of receiving topotecan due to the following: *Progressive disease*: 7 *Sepsis associated with haematological toxicity*: 2 *Other causes*: 2 3/114 patients randomised to C died within 30 days of receiving paclitaxel due to the following: *Progressive disease*: 2 *Suspected pulmonary embolism*: 1 *Haematologic toxicity (ITT population)* *All grades of leukopenia*: I = 110/112 (98.2%), C = 97/114 (85.1%) *Grade 4 leukopenia*: I = 38/112 (33.9%), C = 2/114 (1.8%)	***Authors' conclusions*** Topotecan at 1.5 mg/m^2/day for 5 days every 3 weeks has a response rate that is numerically superior to paclitaxel given at 175 mg/m^2 as a 3-hour infusion every 3 weeks (21 versus 14%; $p = 0.196$). The median response duration was also longer in patients treated with topotecan compared with paclitaxel (25.9 versus 21.6 weeks; $p = 0.476$). Patients treated with topotecan had a longer time to progression than those treated with paclitaxel (18.9 versus 14.7 weeks). Responses to topotecan were also seen in the alternate therapy phase (13.1%). A higher rate of haematological toxicities was observed with topotecan than with this paclitaxel regimen, but these toxicities were reversible, non-cumulative and manageable, and infrequently led to serious sequelae. Non-haematological toxicity with topotecan therapy were relatively mild. Topotecan is an effective new agent for the treatment of advanced ovarian carcinoma ***Comments*** A true ITT analysis was not performed because only 226 patients and not all those randomised (235) were included

continued

A. Clinical effectiveness studies *contd*

Study design	Participants	Interventions	Follow-up/withdrawals and adverse events	Conclusion and comments
contd Fields 2000[57] ***Length of follow-up*** Not stated ***ITT analysis performed*** Yes	***Characteristics*** *Performance status= 0*: I = 41/112 (36.6%), C = 42/114 (36.8%) *Performance status = 1*: I = 51/112 (45.5%), C = 53/114 (46.5%) *Performance status = 2*: I = 20/112 (17.9%), C = 17/114 (14.9%) *Performance status = 3*: I = 0/112 (0.0%), C = 2/114 (1.8%) *Mean weight*: = 65.0 kg (range 41–95), C = 67.7 kg (range 46–136) *Tumour diameter < 5 cm*: I = 56/112 (50.0%), C = 50/114 (43.9%) *Tumour diameter ≥ 5 cm*: I = 56/112 (50.0%), C = 59/114 (51.8%) *Tumour diameter not determined*: I = 2/112 (1.8%), C = 2/114 (1.8%) *Tumour histology malignant serous*: I = 58/112 (51.8%), C = 59/114 (51.8%) *Tumour histology malignant mucinous*: I = 6/112 (5.4%), C = 6/114 (5.3%) *Tumour histology malignant endometriod*: I = 10/112 (8.9%), C = 15/114 (13.2%) *Tumour histology undifferentiated carcinoma*: I = 18/112 (16.1%), C = 8/114 (7.0%) *Tumour histology other*: I = 20/112 (17.9%), C = 26/114 (22.8%) *Histological grade 0–1*: I = 6/112 (5.0%), C = 8/114 (7.0%) *Histological grade 2*: I = 23/112 (20.5%), C = 29/114 (25.4%) *Histological grade 3*: I = 56/112 (50.0%), C = 50/114 (43.9%) *Histological grade 4*: I = 10/112 (8.9%), C = 12/114 (10.5%) *Histological grade not determined*: I = 17/112 (15.2%), C = 15/114 (13.2%)		*All grades of neutropenia*: I = 109/112 (97.3%), C = 97/114 (85.1%) *Grade 4 neutropenia*: I = 89/112 (79.5%), C = 24/114 (21.1%) *All grades of thrombocytopenia*: I = 108/112 (96.4%), C = 21/114 (18.4%) *Grade 4 thrombocytopenia*: I = 30/112 (26.8%), C = 3/114 (2.6%) *All grades of anaemia*: I = 111/112 (99.1%), C = 100/114 (87.7%) *Grade 4 anaemia*: I = 4/112 (3.6%), C = 3/114 (2.6%) *Non-haematological toxicity (ITT population)* *All grades of alopecia*: I = 86/112 (76.8%), C = 106/114 (93.0%) *Grade 4 alopecia*: I = 0/112 (0.0%), C = 0/114 (0.0%) *All grades of nausea*: I = 89/112 (79.5%), C = 39/114 (34.2%) *Grade 4 nausea*: I = 1/112 (0.9%), C = 0/114 (0.0%) *All grades of vomiting*: I = 73/112 (65.2%), C = 35/114 (30.0%) *Grade 4 vomiting*: I = 4/112 (3.6%), C = 1/114 (0.9%) *All grades of fatigue*: I = 47/112 (42.0%), C = 36/114 (31.6%) *Grade 4 fatigue*: I = 0/112 (0.0%), C = 0/114 (0.0%) *All grades of constipation*: I = 50/112 (44.6%), C = 35/114 (30.7%) *Grade 4 constipation*: I = 1/112 (0.9%), C = 0/114 (0.0%) *All grades of diarrhoea*: I = 48/112 (42.9%), C = 44/114 (38.6%) *Grade 4 diarrhoea*: I = 1/112 (0.9%), C = 0/114 (0.0%) *All grades of abdominal pain*: I = 34/112 (30.4%), C = 45/114 (39.5%) *Grade 4 abdominal pain*: I = 2/112 (1.8%), C = 1/114 (0.9%) *All grades of fever*:* I = 31/112 (27.7%), C = 21/114 (18.4%) *Grade 4 fever*:* I = 0/112 (0.0%), C = 0/114 (0.0%) *All grades of stomatitis*: I = 28/112 (25.0%), C = 17/114 (14.9%) *Grade 4 stomatitis*: I = 0/112 (0.0%), C = 0/114 (0.0%) *All grades of asthenia*: I = 26/112 (32.2%), C = 15/114 (13.2%) *Grade 4 asthenia*: I = 2/112 (1.8%), C = 0/114 (0.0%) *All grades of arthralgia*: I = 0/112 (0.0%), C = 39/114 (34.2%) *Grade 4 arthralgia*: I = 0/112 (0.0%), C = 0/114 (0.0%) *All grades of myalgia*: I = 0/112 (0.0%), C = 33/114 (28.9%) *Grade 4 myalgia*: I = 0/112 (0.0%), C = 0/114 (0.0%) *All grades of neuropathy*: I = 0/112 (0.0%), C = 20/114 (17.5%) *Grade 4 neuropathy*: I = 0/112 (0.0%), C = 0/114 (0.0%) *All grades of skeletal pain*: I = 0/112 (0.0%), C = 19/114 (16.7%) *Grade 4 skeletal pain*: I = 0/112 (0.0%), C = 0/114 (0.0%) *All grades of flushing*: I = 0/112 (0.0%), C = 16/114 (14.0%) *Grade 4 flushing*: I = 0/112 (0.0%), C = 0/114 (0.0%) *All grades of paraesthesiae*: I = 0/112 (0.0%), C = 36/114 (31.6%) *Grade 4 paraesthesiae*: I = 0/114 (0.0%), C = 0/114 (0.0%)	The methods section of the report stated that HRs with 95% CIs were calculated. Survival curves were presented for the duration of response, time to progression and survival, but no HRs were reported. HRs are the most appropriate representation of survival or time-to-event data. It was also not clear from the data presented whether the median times quoted were based on Kaplan-Meier estimates CR was defined as the complete disappearance of all known measurable and evaluable disease determined by two measurements not less than 4 weeks apart. PR was defined as a > 50% decrease in the sum of the products of the greatest length and perpendicular width of all measurable lesions for at least 4 weeks with no simultaneous increase in a known lesion (> 25%) or appearance of new lesions or increase in evaluable disease during this period. Stable/no response was defined as a state of response which was less than partial or progression and lasted for ≥ 8 weeks. Progression was 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

continued

A. Clinical effectiveness studies *contd*

Study design	Participants	Interventions	Follow-up/withdrawals and adverse events	Conclusion and comments
contd Fields 2000[57]	***Inclusion/exclusion criteria*** Women included in the study were aged ≥ 18 years; provided informed consent; had a histological diagnosis of metastatic epithelial ovarian cancer; had failed first-line therapy with one regimen containing cisplatin or carboplatin (i.e. Pt-r/-resistant); had measurable disease defined by diagnostic studies; had a ≥ 4-week gap since last surgery, hormonal therapy, chemotherapy or radiotherapy; had a ≥ 60-day gap since last immunotherapy; had a performance status of ≤ 2 (ECOG scale) and life expectancy of ≥ 3 months; had blood and liver laboratory values within listed limits. Women were excluded if they had received more than one previous chemotherapy regimen; had borderline histological diagnosis; had had a previously documented brain/leptomeningeal lesion; had had prior camptothecin treatment; had grade 2 neuropathy; had cardiac problems; had concurrent other severe medical problems; had uncontrolled infection; were receiving another investigational drug Demographic and baseline disease characteristics in the ITT population were comparable between the two treatment groups. Patients were stratified by age (< or ≥ 65 years), ascites (present or absent) and response to prior Pt-based therapy (resistant, early, interim or late relapse)			metastases even if there was response outside of the brain, or significant worsening of the condition presumed to be related to malignancy With the exception of H_1- and H_2-antagonists and dexamethasone prior to paclitaxel infusion, the concomittant medications administered were similar for both groups and were central nervous system agents for relief of pain. The use of anti-emetics, anti-infectives and G-CSF was more frequent in I patients than in C patients Patients who progressed were removed from the study or switched to the alternate drug. Patients whose best response was stable disease after six courses of one regimen could also be removed from the study or switched to the alternate regimen. These patients were considered in the crossover part of this study, but only the ITT results of the randomised (and not the crossover) part of this study were considered here All responses were verified by independent radiological review The numbers of haematological adverse effects presented in this report varied slightly from those presented elsewhere in the submission[28]

continued

A. Clinical effectiveness studies *contd*

Results		
Outcome 1: Response rate (see comments section for definition)	**Outcome 2: Median response duration[†]**	**Outcome 3: QoL[‡]**
Follow-up data *ITT population* *CR*: I = 5/112 (4.5%), C = 3/114 (2.6%) *PR*: I = 18/112 (16.1%), C = 13/114 (11.4%) *TR*: I = 23/112 (20.6%, 95% CI, 13.1 to 28.0), C = 16/114 (14.0%, 95% CI, 7.7 to 20.4); p = 0.196 *Difference in response rate*: 6.5% (95% CI, –3.3 to 16.3) *Total population randomised including those not treated and excluded from the ITT analysis* *TR*: I = 18.8% (95% CI, 11.7 to 25.9), C = 13.6% (95% CI, 7.4 to 19.7) *Subgroup analysis based on ITT population* *Refractory patients* *CR*: I = 0/34 (0.0%), C = 0/33 (0.0%) *PR*: I = 3/34 (8.8%), C = 1/33 (3.0%) *TR*: I = 3/34 (8.8%), C = 1/33 (3.0%) *Early relapse patients* *CR*: I = 0/6 (0.0%), C = 0/11 (0.0%) *PR*: I = 1/6 (16.7%), C = 1/11 (9.1%) *TR*: I = 1/6 (16.7%), C = 1/11 (9.1%) *Interim relapse patients* *CR*: I = 1/20 (5.0%), C = 0/16 (0.0%) *PR*: I = 2/20 (10.0%), C = 2/16 (12.5%) *TR*: I = 3/20 (15.0%), C = 2/16 (12.5%) *Late relapse patients* *CR*: I = 4/52 (7.7%), C = 3/54 (5.6%) *PR*: I = 12/52 (23.1%), C = 9/54 (16.7%) *TR*: I = 16/52 (30.8%), C = 12/54 (22.2%) *Baseline performance status = 0* *CR*: I = 2/41 (4.9%), C = 1/42 (2.4%) *PR*: I = 6/41 (14.6%), C = 7/42 (16.7%) *TR*: I = 8/41 (19.5%), C = 8/42 (19.0%)	***Follow-up data*** I = 25.9 weeks (95% CI, 22.1 to 32.9; n = 23), C = 21.6 weeks (95% CI, 16.0 to 34.0; n = 16); RR = 0.778; p = 0.476	***Baseline data*** See below ***Follow-up data*** *Total population* In I group patients, median changes from baseline to end of best response were only observed for the emotional function and global QoL scales. In C group patients, there was only a median change for the emotional function scale from baseline to end of best response *Emotional function median change*: I = 8 (range –83– +75), C = 8 (range –100– +75) *Global QoL median change*: I = –8 (range –58– +83) Overall, there were minimal changes between topotecan at baseline and end of best response, and between topotecan and paclitaxel *Responders* Amongst responders there were similar median changes in the same QoL scales from baseline to end of best response in I group patients: *Emotional function median change*: I = 9 (range –42– +75) *Global QoL median change*: I = –8 (range –58– +83) However, in C group patients the following changes were observed in responders: *Fatigue median change*: C = –11 (range –45– +12) *Pain median change*: C = –17 (range –67– +33) *Global QoL median change*: C = 16 (range –50– +34) *Sleep disturbance median change*: C = –33 (range –100– +33)

continued

A. Clinical effectiveness studies *contd*

***Results* contd**		
Outcome 1: Response rate	**Outcome 2: Median response duration[†]**	**Outcome 3: QoL[‡]**
Baseline performance status = 1 *CR:* I = 2/51 (3.9%), C = 2/52 (3.8%) *PR:* I = 12/51 (23.5%), C = 5/52 (9.6%) *TR:* I = 14/51 (27.5%), C = 7/52 (13.5%) *Baseline performance status = 2* *CR:* I = 1/20 (5.0%), C = 0/17 (0.0%) *PR:* I = 0/20 (0.0%), C = 1/17 (5.9%) *TR:* I = 1/20 (5.0%), C = 1/17 (5.9%) *Baseline performance status = 3* *CR:* I = 0/0 (0.0%), C = 0/0 (0.0%) *PR:* I = 0/0 (0.0%), C = 0/0 (0.0%) *TR:* I = 0/0 (0.0%), C = 0/0 (0.0%) *Largest baseline tumour < 2 cm* *CR:* I = 0/0 (0.0%), C = 0/0 (0.0%) *PR:* I = 0/0 (0.0%), C = 0/0 (0.0%) *TR:* I = 0/0 (0.0%), C = 0/0 (0.0%) *Largest baseline tumour 2–< 5 cm* *CR:* I = 5/54 (9.3%), C = 2/50 (4.0%) *PR:* I = 13/54 (24.1%), C = 8/50 (16.0%) *TR:* I = 18/54 (33.3%), C = 10/50 (20.0%) *Largest baseline tumour 5–10 cm* *CR:* I = 0/45 (0.0%), C = 1/49 (2.0%) *PR:* I = 5/45 (11.1%), C = 5/49 (10.2%) *TR:* I = 5/45 (11.1%), C = 6/49 (12.2%) *Largest baseline tumour > 10 cm* *CR:* I = 0/9 (0.0%), C = 0/14 (0.0%) *PR:* I = 0/9 (0.0%), C = 0/14 (0.0%) *TR:* I = 0/9 (0.0%), C = 0/14 (0.0%)		

continued

A. Clinical effectiveness studies *contd*

***Results* contd**		
Outcome 4: Median time to response[§]	**Outcome 5: Median survival[¶]**	**Outcome 6: Median time to progression[**]**
Follow-up data I = 7.6 weeks (95% CI, 6.1 to 10.6; *n* = 23), C = 6.0 weeks (95% CI, 5.6 to 9.1; *n* = 16); RR = 0.615, *p* = 0.147	*Follow-up data* *Intervention group* I = 63.0 weeks (95% CI, 46.6 to 71.9), C = 53 weeks (95% CI, 42.3 to 68.7); *p* = 0.093	*Follow-up data* *Total population*: I = 18.9 weeks (95% CI, 12.1 to 23.6; *n* = 112), C = 14.7 weeks (95% CI, 11.9 to 18.3; *n* = 114); RR = 0.764, *p* = 0.072 *Responders only*: I = 37.1 weeks (95% CI, 32.6 to 41.6; *n* = 23), C = 29.9 weeks (95% CI, 23.4 to 39.3; *n* = 16)

[*] *Excludes reports of the verbatim term febrile neutropenia*

[†] *Time from the initial documented response to the first sign of disease progression*

[‡] *Determined using the EORTC QLQ-C30 questionnaire*

[§] *Time from the first dose of study medication to the time of initial documented response*

[¶] *Time from the first dose of study medication until death due to any cause*

[**] *Time from first study drug administration until progressive disease/alternate therapy*

B. Economic evaluations

Study design	Data sources	Clinical outcome data and costs used	Statistical analysis and results	Sensitivity analysis	Authors' conclusions/ implications and comments
Bennett *et al.*, 1999[60] and Stinson *et al.*, 1999[61] ***Source*** Database searches ***Objective*** To compare the out-of-pocket costs and costs to the Medicare system of second-line therapies for Pt-r ovarian cancer using a CMA ***Type of evaluation*** Authors stated that it was a CMA, but it is, in fact, a CCA ***Matrix grading*** Unclear ***Link between cost/ effectiveness data*** Retrospective/ disconnected ***Comparators*** Topotecan (1.5 mg/m^2 as a 30-minute infusion daily for 5 consecutive days every 21 days); paclitaxel (175 mg/m^2 as a 3-hour infusion every 21 days); altretamine	***Source of clinical effectiveness data*** Systematic review/ meta-analysis The assumption of equivalent clinical effectiveness was based on the following outcome data from the identified studies: 1. Median number of cycles 2. Response rate (CRs and PRs) 3. Progressive disease 4. Median time to progression 5. Median overall survival 6. Adverse effects ***Source of cost data*** 1. Physician services (estimated from Oncology Outpatient Medicare Reimbursment Protocol 1996 Relative Value Units and the Primary Care Conversion Factor) 2. Medication costs (based on 1996 USA average wholesale price) 3. Laboratory fees and blood products (hospital fee lists for Medicare reimbursement) 4. Comparative costs were limited to the costs incurred during the time of therapy ***Models used*** A cost-analysis model was used, including the administration protocol and toxicity incidence for each regimen. Probability estimates for the model were obtained from published data. The cost per chemotherapy agent was calculated as the product of the probability estimate for each adverse event and the cost of monitoring and treatment of the event plus the cost of chemotherapy agent	***Clinical effectiveness*** Assumption of equivalent clinical efficacy of the four agents was based on the following data from six studies for paclitaxel (n = 452), three studies for topotecan (n = 234), three studies for altretamine (n = 135) and two studies for etoposide (n = 72), which were identified through a systematic review. *Median number of cycles* *Paclitaxel*: 6 *Topotecan*: 4 *Altretamine*: 6 *Etoposide*: 4 *Response rate (CRs and PRs)* *Paclitaxel*: 7.0–26.0% *Topotecan*: 13.3–16.3% *Altretamine*: 14.0–15.0% *Etoposide*: 26.0–26.8% *Patients with progressive disease* *Paclitaxel*: 31.0–47.0% *Topotecan*: 25.0–63.0% *Altretamine*: 43.0–48.0% *Etoposide*: 61.0% *Median time to progression* *Paclitaxel*: 4.0–10.6 months *Topotecan*: 5.4-8.9 months *Altretamine*: 5.0–12 months *Etoposide*: 5.7 months *Median overall survival* *Paclitaxel*: 6.0–15.6 months *Topotecan*: 10.0–15.2 months *Altretamine*: ≥ 11.0 months (inadequate follow-up) *Etoposide*: 10.8 months	***Statistical analysis used*** See details of model Total costs per patient treatment were calculated in terms of Medicare reimbursable and patient out-of-pocket costs ***Summary of results*** *Paclitaxel* *Total cost*: $15,767 *Medicare cost*: $15,684 *Patient cost*: $83 *Topotecan* *Total cost*: $18,635 *Medicare cost*: $18,598 *Patient cost*: $37 *Altretamine* *Total cost*: $4477 *Medicare cost*: $0 *Patient cost*: $4477 *Etoposide* *Total cost*: $7721 *Medicare cost*: $7655 *Patient cost*: $66 ***Applicable to NHS*** No	***Base estimate*** *Paclitaxel* *Cost per cycle*: $2628 *Total cost*: $15,767 *Topotecan* *Cost per cycle*: $4659 *Total cost*: $18,635 *Altretamine* *Cost per cycle*: $746 *Total cost*: $4477 *Etoposide* *Cost per cycle*: $1930 *Total cost*: $7721 ***Drug acquisition cost reduced by 20%*** *Paclitaxel* *Cost per cycle*: $2293 *Total cost*: $13,761 *Topotecan* *Cost per cycle*: $4149 *Total cost*: $16,598 *Altretamine* *Cost per cycle*: $641 *Total cost*: $3848 *Etoposide* *Cost per cycle*: $1677 *Total cost*: $6708 ***Alternative dosage*** *Paclitaxel* (135 mg/kg) *Cost per cycle*: $2246 *Total cost*: $13,474 *Topotecan* NA	***Authors' conclusions*** Although there was evidence of patient preferences for oral rather than intravenous administration of chemotherapeutic agents, our cost models suggest that, when efficacy and toxicity are equal, the more expensive intravenous agents may be used over less expensive oral alternatives because of concern over out-of-pocket costs to the patient. Although the influx of managed care in Medicare may provide more options and greater cost-saving, less than half of the current Medicare patients are enrolled in these programmes ***Authors' implications*** None stated ***Comments*** A cost-minimisation model (i.e. just considering costs in the model) does not seem appropriate given the differences in clinical effectiveness between the drugs under consideration The same data from this study were also reported in a separate publication.[60] However, both publications showed discrepancies in their reporting of the results in the abstract. The correct values were given in the text and tables of the main body of the reports

continued

B. Economic evaluations *contd*

Study design	Data sources	Clinical outcome data and costs used	Statistical analysis and results	Sensitivity analysis	Authors' conclusions/ implications and comments
Bennett *et al.*, 1999[60] and Stinson *et al.*, 1999[61] (260 mg/m^2 orally daily for 14 days every 21 days); etoposide (50 or 100 mg/m^2 daily for 14–21 days every 21 days) ***Currency*** US$ ***Cost year*** 1996 ***Perspective*** USA third-party payer (Medicare) and patient out-of-pocket costs ***Study population*** Pt-r/-resistant ovarian cancer (62–100% had stage III/IV disease)	administration. The following assumptions were used in the model: 1. Disease stage and prior treatment protocols were similar between studies 2. Patients were assumed to weigh 60 kg and have a body surface area equal to 1.6 m^2 for dosage calculations 3. Administration of chemotherapy was charged as a level 4 office visit 4. Two units of packed red blood cells were infused per cycle for each patient with grade 3/4 anaemia 5. One unit of single-donor platelets were infused per cycle for 50% of patients with grade 3/4 thrombocytopenia 6. 37% of patients with grade 3/4 neutropenia received G-CSF (filgrastim) for 10 days per cycle (5 µg/kg as a subcutaneous injection) 7. Costs for hospitalisation or additional treatment of febrile neutropenia were not included 8. Patients receiving topotecan, paclitaxel or etoposide required twice weekly complete blood counts with grade 3/4 neutropenia, once weekly without, whereas altretamine patients required a complete blood count only at the beginning of each cycle 9. Patients reporting grade 2/3/4 nausea and vomiting received prochlorperazine (Compazine 10 mg daily) for half of the days of the prescribed cycle	***Adverse effects*** *Grade 3/4 neutropenia* *Paclitaxel*: 32.6% *Topotecan*: 77.4% *Altretamine*: < 4.0% *Etoposide*: 39.5% *Grade 3/4 thrombocytopenia* *Paclitaxel*: 3.9% *Topotecan*: 26.1% *Altretamine*: < 4.0% *Etoposide*: 8.9% *Grade 3/4 anaemia* *Paclitaxel*: < 4.0% *Topotecan*: 35.0% *Altretamine*: 9.2% *Etoposide*: 12.0% *Grade 2/3/4 nausea/vomiting* *Paclitaxel*: 36.3% Topotecan: 24.6% Altretamine: 27.5% Etoposide: 30.0% *Mild peripheral neuropathy (severe)* *Paclitaxel*: 39.8% (10.0%) *Topotecan*: < 4.0% (< 4.0%) *Altretamine*: 20.2% (< 4.0%) *Etoposide*: < 4.0% (< 4.0%) *Minor hypersensitivity* *Paclitaxel*: 26.0% *Topotecan*: < 4.0% *Altretamine*: < 4.0% *Etoposide*: < 4.0% *Arthralgia/myalgia* *Paclitaxel*: 33.3% *Topotecan*: < 4.0% *Altretamine*: < 4.0% *Etoposide*: < 4.0%		*Altretamine (6 mg/kg/day)* *Cost per cycle*: $676 *Total cost*: $4054 *Etoposide (50 mg/m^2/day)* *Cost per cycle*: $1227 *Total cost*: $4908 ***Highest reported grade 3/4 neutropenia*** *Paclitaxel (49%)* *Cost per cycle*: $2765 *Total cost*: $16,593 *Topotecan (78%)* *Cost per cycle*: $4656 *Total cost*: $18,623 *Altretamine (0%)* *Cost per cycle*: $746 *Total cost*: $4477 *Etoposide (41%)* *Cost per cycle*: $1971 *Total cost*: $7885 ***Lowest reported grade 3/4 neutropenia*** *Paclitaxel (18%)* *Cost per cycle*: $2499 *Total cost*: $14,997 *Topotecan (71%)* *Cost per cycle*: $4572 *Total cost*: $18,288 *Altretamine (0%)* *Cost per cycle*: $746 *Total cost*: $4477	The authors stated several study limitations including: none of the trials included directly compared all comparators; heterogeneity could be present; the use of average wholesale prices and costs were not assigned to certain toxicities Overall, the study appeared to have a number of flaws not least the fact that it was assumed that the agents have equal clinical effectiveness, which is not the case. The use of a CMA was inappropriate given the differences in effectiveness. Consequently, the assumptions used in the analysis were invalid. They favoured an outcome of no difference in effectiveness, which is not the case, and so this was not the most conservative approach for assessing the cost-effectiveness of the agents. In such instances, a CMA does not reflect the true cost-effectiveness of the agents This was a poor quality study which had little relevance to the NHS setting

continued

B. Economic evaluations *contd*

Study design	Data sources	Clinical outcome data and costs used	Statistical analysis and results	Sensitivity analysis	Authors' conclusions/ implications and comments
		Alopecia *Paclitaxel*: 84.6% *Topotecan*: 79.0% *Altretamine*: < 4.0% *Etoposide*: < 13.4% ***Costs*** Total cost estimates were as follows (assuming median number of cycles for each agent is as above): *Drug administration* Paclitaxel: 6 x $2066 = $12,396 Topotecan: 4 x $3391 = $13,565 Altretamine: 6 x $675 = $4051 Etoposide: 4 x $1438 = $5752 *Toxicity treatment/monitoring* Paclitaxel: 6 x $562 = $3371 Topotecan: 4 x $1268 = $5070 Altretamine: 6 x $71 = $426 Etoposide: 4 x $492 = $1969		*Etoposide (16%)* *Cost per cycle*: $1766 *Total cost*: $7064 ***Undated anti-emetic co-medication (ondansetron)*** *Paclitaxel* *Cost per cycle*: $2789 *Total cost*: $16,733 *Topotecan* *Cost per cycle*: $4863 *Total cost*: $19,452 *Altretamine* *Cost per cycle*: $956 *Total cost*: $5736 *Etoposide* *Cost per cycle*: $2295 *Total cost*: $9182	

B. Economic evaluations *contd*

Study design	Data sources	Clinical outcome data and costs used	Statistical analysis and results	Sensitivity analysis	Authors' conclusions/implications and comments
Drummond and Smith, 2000[62] ***Source*** Company submission ***Objective*** To compare the costs of caelyx versus topotecan for the treatment of advanced epithelial ovarian cancer ***Type of evaluation*** CMA ***Matrix grading*** H in favour of caelyx ***Link between cost/effectiveness data*** Retrospective/disconnected ***Comparators*** Caelyx (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 consecutive days every 21days) ***Currency*** Euro and £ ***Cost year*** 1999/2000 ***Perspective*** UK NHS ***Study population*** Patients (n = 474; ITT population) from the multicentre open-label RCT 30-49 (Schering-Plough Ltd.)[59] with advanced epithelial ovarian carcinoma (FIGO stage III/IV) who had failed first-line chemotherapy with a Pt-based regimen. The trial was based in multiple centres in both Europe and the USA. Patients were stratified prospectively for Pt-sensitivity and bulky disease and could not receive any more that one prior Pt-based regimen	***Source of clinical effectiveness data*** Single trial (30-49, Schering-Plough Ltd.) ***Source of cost data*** MIMS, Chartered Institute of Public Finance and Accountancy database and UK cancer centre tariffs (resources were estimated using expert opinion). Cost year 1999/2000	Details in this column were commercial in confidence and have, therefore, been excluded	***Summary of results*** The total per-person cost of caelyx was estimated to be Euros 16,266 while the per-person cost of topotecan was estimated at Euros 22,858. In terms of £, the costs per person were £9979 for caelyx versus £14,023 for topotecan ***Applicable to NHS*** Yes	Details in this column were commercial in confidence and have, therefore, been excluded	***Authors' conclusions*** This analysis indicates that caelyx is the dominant therapy, that is, the effects are at least as good as topotecan but at a lower cost. This effect is apparent even with an extreme analysis that favours topotecan, indicating that the finding is robust to some changes in resource-use patterns ***Comments*** This was a reasonable quality study, but there were methodological issues of concern that should be considered when interpreting the findings of the study

B. Economic evaluations *contd*

Study design	Data sources	Clinical outcome data and costs used	Statistical analysis and results	Sensitivity analysis	Authors' conclusions/ implications and comments
SmithKine Beecham, 2000[28] ***Source*** Company submission ***Objective*** To develop an economic model relevant to the UK NHS describing the cost-effectiveness of topotecan in advanced or metastatic ovarian cancer after the failure of first-line therapy ***Type of evaluation*** CEA ***Matrix grading*** A in favour of topotecan ***Link between cost/effectiveness data*** Retrospective/disconnected ***Comparators*** Topotecan (1.5 mg/m^2 as a 30-minute infusion for 5 consecutive days every 21 days) versus paclitaxel (175 mg/m^2 as a 3-hour infusion every 21 days). The model was based on six cycles for each agent ***Currency*** £ ***Cost year*** 2000 ***Perspective*** UK NHS ***Study population*** The cost-effectiveness model used is based on a simulation of 1000 patients with FIGO stage IIIb/IV ovarian cancer receiving second-line therapy	***Source of clinical effectiveness data*** Single trial (039, SmithKline-Beecham) ***Source of cost data*** MIMS and NHS Trust data. Cost year 2000 ***Model used*** A decision tree model based on trial 039 was used to estimate cost-effectiveness	Details in this column were commercial in confidence and have, therefore, been excluded	***Summary of results*** The cost-effectiveness ratios for topotecan were generally superior as compared with paclitaxel, except for cost per TWIST *Cost per week of survival*: topotecan = £106, paclitaxel = £122; incremental cost-effectiveness ratio of topotecan = £20 *Cost per patient with CR*: topotecan = £148,115, paclitaxel = £248,691; incremental cost-effectiveness ratio of topotecan = £10,485 *Cost per patient with PR*: topotecan = £41,399, paclitaxel = £56,719; incremental cost-effectiveness ratio of topotecan = £4238 *Cost per patient with any response*: topotecan = £32,513, paclitaxel = £46,186; incremental cost-effectiveness ratio of topotecan = £3065 *Cost per week of response*: topotecan = £257,343, paclitaxel = £299,351; incremental cost-effectiveness ratio of topotecan = £46,327 *Cost per TWIST*: topotecan = £1503, paclitaxel = £987; incremental cost-effectiveness ratio of topotecan = –£94 ***Applicable to NHS*** Yes	Details in this column were commercial in confidence and have, therefore, been excluded	***Authors' conclusions*** This analysis has demonstrated that the use of topotecan in women who have relapsed after first-line therapies is a valuable cost-effective addition to the management options for these cases. Assumptions in the model are assumed conservative. There are unquantifiable attributes associated with topotecan that cannot easily be captured. Hence, in clinical practice, topotecan may be even more cost-effective and acceptable to women with metastatic ovarian cancer than described in this submission ***Comments*** This study was of reasonable quality, but does suffer from methodological problems that are of concern. In view of these issues, the findings of the study should be treated with caution

Appendix 9

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The following individuals have provided comments on draft versions of both the protocol and final report, in addition to providing advice on clinical and methodological issues.

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Appendix 10

Levels of evidence (adapted from the Canadian Task Force on the Periodic Health Examination, 1979 and Sackett, 1986)

Grade	Level of evidence	Therapy
A	1A	Systematic review of homogeneous RCTs
	1B	Individual RCT (with narrow CIs)
	1C	Other RCT
B	2A	Systematic review of homogeneous cohort studies
	2B	Individual cohort study (including low-quality RCT, e.g. < 80% follow-up)
	2C	'Outcomes' research
	3A	Systematic review of homogeneous case-control studies
	3B	Individual case-control study
C	4	Case-series (and poor-quality cohort and case-control studies*)
D	5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or 'first principles'

* *A poor-quality cohort study means one that fails to clearly define comparison groups and/or fails to measure exposures and outcomes in the same time period (preferably failing to identify or appropriately control known confounders and/or failing to carry out a sufficiently long and complete follow-up of patients). A poor-quality case-control study means one that fails to clearly define comparison groups and/or fails to measure exposures and outcomes in the same objective way (preferably blinded) in both cases and controls and/or fails to identify or appropriately control known confounders*

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

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We look forward to hearing from you.

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